2018 EAU Male Hypogonadism Guidelines Scope Search

Database: Embase <1974 to 2017 June 2>, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials <April 2017>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 31, 2017>

Search Strategy:

1. exp hypogonadism/ (27031)
2. (eugonadal or hypogonadism or hypogonadal or gonadal).tw.kw. (83468)
3. ((low or lower or reduction or absence) adj5 (testosterone* or (hormone and testes])).tw. (17714)
4. 1 or 2 or 3 (107893)
5. limit 4 to yr="2011 -Current" (30615)
6. female/ not (exp male/ or (men or man or male*).tw.) (5254378)
7. female to male transgender/ or (male transgender* or transsexual or trans men).tw. (2856)
8. 5 not (6 or 7) (26388)
9. randomized controlled trial.pt. (886547)
10. random:.mp. (3143566)
11. controlled clinical trial.pt. (183474)
12. clinical trial:.mp. or clinical trial.pt. (2862164)
13. double-blind:.mp. or blind:.tw. (942264)
14. (trial or groups or placebo).ab. (5434601)
15. (Systematic review or meta-analysis).tw.kw. (375335)
16. Meta analysis/ or "systematic review"/ (294690)
17. (Medline or Pubmed Embase or Cochrane or literature search or literature review).ab. (379762)
18. or/9-17 (8720691)
19. 8 and 18 (6971)
20. ((exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/) not (humans/ or human/)) or ((rats or mice or mouse or cats or dogs or animal* or cell lines) not (human* or men or women)).ti. (11027679)
21. ((child/ or Pediatrics/ or Adolescent/ or Infant/ or adolescence/ or newborn/) not adult/) or ((child or children or pediatric* or paediatric* or peadiatric* or infant* or new born or adolescent or preschool or pre-school or youth* or student*) not (aged or adult* or senior or men or women)).ti. (4364675)
22. conference abstract.pt. or Congresses as Topic/ (2673462)
1. Dopa-testotoxicosis: disruptive hypersexuality in hypogonadal men with prolactinomas treated with dopamine agonists
   De Sousa SMC, Chapman IM, Falhammar H, Torpy DJ
   EBM Reviews - Cochrane Central Register of Controlled Trials
   [Journal: Article]
   AN: CN-01327741 NEW
   Dopamine agonists are the first line of therapy for prolactinomas, with high rates of biochemical control and tumour shrinkage. Toxicity is considered to be low and manageable by switching of agents and dose reduction. Dopamine agonist-induced impulse control disorders are well
described in the neurology setting, but further data are required regarding this toxicity in prolactinoma patients. We performed a multicenter retrospective cohort study of eight men with prolactinomas and associated central hypogonadism. The eight men had no prior history of psychiatric disease, but each developed disruptive hypersexuality whilst on dopamine agonist therapy at various doses. Cabergoline, bromocriptine and quinagolide were all implicated. Hypersexuality had manifold consequences, including relationship discord, financial loss, reduced work performance, and illicit activity. We hypothesise that this phenomenon is due to synergy between reward pathway stimulation by dopamine agonists, together with rapid restoration of the eugonadal state after prolonged hypogonadism. We refer here to this distinct drug toxicity as 'dopa-testotoxicosis'. Given the profound impact in these patients and their families, cessation of dopamine agonists should be considered in men who develop hypersexuality, and pituitary surgery may be required to facilitate this. Awareness of this distinct impulse control disorder should enable further research into the prevalence, natural history and management of dopa-testotoxicosis. The condition is likely under-reported due to the highly personal nature of the symptoms and we suggest a simple written questionnaire to screen for hypersexuality and other behavioural symptoms within the first six months of dopamine agonist treatment. Copyright (C) 2016, Springer Science+Business Media New York.

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Publisher
Humana Press Inc. (E-mail: humana@humanapr.com)

2.
Expression of hypothalamic-pituitary-gonadal axis-related hormone receptors in low-grade serous ovarian cancer (LGSC)
Feng Z, Wen H, Ju X, Bi R, Chen X, Yang W, Wu X
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Article]
AN: CN-01327789 NEW
Background: The aim of our study was to investigate the clinical features and expression levels of hypothalamic-pituitary-gonadal axis-related hormone receptors in low-grade serous ovarian cancer.
cancer (LGSC). Methods: We retrospectively investigated the clinical features of 26 consecutive patients with LGSC who underwent primary staging or debulking surgery between April 2005 and June 2013 in our center; concomitant primary high-grade serous ovarian cancer (HGSC) patients were randomly selected at a 2:1 ratio for comparison. Tissue microarrays were constructed from the LGSC and HGSC specimens, and the expression levels of six hormone receptors in the hypothalamic pituitary-gonadal axis were analyzed by immunohistochemistry. Results: The median (range) age of patients with LGSC was 54 (27-77) years. According to the FIGO staging system, the cases were distributed as follows: stage I, 6 (23.1%); stage II, 0 (0%); stage III, 19 (73.1%); and stage IV, 1 (3.8%). The 2-year and 5-year overall survival rates for LGSC were 91.8% and 67.5%, respectively. The expression levels of the hormone receptors were as follows: ER, 80.8%; PR, 34.6%; AR, 53.8%; FSHR, 84.0%; LHR, 65.4%; and GnRHR, 100%. Hormone receptor-positive patients had a better prognosis compared with hormone receptor-negative patients, but the difference was not significant. Conclusions: Our study presented a higher overall survival rate and distinctive hormone receptor expression levels of LGSC patients compared with the HGSC cohort. Patients with positive hormone receptor expression tended to have a better prognosis than the corresponding hormone receptor negative patients. Copyright (C) 2017 The Author(s).

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3.
Dopa-testotoxicosis: a novel drug toxicity of dopamine agonists in male prolactinoma patients
De Sousa SMC, Chapman IM, Falhammar H, Torpy DJ

EBM Reviews - Cochrane Central Register of Controlled Trials

AN: CN-01334018 NEW

Background: Impulse control disorders (ICD) including gambling, hypersexuality, compulsive shopping and binge eating have recently been recognised as side effects of dopamine agonists
(DAs). The vast majority has been described in the treatment of Parkinson's disease and restless legs syndrome where pathological gambling is the predominant DA-associated ICD (1). Little is known about the nature of ICDs in the prolactinoma setting where endocrine factors, specifically testosterone fluctuations, may influence behaviour (2). Methods: We performed a multicenter retrospective cohort study of eight men who developed hypersexuality following initiation of DA therapy for prolactinomas. Results: The men had no prior history of psychiatric disease, but each developed disruptive hypersexuality with manifold consequences, including relationship discord, financial loss, reduced work performance, and illicit activity. Two men also developed pathological gambling. Cabergoline, bromocriptine and quinagolide were all implicated. The onset of hypersexuality ranged from days to years after DA commencement. Some men notably had normal pre-treatment testosterone levels, however these values were in the lower half of the reference range and rose into the upper half with DA initiation suggesting they had relative hypogonadism at baseline. Six men received no androgen replacement and increases in testosterone were solely attributable to DA therapy. Prolactin and testosterone consistently improved to be close or within the reference range by the time of symptom onset. Symptoms were reversible with DA cessation. Conclusions: We hypothesise that this phenomenon is due to synergy between mesolimbic reward pathway stimulation by DAs, together with rapid restoration of the eugonadal state after prolonged hypogonadism. We refer to this unique drug toxicity as 'dopa-testotoxicosis'. The condition is likely under-reported due to the highly personal nature of the symptoms and we suggest a simple written questionnaire to screen for it. Treatment will generally include cessation of DAs in affected men, and often pituitary surgery for prolactinoma resection.

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Publisher
Blackwell Publishing Ltd

4.
Testosterone treatment increases loss of body fat and prevents loss of lean mass in obese men with low testosterone levels on a hypocaloric diet: a randomized trial
Fui MNT, Prendergast LA, Dupuis P, Raval M, Strauss B, Zajac J, Grossmann M
EBM Reviews - Cochrane Central Register of Controlled Trials
Importance: Obesity is strongly associated with low testosterone levels in men. Whether testosterone treatment has benefits on body composition over and above caloric restriction is unknown. Objective: To determine whether testosterone treatment augments diet-induced loss of fat mass and prevents loss of muscle mass. Design: Randomised double-blind, placebo-controlled trial. Participants: Obese men with total testosterone <12 nmol/L. Intervention: One hundred participants receiving 10 weeks of a very low energy diet (VLED) followed by weight maintenance were randomised at baseline to 56 weeks of intramuscular testosterone undecanoate (n = 49, cases) or placebo (n = 51, controls). Main Outcomes: The primary outcome was the between-group difference in fat mass at study end (56 weeks), quantified by dual-energy Xray absorptiometry (DXA). Other main outcomes: change in lean mass, visceral fat and body weight. Results: Cases and controls lost the same weight (testosterone -11.4 kg; placebo -10.9 kg) at study end (P = 0.80). Cases had greater reductions in total fat, mean adjusted between-group difference (MAD) -2.9 kg, P = 0.04, and in visceral fat, MAD -2,678 mm$^{2}$, P = 0.04. Although both groups lost the same lean mass following VLED (cases -3.9 kg; controls -4.8 kg, P = 0.36), cases regained lean mass (3.3 kg, P < 0.001) during weight maintenance, in contrast to controls, 0.8 kg, P = 0.29 so at study end, cases had an attenuated reduction in lean mass compared to controls, MAD 3.4 kg, P = 0.002. Conclusions: Among obese men with lowered testosterone, testosterone treatment augmented diet-induced loss of total and visceral fat mass, and prevented diet-induced loss of lean mass. While men receiving placebo lost both fat and lean mass, the weight lost with testosterone treatment was almost exclusively due to loss of fat.

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Publisher
Blackwell Publishing Ltd

5.
An open-label clinical trial to investigate the efficacy and safety of corifollitropin alfa combined with hCG in adult men with hypogonadotrophic hypogonadism
Background: Hypogonadotropic hypogonadism (HH) in men results in insufficient testicular function and deficiencies in testosterone and spermatogenesis. Combinations of human chorionic gonadotropin (hCG) and recombinant follicle-stimulating hormone (recFSH) have been successful in the treatment of HH. Corifollitropin alfa is a long-acting FSH-analog with demonstrated action in women seeking infertility care. The aim of this study was to investigate the efficacy and safety of corifollitropin alfa combined with hCG to increase testicular volume and induce spermatogenesis in men with HH. Methods: This was a Phase III, multi-center, open-label, single-arm trial of corifollitropin alfa in azoospermic men aged 18 to 50 years with HH. After 16 weeks of pretreatment of 23 subjects with hCG alone, 18 subjects with normalized testosterone (T) levels who remained azoospermic entered the 52-week combined treatment phase with hCG twice-weekly and 150 mug corifollitropin alfa every other week. The increase in testicular volume (primary efficacy endpoint) and induction of spermatogenesis resulting in a sperm count >1 x 10^6/mL (key secondary efficacy endpoint) during 52 weeks of combined treatment were assessed. Safety was evaluated by the presence of anti-corifollitropin alfa antibodies and the occurrence of adverse events (AEs). Results: Mean (+/-SD) testicular volume increased from 8.6 (+/-6.09) mL to 17.8 (+/-8.93) mL (geometric mean fold increase, 2.30 [95% CI: 2.03, 2.62]); 14 (77.8%) subjects reached a sperm count >1 x 10^6/mL. No subject developed confirmed anti-corifollitropin alfa antibodies during the trial. Treatment was generally well tolerated. Conclusions: Corifollitropin alfa 150 mug administrated every other week combined with twice-weekly hCG for 52 weeks increased testicular volume significantly, and induced spermatogenesis in >75% of men with HH who had remained azoospermic after hCG treatment alone. Trial registration: ClinicalTrials.gov: NCT01709331. Copyright (C) 2017 The Author(s).
6. Efficacy and safety of testosterone replacement gel for treating hypogonadism in men: phase III open-label studies
EBM Reviews - Cochrane Central Register of Controlled Trials Andrologia. Vol.(no pagination), 2017.
[Journal: Article In Press]
AN: CN-01339263 NEW
Efficacy and safety of testosterone gel 2% (TG) were evaluated in two phase 3, open-labelled, single-arm, multicentre studies (000023 and extension study 000077). Hypogonadal men having serum testosterone levels <300 ng/dl at two consecutive measurements were included. Study duration was 9 months (000023: 3 months; 000077: 6 months). Starting dose of TG (46 mg) was applied on upper arm/shoulder. The primary endpoint (000023) was responder rate (subjects with average 24-hour serum testosterone concentration 300-1050 ng/dl on Day 90). Study 000077 evaluated the safety of TG in patients rolling over from study 000023 over a period of 6 months. Of 180 subjects in 000023, 172 completed and 145 rolled over to 000077, with 127 completers. The responder rate was 85.5%. Fewer subjects in 000077 (12.7%) versus 000023 (31.8%) had maximum testosterone concentration (C<sub>max</sub>) >1500 ng/dl, with no significant safety concerns. Significant improvements in sexual function and quality of life were noted in both studies. Subjects experienced few skin reactions without notable increases in prostate-specific antigen and haematocrit levels. TG was efficacious with an acceptable safety profile. C<sub>max</sub> >1500 ng/dl did not exhibit distinct impact on safety parameters. However, further optimisation of titration schema to reduce C<sub>max</sub> is warranted while maintaining the average steady state total testosterone concentration. Copyright (C) 2017 Blackwell Verlag GmbH.
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Publisher
Blackwell Publishing Ltd (E-mail: customerservices@oxonblackwellpublishing.com)
Androgen Treatment Effects on Motor Function, Cognition, and Behavior in Boys with Klinefelter Syndrome

Ross JL, Kushner H, Kowal K, Bardsley M, Davis S, Reiss AL, Tartaglia N, Roeltgen D

EBM Reviews - Cochrane Central Register of Controlled Trials


[Journal: Article In Press]

AN: CN-01340267 NEW

Objectives: To examine the effects of early low-dose androgen on motor, cognitive, and behavioral function in prepubertal boys with Klinefelter syndrome (47,XXY). Study design: Double-blind trial of 84 boys, ages 4-12 years, randomized to oxandrolone (Ox; 0.06 mg/kg daily; n = 43) or placebo (Pl; n = 41) for 24 months. Standardized assessments were performed at baseline and every 12 months for 24 months evaluating motor, cognitive, and behavioral function.

Results: The 24-month outcomes were better in the Ox vs. Pl group on 1 of 5 primary endpoints (motor function/strength): Bruininks Visual-Motor scale (P = .005), without significant differences between the 2 groups for the other 4 components. Secondary analyses suggested improvement in the Ox vs. Pl group in the anxiety/depression (P = .03) and social problems (P = .01) scales on the Child Behavior Checklist, anxiety (P = .04) on the Piers Harris Self Concept Scale, and interpersonal problems (P = .02) on the Children’s Depression Inventory, without significant differences in hyperactive or aggressive behaviors. Conclusions: This double-blind, randomized trial demonstrates that 24 months of childhood low-dose androgen treatment in boys with Klinefelter syndrome benefited 1 of 5 primary endpoints (visual-motor function). Secondary analyses demonstrated positive effects of androgen on aspects of psychosocial function (anxiety, depression, social problems), without significant effects on cognitive function, or hyperactive or aggressive behaviors. Trial registration: ClinicalTrials.gov: NCT00348946. Copyright (C) 2017 Elsevier Inc.

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Publisher
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Introduction: The prevalence of metabolic syndrome (MetS) is rapidly increasing in the United States and, because of its strong association with male hypogonadism, has become a significant topic of interest in the sexual medicine community. At the center of this conversation is the efficacy and safety of testosterone replacement therapy (TRT) as a therapeutic option for HG and MetS. Aim: To provide a review of the current literature pertaining to TRT and MetS. Methods: A thorough literature review was performed to review the relation between TRT and MetS using the PubMed online database from 1976 through 2016 with the keywords testosterone, hypogonadism, metabolic syndrome, and testosterone therapy. Main Outcome Measures: Outcomes pertaining to MetS including weight, waist circumference, body mass index, blood glucose control, cholesterol parameters, blood pressure, and quality of life. Results: From the plethora of contrasting literature on the efficacy and safety of TRT, it is increasingly clear that more well-designed studies are needed to clarify the efficacy and safety of TRT. Although most of the current literature shows that TRT has the potential to significantly lower the studied outcome variables associated with MetS, several studies provide more mixed results. Conclusion: TRT has the potential to alleviate some of the morbidity associated with hypogonadism and MetS. Larger multicenter well-designed studies are needed to better describe and quantify the relation between MetS and TRT. Anaissie J, Roberts NH, Wang P, et al. Testosterone Replacement Therapy and Components of the Metabolic Syndrome. Sex Med Rev 2017;X:XXX-XXX. Copyright (C) 2017 International Society for Sexual Medicine.
Objective: Rare congenital conditions with incongruence of chromosomal, gonadal and phenotypic sex have been classified as differences/disorders of sex development (DSD). Included in DSD are conditions with diverse genetic aetiology, varying levels of prenatal androgen effects, phenotypes and, subsequently, different medical treatments. Quality of life (QoL) and psychological well-being are indicators of successful psychosocial adaptation to the conditions. We sought to investigate the HRQoL and psychological well-being in this population. Design: This multicentre clinical evaluation study was part of a German network related to DSD funded by the German Ministry of Science and Education (BMBF 2003 to 2007). Methods: To assess health-related quality of life (HRQoL), we used the Short Form Health Survey (SF-36), and for psychological well-being, the Brief Symptom Inventory (BSI). Participants were classified into five groups: females with CAH, females with XY DSD conditions where there is a partial androgen effect (partial androgen insensitivity, mixed/partial gonadal dysgenesis, disorders of androgen biosynthesis), females with XY DSD without androgen effect (complete androgen insensitivity, complete gonadal dysgenesis), males with XY DSD, and individuals with DSD conditions and other gender. Results: Participants included 110 adults with DSD (age range 17-62). We found a trend of lowered mental HRQoL and significant higher physical HRQoL for participants as compared to the norm. The high physical HRQoL especially applied to females with androgen effect and XY karyotype. Participants reported significant higher psychological distress compared to the norm. Forty-seven participants (42.7%) reported distress in a clinically relevant range on the BSI. Conclusions: Although we did not find significant impairments in overall HRQoL, participants reported significant impaired psychological well-being. Specialized interdisciplinary care should focus in particular on psychological issues to ensure good overall health and well-being. Copyright (C) 2017 John Wiley & Sons Ltd.

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Publisher
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Testosterone administration does not affect men's rejections of low ultimatum game offers or aggressive mood

Cueva C, Roberts RE, Spencer TJ, Rani N, Tempest M, Tobler PN, Herbert J, Rustichini A

EBM Reviews - Cochrane Central Register of Controlled Trials


Correlative evidence suggests that testosterone promotes dominance and aggression. However, causal evidence is scarce and offers mixed results. To investigate this relationship, we administered testosterone for 48 h to 41 healthy young adult men in a within-subjects, double-blind placebo-controlled balanced crossover design. Subjects played the role of responders in an ultimatum game, where rejecting a low offer is costly, but serves to destroy the proposer's profit. Such action can hence be interpreted as non-physical aggression in response to social provocation. In addition, subjects completed a self-assessed mood questionnaire. As expected, self-reported aggressiveness was a key predictor of ultimatum game rejections. However, while testosterone affected subjective ratings of feeling energetic and interested, our evidence strongly suggests that testosterone had no effect on ultimatum game rejections or on aggressive mood. Our findings illustrate the importance of using causal interventions to assess correlative evidence.

Symptomatic response to testosterone treatment in dieting obese men with low testosterone levels in a randomized, placebo-controlled clinical trial

Ng Tang Fui M, Hoermann R, Prendergast LA, Zajac JD, Grossmann M

EBM Reviews - Cochrane Central Register of Controlled Trials

Background: Obese men commonly have reductions in circulating testosterone and report symptoms consistent with androgen deficiency. We hypothesized that testosterone treatment improves constitutional and sexual symptoms over and above the effects of weight loss alone. Methods: We conducted a pre-specified analysis of a randomized double-blind, placebo-controlled trial at a tertiary referral center. About 100 obese men (body mass index (BMI) $\geq 30$ kg/m$^2$) with a repeated total testosterone level $\geq 12$ nmol/l and a median age of 53 years (interquartile range 47-60) receiving 10 weeks of a very-low-energy diet (VLED) followed by 46 weeks of weight maintenance were randomly assigned at baseline to 56 weeks of intramuscular testosterone undecanoate (n=49, cases) or matching placebo (n=51, controls). Pre-specified outcomes were the between-group differences in Aging Male Symptoms scale (AMS) and international index of erectile function (IIEF-5) questionnaires. Results: Eighty-two men completed the study. At study end, cases showed significant symptomatic improvement in AMS score, compared with controls, and improvement was more marked in men with more severe baseline symptoms (mean adjusted difference (MAD) per unit of change in AMS score $-0.34$ (95% confidence interval (CI) $-0.65$, $-0.02$), $P=0.04$). This corresponds to improvements of 11% and 20% from baseline scores of 40 and 60, respectively, with higher scores denoting more severe symptoms. Men with erectile dysfunction (IIEF-5$\leq 20$) had improved erectile function with testosterone treatment. Cases and controls lost the same weight after VLED (testosterone $-12.0$ kg; placebo $-13.5$ kg, $P=0.40$) and maintained this at study end (testosterone $-11.4$ kg; placebo $-10.9$ kg, $P=0.80$). The improvement in AMS following VLED was not different between the groups ($-0.05$ (95% CI $-0.28$, $0.17$), $P=0.65$). Conclusions: In otherwise healthy obese men with mild to moderate symptoms and modest reductions in testosterone levels, testosterone treatment improved androgen deficiency symptoms over and above the improvement associated with weight loss alone, and more severely symptomatic men achieved a greater benefit. International Journal of Obesity advance online publication, 17 January 2017; doi:10.1038/ijo.2016.242. Copyright (C) 2017 Macmillan Publishers Limited, part of Springer Nature.

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Publisher
Nature Publishing Group (Houndmills, Basingstoke, Hampshire RG21 6XS, United Kingdom)
Disorders of sex development (DSD): Clinical service delivery in the United States. Rolston AM; Gardner M; van Leeuwen K; Mohnach L; Keegan C; Delot E; Vilain E; Sandberg DE; members of the DSD-TRN Advocacy; Advisory Network Accord Alliance.

UI: 28557237

Following the principles of care recommended in the 2006 Consensus Statement on Disorders of Sex Development (DSD), along with input from representatives of peer support and advocacy groups, this study surveyed DSD clinical management practices at healthcare facilities in the United States. DSD are congenital conditions in which development of chromosomal, gonadal, or anatomic sex is atypical. Facilities providing care for patients with DSD were targeted for participation. Specialty providers completed a survey with questions in six broad categories: Institution Information, Nomenclature and Care Guidelines, Interdisciplinary Services, Staff and Community Education, DSD Management, and Research. Twenty-two of 36 targeted sites (61%) participated. Differences were observed between sites with regard to what conditions were considered to be DSD. All sites reported some degree of involvement of pediatric urology and/or surgery and pediatric endocrinology in the care of DSD patients. Gynecology and neonatology were most frequently not represented. Wide variation was observed across sites in continuing education standards, obtaining informed consent for clinical procedures, and in specific clinical management practices. This survey is the first to assess DSD clinical management practices in the United States. The findings establish a baseline of current practices against which providers delivering care to these patients and their families can benchmark their efforts. Such surveys also provide a practical framework for collaboration in identifying opportunities for change that enhance health and quality of life outcomes for patients and families affected by DSD.

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A practical guide for evaluating gonadal germ cell tumor predisposition in differences of sex development. [Review]
Differences of Sex Development (DSD) includes a wide spectrum of etiologies and phenotypes. A subset of individuals with DSDs are predisposed to gonadal germ cell tumor (GCT). In this setting, GCT risk varies widely, depending on the DSD molecular etiology and penetrance. Prognostication based on molecular diagnosis remains challenging, as natural history data specific to recently identified molecular causes of DSD is lacking. In this review, we provide a framework for the clinical geneticist to consider GCT tumor risk in the patient with DSD. We discuss germ cell development and etiology of GCT growth, along with parameters to consider when recommending prophylactic gonadectomy including fertility, hormonal output, and malignant GTC treatment outcomes. Shortly after the 2006 reorganization of DSD nomenclature, literature reviews of natural history publications stratified GCT risk by a chromosomal, pathological, and hormonal taxonomy. Our 2017 literature review reveals a larger body of publications. However, the broad DSD GCT risk stratification within the 2006 taxonomy remains stable. We discuss precise GCT risk assessment for specific diagnoses, including androgen insensitivity, Smith-Lemli-Opitz, and 46,XY with MAP3K1 mutations and gonadal dysgenesis, as examples. We also examine the GCT risk in non-DSD syndromes, in addition to the cancer risks in DSD patients with dimorphic gonads and genitalia. This review is intended to provide a nuanced assessment of relative germ cell tumor risk in the DSD patient, including modern precise molecular diagnosis, for use by the clinical geneticist.
INTRODUCTION: A rapid increase in awareness of androgen deficiency has led to substantial increases in prescribing of testosterone therapy (TTh), with benefits of improvements in mood, libido, bone density, muscle mass, body composition, energy, and cognition. However, TTh can be limited by its side effects, particularly erythrocytosis. This review examines the literature on testosterone-induced erythrocytosis and polycythemia.

AIM: To review the available literature on testosterone-induced erythrocytosis, discuss possible mechanisms for pathophysiology, determine the significance of formulation, and elucidate potential thromboembolic risk.

METHODS: A literature review was performed using PubMed for articles addressing TTh, erythrocytosis, and polycythemia.

MAIN OUTCOME MEASURES: Mechanism, pharmacologic contribution, and risk of testosterone-induced erythrocytosis.

RESULTS: For men undergoing TTh, the risk of developing erythrocytosis compared with controls is well established, with short-acting injectable formulations having the highest associated incidence. Potential mechanisms explaining the relation between TTh and erythrocytosis include the role of hepcidin, iron sequestration and turnover, erythropoietin production, bone marrow stimulation, and genetic factors. High blood viscosity increases the risk for potential vascular complications involving the coronary, cerebrovascular, and peripheral vascular circulations, although there is limited evidence supporting a relation between TTh and vascular complications.
CONCLUSION: Short-acting injectable testosterone is associated with greater risk of erythrocytosis compared with other formulations. The mechanism of the pathophysiology and its role on thromboembolic events remain unclear, although some data support an increased risk of cardiovascular events resulting from testosterone-induced erythrocytosis. Ohlander SJ, Varghese B, Pastuszak AW. Erythrocytosis Following Testosterone Therapy. Sex Med Rev 2017;X:XXX-XXX.

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2017

15.
Childhood, adolescent and young adult cancer incidence in Japan in 2009-2011. Katanoda K; Shibata A; Matsuda T; Hori M; Nakata K; Narita Y; Ogawa C; Munakata W; Kawai A; Nishimoto H.
[Journal Article]
UI: 28541571
Little is known about cancer incidence among children and youths in Japan. We aimed to describe cancer incidence in Japan focusing on childhood, adolescence and young adulthood (AYA). Cancer incidence data were obtained from the Monitoring of Cancer Incidence in Japan project. For the 2009-2011 incidence, the data were collected from 40 prefectures, of which data from 27 prefectures meeting quality standards were analyzed (population coverage: 38.6%). Cancers diagnosed in 0-39 years of age were classified according to the International Classification of Childhood Cancer (version 3). Crude incidence rates of cancer (including benign or behavior-unknown brain tumors) were 122.7, 142.2, 310.7, and 910.6 for the 0-14, 15-19, 20-29, and 30-39 age groups, respectively (per million population). Using the sex- and age-specific incidence rates, the national estimates of cancer incidence were 2055 for 0-14 years (1118 males and 937 females), 864 for 15-19 years (450 males and 414 females), 4246 for 20-29 years (1699 males and 2547 females), and 16 295 for 30-39 years of age (5101 males and 11 194 females). The five leading cancers were leukemia, cancer of the central nervous system (CNS), lymphoma, malignant germ cell and other gonadal tumors, and neuroblastoma in childhood cases (0-14 years old); leukemia, malignant germ cell and other gonadal tumors, lymphoma, CNS, and malignant bone tumors in adolescence (15-19 years old). The leading cancer in 20-29 years of age was malignant germ cell other gonadal tumors (mainly testis and ovary), whereas female breast cancer was most frequent in 30-39 years of age. These results provide an overall picture of childhood and AYA cancer in Japan.

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Pituitary dysfunction in granulomatosis with polyangiitis. [Review] Esposito D; Trimpou P; Giugliano D; Dehlin M; Ragnarsson O. OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present Pituitary. , 2017 May 24. [Journal Article. Review] UI: 28540625

PURPOSE: Granulomatosis with polyangiitis (GPA) is a multisystem disease, characterized by necrotizing small-vessel vasculitis, which mainly affects the respiratory tract and the kidneys. Pituitary involvement in GPA is rare, present in about 1% of all cases of GPA. To date, only case reports or small case series have been published. Herein we report clinical features, imaging findings, treatment and outcomes in three patients with GPA-related pituitary dysfunction (PD).

METHODS: A retrospective analysis of three cases of GPA-related PD was conducted, followed by systematic review of the English medical literature using PubMed.

RESULTS: The three cases include three women aged between 32 and 37 years. PD was the presenting feature in one and two developed PD in the course of the disease. All patients had a pituitary lesion on MRI. Conventional treatment with high doses of glucocorticoids and cyclophosphamide led to resolution or improvement of the MRI abnormalities, whereas it was not effective in restoring PD. A systematic review identified 51 additional patients, showing that GPA can lead to partial or global PD, either at onset or, during the course of the disease. Secondary
hypogonadism is the predominant manifestation, followed by diabetes insipidus (DI). Sellar mass with central cystic lesion is the most frequent radiological finding.

CONCLUSION: GPA should be carefully considered in patients with a sellar mass and unusual clinical presentation with DI and systemic disease. Although conventional induction-remission treatment improves systemic symptoms and radiological pituitary abnormalities, hormonal deficiencies persist in most of the patients. Therefore, follow-up should include both imaging and pituitary function assessment.

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 Thyroid disrupting pesticides impair the hypothalamic-pituitary-testicular axis of a wildlife bird, Amandava amandava.

Mohanty B; Pandey SP; Tsutsui K.

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Reproductive Toxicology. 71:32-41, 2017 Apr 19.
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The effect of two thyroid disrupting pesticides (TDPs) mancozeb (MCZ) and imidacloprid (IMI) on the hypothalamic-pituitary-gonadal/testicular (HPG) axis of a seasonally breeding bird, Amandava amandava has been evaluated. Male birds (n=8/group) were exposed to each of the pesticide (0.25% LD50 of respective pesticide) as well as to their two equimixture doses (0.25% of LD50 of each and 0.5% LD50 of each) through food for 30d during pre-breeding stage of the reproductive cycle. Reduction in weight, volume and other histopathological features revealed testicular regression. Suppression of gonadotropin releasing hormone, increased expression of gonadotropin inhibitory hormone in the hypothalamus of exposed groups as well as impairment of plasma levels of the reproduction related hormones indicated the disruption of the HPG axis. The pesticides interference of the thyroid function during the critical phase of reproductive development impaired the HPG axis; more significantly in co-exposed groups suggesting the cumulative toxicity.

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This study aimed to evaluate the protective effect of a gonadotropin-releasing hormone (GnRH) agonist against docetaxel-induced gonadotoxicity in a mouse model. Forty mice (female B6, 6-8 weeks old, weighing 16-18g) were divided randomly into four groups. Groups 1 and 2 were treated with a single intraperitoneal dose of 0.1mL normal saline; Groups 3 and 4 received 30mg/kg docetaxel. Groups 2 and 4 were pre-treated with a subcutaneous injection of 0.3mg leuprolide acetate, 2 weeks before the administration of docetaxel. The ovaries were removed 6 weeks after docetaxel or saline injection. Total follicle number decreased in Group 3 compared to Group 1. There was a significant difference between the Groups 3 and 4 in the total follicle number. Many ovarian follicles were stained for Ki-67 in Groups 1, 2, and 4; however, in Group 3, only a small number were stained and destruction of the ovarian structure was observed. There was no immunohistochemistry staining with gamma-H2AX in Groups 1, 2, and 4. However, gamma-H2AX staining of the primordial follicles was observed in Group 3. GnRH agonists may protect ovarian follicles from docetaxel-induced ovarian damage considering the total follicle number, follicle proliferation, and double-strand DNA breaks. Impact statement Protection of the ovarian reserve and prevention of infertility are the primary quality of life issues in young cancer patients. In this study, ovarian suppression by gonadotropin-releasing hormone agonists protected ovarian follicles from docetaxel-induced ovarian damage considering the total follicle number, follicle proliferation, and double-strand DNA break. The findings of our study will provide useful information for fertility preservation in women with cancer, undergoing chemotherapy with docetaxel.
19.
Testosterone Replacement Therapy: Long-Term Safety and Efficacy. [Review]
Corona G; Sforza A; Maggi M.
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[Journal Article. Review]
UI: 28497912
Recent position statements and guidelines have raised the distinction between a true and false, age-related hypogonadism (HG) or late-onset hypogonadism (LOH). The former is the
consequence of congenital or acquired "organic" damage of the brain centers or of the testis. The latter is mainly secondary to age-related comorbidities and does not require testosterone (T) therapy (TTh). In addition, concerns related to cardiovascular (CV) safety have further increased the scepticism related to TTh. In this paper, we reviewed the available evidence supporting the efficacy of TTh in non-organic HG and its long term safety. A large amount of evidence has documented that sexual symptoms are the most specific correlates of T deficiency. TTh is able to improve all aspects of sexual function independent of the pathogenetic origin of the disease supporting the scientific demonstration that LOH does exist according to an "ex-juvantius" criterion. Although the presence of metabolic derangements could mitigate the efficacy of TTh on erectile dysfunction, the positive effect of TTh on body composition and insulin sensitivity might counterbalance the lower efficacy. CV safety concerns related to TTh are essentially based on a limited number of observational and randomized controlled trials which present important methodological flaws. When HG is properly diagnosed and TTh correctly performed no CV and prostate risk have been documented.

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20.

Effects of testosterone replacement therapy on metabolic syndrome among Japanese hypogonadal men: A subanalysis of a prospective randomised controlled trial (EARTH study).
We investigated the effects of testosterone replacement therapy (TRT) on metabolic factors among hypogonadal men with a metabolic syndrome. From the study population of the EARTH study, which was a randomised controlled study in Japan, 65 hypogonadal patients with a metabolic syndrome, comprising the TRT group (n = 32) and controls (n = 33), were included in this study analysis. The TRT group was administered 250mg of testosterone enanthate as an intramuscular injection every 4 weeks for 12 months. Waist circumference, body mass index, body fat volume and blood pressure were measured in all patients at baseline and at 12 months. In addition, blood biochemical data, including total cholesterol, triglyceride (TG), HDL cholesterol, fasting plasma glucose (FPG) and haemoglobin A1c (HbA1c) levels, were also evaluated. Changes in these categories from baseline to 12 months were compared between the TRT and control groups, with significant differences observed in waist circumference, body fat percentage, FPG, TG and HbA1c levels. No significant differences were observed in other parameters. TRT for 1 year was associated with improvements in some metabolic factors among Japanese men with hypogonadism and metabolic syndrome.

Copyright © 2017 Blackwell Verlag GmbH.
Testosterone treatment and cardiovascular and venous thromboembolism risk: what is 'new'?.
Corona G; Dicuio M; Rastrelli G; Maseroli E; Lotti F; Sforza A; Maggi M.
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[Journal Article]
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In men, testosterone (T) production declines as a function of ageing. Late-onset hypogonadism (LOH) is the most commonly used term to indicate this age-related condition. In LOH, the relative clinical significance and the potential benefit of testosterone treatment (TTh) are still the subject of strong criticisms in the scientific community. The debate is further complicated by the recent position statement of the US Food and Drug Administration (FDA) emphasizing that, in LOH, the benefits and safety of TTh have not been fully established. Hence, the FDA required a labeling
change to inform patients about a possible increased cardiovascular (CV) risk of TTh. Similar considerations were previously released by the FDA and by Health Canada concerning a TTh-related venous thromboembolism (VTE) risk. In this review, we will summarize the available evidence concerning a possible link among TTh and CV and VTE risks. For this purpose, data derived from epidemiological studies analyzing relationships between the aforementioned risks and endogenous T levels will be analyzed. In addition, evidence deriving from interventional studies including pharmacoepidemiological and placebo-controlled randomized controlled trials (RCTs) will be examined. Our analysis shows that available data do not support an increased CV risk related to TTh. Similar considerations can be drawn for the relationship between TTh and VTE. The previously reported cases of TTh-related VTE were frequently related to a previously undiagnosed thrombophilia-hypofibrinolysis status. Hence, an anamnestic screening for thrombophilia before starting TTh is recommended, just as it is for the use of oral contraceptives.

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Pulsatile GnRH therapy may restore hypothalamus-pituitary-testis axis function in patients with congenital combined pituitary hormone deficiency: a prospective, self-controlled trial.
Zheng J; Mao J; Xu H; Wang X; Huang B; Liu Z; Cui M; Xiong S; Ma W; Min L; Kaiser UB; Nie M; Wu X.

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Journal of Clinical Endocrinology & Metabolism. , 2017 Mar 27.

Context: The effectiveness of pulsatile gonadotropin-releasing hormone (GnRH) therapy in congenital combined pituitary hormone deficiency (CCPHD) patients has not been investigated due to the limited number of patients as well as these patients' presumed pituitary hypoplasia, poor gonadotrophic cell reserve, and impaired gonadotrophic response to GnRH.

Objective: To assess the pituitary response to pulsatile GnRH therapy in men with CCPHD.

Design: A prospective, self-controlled, 3 months clinical trial.

Settings: A University Endocrine Clinic.

Patients: Men with hypogonadotropic hypogonadism caused by CCPHD.

Intervention(s): Pulsatile GnRH was administered subcutaneously for three months.

Main outcome measures: Primary endpoints were total serum testosterone, testicular volume, and LH and FSH levels. Secondary endpoints included occurrence of spermatogenesis.

Results: A total of 40 male CCPHD patients completed the study. Of these, 60% (24/40) showed a good response to pulsatile GnRH treatment (response group), and their LH and FSH levels increased into the normal range and testosterone levels also increased to 8.67+/4.83 nmol/L at three months. Of the patients in the response group, 33.3% (8/24) of them achieved spermatogenesis. The remaining 40% (16/40) of patients had a poor response to pulsatile GnRH treatment. MRI did not reveal any correlation between pituitary response and pituitary height and/or integrity of the pituitary stalk.

Conclusions: This study suggests that gonadotrophs in CCPHD patients can exist and be functional- even with MRI evidence of pituitary hypoplasia or dysplasia. Pulsatile GnRH therapy restored pituitary-testis axis function in 60% of patients with CCPHD. These results may directly guide the clinical therapeutic choice.

Publisher
Prevalence of 'obesity-associated gonadal dysfunction' in severely obese men and women and its resolution after bariatric surgery: a systematic review and meta-analysis.

Escobar-Morreale HF; Santacruz E; Luque-Ramirez M; Botella Carretero JI.

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BACKGROUND: Sexual dimorphism manifests noticeably in obesity-associated gonadal dysfunction. In women, obesity is associated with androgen excess disorders, mostly the polycystic ovary syndrome (PCOS), whereas androgen deficiency is frequently present in obese men in what has been termed as male obesity-associated secondary hypogonadism (MOSH). Obesity-associated gonadal dysfunction, consisting of PCOS in women and MOSH in men, is a frequent finding in patients with severe obesity and it may be ameliorated or even resolve with marked weight loss, especially after bariatric surgery.

OBJECTIVE AND RATIONALE: We aimed to obtain an estimation of the prevalence of obesity-associated gonadal dysfunction among women and men presenting with severe obesity and to evaluate the response to bariatric surgery in terms of resolution and/or improvement of this condition and changes in circulating sex hormone concentrations.

SEARCH METHODS: We searched PubMed and EMBASE for articles published up to June 2016. After deleting duplicates, the abstract of 757 articles were analyzed. We subsequently excluded 712 articles leaving 45 studies for full-text assessment of eligibility. Of these, 16 articles were excluded. Hence, 29 studies were included in the quantitative synthesis and in the different meta-analyses. Quality of the studies was assessed using the Quality index for prevalence studies and the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group available from the National Heart, Lung and Blood Institute. For meta-analyses including more than 10 studies, we used funnel and Doi plots to estimate publication bias.

OUTCOMES: In severely obese patients submitted to bariatric surgery, obesity-associated gonadal dysfunction was very prevalent: PCOS was present in 36% (95CI 22-50) of women and MOSH was present in 64% (95CI 50-77) of men. After bariatric surgery, resolution of PCOS was found in 96% (95CI 89-100) of affected women and resolution of MOSH occurred in 87% (95CI 76-95) of affected men. Sex hormone-binding globulin concentrations increased after bariatric surgery in women (22 pmol/l, 95CI 2-47) and in men (22 pmol/l, 95CI 19-26) and serum estradiol concentrations decreased in women (-104 pmol/l, 95CI -171 to -39) and to a lesser extent in men
(-22 pmol/l, 95CI -38 to -7). On the contrary, sex-specific changes were observed in serum androgen concentrations: for example, total testosterone concentration increased in men (8.1 nmol/l, 95CI 6-11) but decreased in women (-0.7 nmol/l, 95CI -0.9 to -0.5). The latter was accompanied by resolution of hirsutism in 53% (95CI 29-76), and of menstrual dysfunction in 96% (95CI 88-100), of women showing these symptoms before surgery.

WIDER IMPLICATIONS: Obesity-associated gonadal dysfunction is among the most prevalent comorbidities in patients with severe obesity and should be ruled out routinely during their initial diagnostic workup. Considering the excellent response regarding both PCOS and MOSH, bariatric surgery should be offered to severely obese patients presenting with obesity-associated gonadal dysfunction.
Characterization and expression of StAR2a and StAR2b in the olive flounder Paralichthys olivaceus.

Liang D; Fan Z; Weng S; Jiao S; Wu Z; Zou Y; Tan X; Li J; Zhang P; You F.

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[Journal Article]

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Steroidogenic acute regulatory protein 2 (STAR2) is a key protein in transporting cholesterol from the outer mitochondria membrane to the inner mitochondria membrane for sex steroid synthesis. In this study, two STAR2 gene isoforms, STAR2a and STAR2b, were isolated from the olive flounder Paralichthys olivaceus gonads. Semi-quantitative RT-PCR results indicated that their expression levels were higher in testis than those in ovary. STAR2a was mainly expressed in the thecal cells and ooplasm of ovary, and Leydig cells and spermatid of testis according to the results of in situ hybridization. The quantitative real-time PCR results showed that the expressions of STAR2a and STAR2b were high in undifferentiation gonads and differentiating testis, and then decreased in differentiated testis in the high temperature (28degreeC) and exogenous testosterone treatment groups. While, in the exogenous 17beta-estradiol treatment group, both genes' expression levels were high in differentiating ovary, and then significantly decreased in differentiated ovary (P<0.05). STAR2a and STAR2b expression levels were significantly down-regulated in the cultured testis cells treated with the 75 and 150muM cAMP, but significantly up-regulated in the cultured testis cells treated with the 300muM cAMP (P<0.05). Moreover, their expression levels were significantly up-regulated by transfecting the cultured testis cells with pcDNA3.1-NR5a2 and pcDNA3.1-NR0b1 (P<0.05). Further study showed that expression of STAR2 was regulated by cAMP and the transcription factors, NR5a2 and NR0b1, indicating that STAR2 may have functions in flounder gonadal differentiation and maintenance.

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Correlates and prevalence of hypogonadism in patients with early- and late-onset type 2 diabetes.

Li Y; Zhang M; Liu X; Cui W; Rampersad S; Li F; Lin Z; Yang P; Li H; Sheng C; Cheng X; Qu S.

This study aims to compare the prevalence of hypogonadism between male patients with early-onset type 2 diabetes mellitus (T2DM) and late-onset type 2 diabetes. A total of 122 male patients with early-onset T2DM (diagnosis age <=40 years) and 100 male patients with late-onset T2DM (diagnosis age >40 years) were recruited from our in-patient department between 1 January 2013 and 28 December 2015. Serum FSH, LH, testosterone, lipid profile, uric acid, HbA1c, and beta-cell function were determined in blood samples. The diagnosis of hypogonadism was based on the levels of LH, FSH, and total testosterone. The mean onset age was 29.86 +/- 6.31 and 54.47 +/- 9.97 years old in the early-onset group and late-onset group, respectively. Compared with late-onset T2DM, those with early-onset T2DM had a higher proportion of new-onset diabetes, were more likely to be obese, and had worse glycemic control, lipid control, and lower sex
hormone-binding globulin (SHBG). The prevalence of hypogonadism was much higher in the early-onset group than in the late-onset group (48.0% vs. 26.7%, p < 0.05). The rate of secondary hypogonadism in the early-onset group and late-onset group were 44.3% and 25.0%, respectively (p < 0.05). Obesity, waist circumference, and SHBG were significantly associated with serum total testosterone level in all, early-onset, and late-onset T2DM. Both all and early-onset T2DM groups had positive correlations between total testosterone and fasting C-peptide, total cholesterol, triglycerides, and uric acid. Our results indicate that in a population of admission to a large urban hospital in China, the prevalence of hypogonadism was higher in the patients with early-onset T2DM than that of late-onset T2DM. This prevalence might be attributable to greater obesity, worse lipid control, and lower SHBG levels in those patients.

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Scrotal skin is thin and has high steroid permeability, but the pharmacokinetics of testosterone via the scrotal skin route has not been studied in detail. The aim of this study was to define the pharmacokinetics of testosterone delivered via the scrotal skin route. The study was a single-center, three-phase cross-over pharmacokinetic study of three single doses (12.5, 25, 50 mg) of testosterone cream administered in random sequence on different days with at least 2 days between doses to healthy eugonadal volunteers with endogenous testosterone suppressed by administration of nandrolone decanoate. Serum testosterone, DHT and estradiol concentrations were measured by liquid chromatography, mass spectrometry in extracts of serum taken before and for 16 h after administration of each of the three doses of testosterone cream to the scrotal skin. Testosterone administration onto the scrotal skin produced a swift (peak 1.9-2.8 h), dose-dependent (p < 0.0001) increase in serum testosterone with the 25 mg dose maintaining physiological levels for 16 h. Serum DHT displayed a time- (p < 0.0001), but not dose-dependent,
increase in concentration reaching a peak concentration of 1.2 ng/mL (4.1 nm) at 4.9 h which was
delayed by 2 h after peak serum testosterone. There were no significant changes in serum
estradiol over time after testosterone administration. We conclude that testosterone
administration to scrotal skin is well tolerated and produces dose-dependent peak serum
testosterone concentration with a much lower dose relative to the non-scrotal transdermal route.

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Extended day length in late winter/early spring, with a return to natural day length of shorter duration, increased plasma testosterone and sexual performance in rams with or without melatonin implants.

Abecia JA; Chemineau P; Keller M; Delgadillo JA.
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Reproduction in Domestic Animals. , 2017 Apr 29.
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Sixteen rams were used to quantify the effects of long days, imposed during late winter/early spring, with or without exogenous melatonin, on plasma testosterone concentrations and ram serving capacity. Rams were assigned to two groups: photoperiod-treated rams (Artificial Photoperiod, AP; n = 8), exposed to 2 months of long days (16 hr of light/day) between 22 December and 22 February, and control rams (Natural Photoperiod, NP; n = 8). At the end of the long-day period, AP rams were returned to the natural photoperiod, and each ram in the two groups either did (+M) or did not (-M) receive three subcutaneous melatonin implants. Four groups were created as follows: AP+M (n = 4), AP-M (n = 4), NP+M (n = 4) and NP-M (n = 4).

Thirty days after of the onset of photoperiodic treatment, AP rams (13.5 +/- 2.8 ng/ml) had significantly (p < .05) lower testosterone levels than NP rams (36.7 +/- 1.0), and similar differences were not apparent at the end of the photoperiod treatment. A month later, AP rams (24.3 +/- 7.9) had higher (p < .10) testosterone levels than NP rams (13.1 +/- 5.0), with no effect of melatonin treatment. Fifty days after melatonin implantations, rams were exposed for 20 min to three oestrous ewes. AP rams (2.50 +/- 0.42) exhibited significantly (p < .05) more serves than did NP rams (1.11 +/- 0.39), and melatonin treatment had no significant effect; however, the interaction between treatments was significant. Time to first serve was significantly (p < .05) shorter in AP (2.30 +/- 1.20 min) than it was in NP rams (5.58 +/- 0.68 min). In conclusion, exposure to 2 months of long days in late winter/early spring, with a return to natural day length of shorter duration, increased plasma testosterone concentrations and sexual performance in rams with or without exogenous melatonin. This particular management is an option if a non-hormonal reproductive strategy is scheduled; yet, if the use of exogenous hormones is feasible, melatonin implants increase the mating efficiency of rams.

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28.
Influences of flavones on cell viability and cAMP-dependent steroidogenic gene regulation in MA-10 Leydig cells.
Cormier M; Ghouili F; Roumaud P; Bauer W; Toulaibia M; Martin LJ.
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Cell Biology & Toxicology. , 2017 Apr 28.
[Journal Article]
UI: 28455626

Testicular Leydig cells are major contributors of androgen synthesis and secretion, which play an important role in testis development, normal masculinization, maintenance of spermatogenesis, and general male fertility. The rate-limiting step in testosterone biosynthesis involves the transfer of cholesterol to the mitochondrial inner membrane by the steroidogenic acute regulatory (Star) protein, a critical factor in steroid hormone biosynthesis. Once inside the mitochondria, cholesterol is metabolized by the steroidogenic enzyme Cyp11a1 to pregnenolone, which is
further converted to testosterone by the action of other steroidogenic enzymes. Interestingly, the Star protein level declines during Leydig cell aging, resulting in defective mitochondrial cholesterol transfer and lower testosterone production. It is possible to delay the age-related decline in testosterone production by increasing Star and/or Cyp11a1 gene expression using supplementation with flavonoids, a group of polyphenolic compounds widely distributed in fruits and vegetables. In this study, we examined whether the distribution of hydroxyl groups among flavones could influence their potency to stimulate steroidogenesis within Leydig cells. Low levels of apigenin, luteolin, chrysin, and baicalein (10 μM) stimulated cAMP-dependent Star, Cyp11a1, and Fdx1 promoters’ activation and may increase steroidogenesis within Leydig cells. Indeed, luteolin effectively increased cAMP-dependent accumulation of progesterone from MA-10 Leydig cells, possibly through activation of Star and Fdx1 transcription. Thus, dietary luteolin could be potentially effective to maintain steroid production within aging males.

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Does pituitary suppression affect live birth rate in women with congenital hypogonadotrophic hypogonadism undergoing intra-cytoplasmic sperm injection? A multicenter cohort study.

Mumusoglu S; Ata B; Turan V; Demir B; Kahyaoglu I; Aslan K; Seyhan Ata A; Yilmaz B; Yakin K; Avci B; Uncu G; Bozdag G.

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Gynecological Endocrinology. 1-5, 2017 Apr 27.

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UI: 28447505

In this retrospective multicenter cohort study, women with congenital hypogonadotrophic hypogonadism (CHH) (n=57) who underwent intra-cytoplasmic sperm injection in-between 2010-2014 were compared to age-matched controls with tubal factor infertility (n=114) to assess ovarian stimulation cycle and pregnancy outcomes. Live birth rates (LBRs) per started cycle were 31.6 and 24.6% in CHH and controls groups, respectively (p=0.36). Comparable success rates were also confirmed with the logistic regression analysis (OR: 1.44, 95% CI: 0.78-2.67, p=0.24).

Of the 57 women with CHH, 19 were stimulated with the gonadotropin-releasing hormone (GnRH) antagonist protocol, 13 with the long-GnRH-agonist protocol. Pituitary suppression (PS) was not employed in the remaining 25 cases. Compared to women with PS, women without PS had significantly higher embryo implantation rates (21.6 versus 52.6%, p=0.03). Although there was a trend favoring no PS, LBRs (25.0 versus 40.0%, p=0.26) per cycle were short of statistical significance. LBRs per cycle (57.1 versus 31.2%, p=0.11) and miscarriage rates (11.1 versus 16.7%, p=0.75) were similar between CHH women who were given estrogen+progesterone and progesterone alone to support the luteal phase. In conclusion, the optimal stimulation protocol appears to be exogenous gonadotropin stimulation alone, without PS, and progesterone-only luteal phase support in CHH patients.
Meta-analysis of Results of Testosterone Therapy on Sexual Function Based on International Index of Erectile Function Scores.

Corona G; Rastrelli G; Morgentaler A; Sforza A; Mannucci E; Maggi M.

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CONTEXT: The interpretation of available clinical evidence related to the effect of testosterone (T) treatment (TTh) on sexual function has been inconsistent, in part due to the use of different and self-reported measures to assess outcomes. The International Index of Erectile Function (IIEF) is the most frequently used validated tool to assess male sexual function.

OBJECTIVE: To perform a meta-analysis of available data evaluating the effect of TTh on male sexual function using IIEF as the primary outcome.

EVIDENCE ACQUISITION: An extensive Medline, Embase, and Cochrane search was performed including all placebo-controlled randomized clinical trials enrolling men comparing the effect of TTh on sexual function.

EVIDENCE SYNTHESIS: Out of 137 retrieved articles, 14 were included in the study enrolling 2298 participants, with a mean follow-up of 40.1 wk and mean age of 60.2+/−6.5 yr. Using IIEF-erectile function domain (IIEF-EFD) as the outcome, we found that TTh significantly improved erectile function compared with placebo (mean difference=2.31 [1.41;3.22] IIEF-EFD score, p<0.0001). Patients with more severe hypogonadism (total T<8 nmol/l) reported greater changes in final IIEF-EFD score when compared with those with a milder T deficiency (total T<12 nmol/l; 1.47 [0.90;2.03] and 2.95 [1.86;4.03] for total T<12 nmol/l and <8 nmol/l, respectively, Q=5.61, p=0.02). The magnitude of the effect was lower in the presence of metabolic derangements, such as diabetes and obesity. Other aspects of sexual function, as evaluated by IIEF subdomains, were also improved with TTh including libido, intercourse satisfaction, orgasm, and overall sexual satisfaction.

CONCLUSIONS: TTh significantly improves erectile function and other sexual parameters as measured by IIEF in hypogonadal men. These results argue that sexual dysfunction should be considered a hallmark manifestation of T deficiency, since those symptoms can be significantly improved with normalization of serum T. In addition, these results suggest that TTh alone may be considered a reasonable treatment for hypogonadal men with milder degrees of erectile dysfunction, whereas the addition of other treatments, such as phosphodiesterase type 5 inhibitors, may be more appropriate for men with more severe erectile dysfunction.

PATIENT SUMMARY: We investigated the effect of testosterone treatment on sexual function by performing a meta-analysis of all available studies that used the most frequently used assessment tool, the International Index of Erectile Function. We found that testosterone treatment significantly improves erectile dysfunction, as well as other aspects of sexual function, in men with testosterone deficiency. This treatment may be all that is required for hypogonadal men with milder erectile dysfunction; however, additional treatments may be necessary in more severe cases.
31.
Development of a human cadaver model for training in laparoscopic donor nephrectomy.
Sutton ERH; Billeter A; Druen D; Roberts H; Rice J.
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Clinical Transplantation. , 2017 Mar 25.
[Journal Article]
UI: 28342285
BACKGROUND: The organ procurement network recommends a surgeon record 15 cases as surgeon or assistant for laparoscopic donor nephrectomies (LDN) prior to independent practice. The literature suggests that the learning curve for improved perioperative and patient outcomes is closer to 35 cases. In this article, we describe our development of a model utilizing fresh tissue and objective, quantifiable endpoints to document surgical progress, and efficiency in each of the major steps involved in LDN.

MATERIALS AND METHODS: Phase I of model development focused on the modifications necessary to maintain visualization for laparoscopic surgery in a human cadaver. Phase II tested proposed learner-based metrics of procedural competency for multiport LDN by timing procedural steps of LDN in a novice learner.

RESULTS: Phases I and II required 12 and nine cadavers, with a total of 35 kidneys utilized. The following metrics improved with trial number for multiport LDN: time taken for dissection of the gonadal vein, ureter, renal hilum, adrenal and lumbrical veins, simulated warm ischemic time (WIT), and operative time.

CONCLUSION: Human cadavers can be used for training in LDN as evidenced by improvements in timed learner-based metrics. This simulation-based model fills a gap in available training options for surgeons.

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Small Numbers, Big Challenges: Adolescent and Young Adult Cancer Incidence and Survival in New Zealand.
Ballantine KR; Watson H; Macfarlane S; Winstanley M; Corbett RP; Spearing R; Stevanovic V; Yi M; Sullivan MJ.
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Journal of Adolescent & Young Adult Oncology, 2017 Feb 16.
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UI: 28207291
PURPOSE: This study was undertaken to determine cancer survival and describe the unique spectrum of cancers diagnosed among New Zealand’s adolescents and young adult (AYA) population.
METHODS: Registrations for 1606 15-24 year olds diagnosed with a new primary malignant tumor between 2000 and 2009 were obtained from the New Zealand Cancer Registry and classified according to AYA diagnostic group and subgroup, age, sex, and prioritized ethnicity. Age-standardized incidence rates (IRs) per million person years and 5-year relative survival ratios were calculated.
RESULTS: Cancer incidence was 228.6 per million for adolescents aged 15-19 years and 325.7 per million for young adults aged 20-24 years. Overall IRs were consistent across all ethnic groups but there were unique ethnic differences by tumor group including a higher incidence of bone tumors, carcinoma of the gastrointestinal tract, and gonadal germ cell tumors among Maori, a higher incidence of leukemia among Pacific peoples, and a higher incidence of melanoma among non-Maori/non-Pacific peoples. Five-year relative survival for adolescents (75.1%) and AYA overall (80.6%) appeared poorer than had been achieved in other high-income countries. Maori (69.5%) and Pacific (71.3%) AYA had lower 5-year survival compared to non-Maori/non-Pacific peoples (84.2%).
CONCLUSION: The survival disparities observed require further investigation to identify and address the causes of these inferior outcomes. The newly established AYA Cancer Network Aotearoa has been tasked with improving cancer survival and care and ensuring equality of access for New Zealand AYAs with cancer.
Polyembryoma of the testis: a report of two cases dominant within mixed germ cell tumors and review of gonadal polyembryomas. [Review]
Stall JN; Young RH.
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Modern Pathology, 2017 Apr 21.
[Journal Article. Review]
UI: 28429716
Two testicular mixed germ cell tumors, from men of 21 and 41 years, in which polyembryoma predominated are described. A literature review uncovered an additional five testicular and nine ovarian cases. One tumor occurred in a 60-year-old man, but all others occurred within the typical age range of gonadal germ cell tumors. One male presented with gynecomastia and one female with sexual precocity, but all otherwise had standard clinical manifestations. These tumors are typically large with non-specific gross features, but a few have a prominent hemorrhagic appearance. No tumor is known to have been entirely composed of embryoid bodies, the unit upon which the diagnosis of polyembryoma is based. The most common additional germ cell tumor component is teratoma, present in the great majority of cases, with an approximately equal smaller number of tumors being associated with embryonal carcinoma and yolk-sac tumor, manifest as overgrowths of these elements, derived from the parent epithelium within the embryoid body. Rarely there is choriocarcinoma, and syncytiotrophoblast and hepatoid cells are occasionally present. The microscopic features of the tumors vary according to the arrangement of embryoid bodies with other elements, the prominence of associated typically myxoid to edematous stroma, and the degree to which embryoid bodies are perfectly or imperfectly formed. Although its presence in a gonadal mixed germ cell tumor is probably not associated with any special behavior, its unique features should result in polyembryoma being recorded, particularly when present in significant amount. Furthermore, awareness of its features may facilitate recognition, particularly when seen at metastatic sites or extra-gonadal sites of primary germ cell neoplasia. Whether polyembroma should be considered a distinctive pattern of mixed germ cell neoplasia or a particular variant of high-grade immature teratoma is considered, herein, and arguments can be made in favor of each viewpoint. Modern Pathology advance online publication, 21 April 2017; doi:10.1038/modpathol.2017.25.
34. Significance of serum endothelial cell specific molecule-1 (Endocan) level in patients with erectile dysfunction: a pilot study.
Karabakan M; Bozkurt A; Akdemir S; Gunay M; Keskin E.
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present International Journal of Impotence Research. , 2017 Apr 20.
[Journal Article]
UI: 28424502
This study aimed to measure the serum endocan level of patients with erectile dysfunction (ED) and to investigate the possible association between the Endothelial-specific molecule-1 (Endocan) level and ED. Twenty healthy and sixty-four male patients included in the study were divided into four groups: severe ED (19 patients), moderate ED (24 patients), mild ED (21 patients) and control group (20 healthy men). The erectile function of all the patients was evaluated using the International Index of Erectile Function-5 (IIEF-5) questionnaire. The body mass index (BMI) of each participant was determined, together with levels of fasting blood glucose, total testosterone, low- and high-density lipoprotein cholesterol, triglyceride and endocan in serum samples. No significant difference was found between the three ED groups and the control group in terms of the mean age, BMI and the levels of cholesterol and fasting blood glucose (P>0.05). The mean serum endocan level was found to 1.076+/-.05, 0.674+/-0.40 and 0.671+/-0.3ngml-1 in the severe, moderate and mild ED groups, respectively. This indicated that the highest value was obtained from the severe ED group, and the difference between the severe ED group and the other groups was statistically significant. In the control group, the serum endocan level was 0.73+/-0.46ngml-1, which was significantly higher compared to the moderate
and mild ED groups (P<0.05). The significant difference between the control and ED groups in terms of the serum endocan level can assist in the evaluation of endothelial pathologies in the etiology ED. International Journal of Impotence Research advance online publication, 20 April 2017; doi:10.1038/ijir.2017.19.

Karabakan, M; Bozkurt, A; Akdemir, S; Gunay, M; Keskin, E.

In the absence of large, prospective, placebo-controlled studies of longer duration, substantial evidence regarding the safety and risk of testosterone (T) therapy (TTh) with regard to cardiovascular disease in men with hypogonadism.

OBJECTIVES: In the absence of large, prospective, placebo-controlled studies of longer duration, substantial evidence regarding the safety and risk of testosterone (T) therapy (TTh) with regard to cardiovascular disease in men with hypogonadism.
cardiovascular (CV) outcomes can only be gleaned from observational studies. To date, there are limited studies comparing the effects of long-term TTh in men with hypogonadism who were treated or remained untreated with T, for obvious reasons. We have established a registry to assess the long-term effectiveness and safety of T in men in a urological setting. Here, we sought to compare the effects of T on a host of parameters considered to contribute to CV risk in treated and untreated men with hypogonadism (control group).

PATIENTS AND METHODS: Observational, prospective, cumulative registry study in 656 men (age: 60.7 +/- 7.2 years) with total T levels <=12.1 nmol/L and symptoms of hypogonadism. In the treatment group, men (n = 360) received parenteral T undecanoate (TU) 1000 mg/12 weeks following an initial 6-week interval for up to 10 years. Men (n = 296) who had opted against TTh served as controls. Median follow-up in both groups was 7 years. Measurements were taken at least twice a year, and 8-year data were analyzed. Mean changes over time between the 2 groups were compared by means of a mixed-effects model for repeated measures, with a random effect for intercept and fixed effects for time, group, and their interaction. To account for baseline differences between the 2 groups, changes were adjusted for age, weight, waist circumference, fasting glucose, blood pressure, and lipids.

RESULTS: There were 2 deaths in the T-treated group, none was related to CV events. There were 21 deaths in the untreated (control) group, 19 of which were related to CV events. The incidence of death in 10 patient-years was 0.1145 in the control group (95% confidence interval [CI]: 0.0746-0.1756; P < .000) and 0.0092 in the T-treated group (95% CI: 0.0023-0.0368; P < .000); the estimated difference between groups was 0.0804 (95% CI: 0.0189-0.3431; P < .001). The estimated reduction in mortality for the T-group was between 66% and 92%. There were also 30 nonfatal strokes and 26 nonfatal myocardial infarctions in the control group and none in the T-treated group.

CONCLUSION: Long-term TU was well tolerated with excellent adherence suggesting a high level of patient satisfaction. Mortality related to CV disease was significantly reduced in the T-group.

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36. Low serum testosterone is associated with impaired graft function early after heart transplantation.

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Clinical Transplantation. , 2017 Mar 17.

[Journal Article]

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BACKGROUND: We sought to investigate a correlation between serum testosterone levels and graft function early after heart transplantation.

METHODS: In a cross-sectional study, we measured serum testosterone levels 4 weeks after heart transplantation in 49 consecutive male recipients. Echocardiography was carried out to evaluate graft function. Low serum testosterone was defined as <11 nmol/L.

RESULTS: Low serum testosterone was present in 21 (43%) recipients (Group A), and 28 (57%) had normal testosterone levels (Group B). The two groups did not differ in age and presence of renal dysfunction, arterial hypertension, diabetes, or hyperlipidemia. Donor age and allograft ischemic time were not different between the two groups. Both groups had comparable tacrolimus through levels, dose of mycophenolate mophetil, and methylprednisolone. Patients in Group A had significantly lower LVEF (58+/-5% vs 65+/-6% vs Group B, P=.001) and TAPSE (1.3+/-0.3 cm vs 1.6+/-0.3 cm in Group B, P=.01). In comparison with Group B, more patients in Group A were found to have low grade (1R) rejection (25% vs 3%; P=.02).
CONCLUSION: Low serum testosterone levels appear to be associated with impaired graft function and an increased incidence of low-grade rejection episodes early after heart transplantation.

Molecular and structural changes related to hepatitis E virus antigen and its expression in testis inducing apoptosis in Mongolian gerbil model.

Soomro MH; Shi R; She R; Yang Y; Wang T; Wu Q; Li H; Hao W.

Journal of Viral Hepatitis. , 2017 Feb 09.
Hepatitis E virus (HEV) infection has been associated with a wide range of extrahepatic manifestations, so this study was designed to examine the effect and role of HEV on structural and molecular changes in the testicular tissues of Mongolian gerbils experimentally infected with swine HEV. HEV RNA was first detected in testis at 14 days post-inoculation and reached a peak between 28 and 42 days later with viral load between 3.12 and 6.23 logs/g by PCR assays. Changes including vacuolation, sloughing of germ cells, formation of multinuclear giant cells, degeneration, necrosis of tubules and damaged blood-testis barrier were observed through transmission electron microscopy. HEV ORF2 antigen was detected in the sperm cell cytoplasm along with decrease in relative protein of zonula occludens-1 through immunohistochemistry. HEV ORF3 antigen and ZO-1 protein were detectable by Western blotting. Lower (P<.05) serum testosterone and higher (P<.05) blood urea nitrogen level was observed in inoculated Mongolian gerbils. Likewise, increased (P<.05) germ cell apoptosis rate was detected with significant increased expression of Fas-L and Fas in HEV-inoculated groups at each time points. Up-regulation (P<.05 or P<.01) in mRNA level of Fas-L, Fas, Bax, Bcl-2 and caspase-3 was observed in HEV RNA-positive testes. Our study demonstrated that after experimental inoculation, HEV can be detected in testis tissues and viral proteins produce structural and molecular changes that in turn disrupt the blood-testis barrier and induce germ cell apoptosis.

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Soomro, M H; Shi, R; She, R; Yang, Y; Wang, T; Wu, Q; Li, H; Hao, W.

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38.
Calcium and bone turnover markers in acromegaly: a prospective controlled study.
Constantin T; Tangpricha V; Shah R; Oyesiku NM; Ioachimescu OC; Ritchie J; Ioachimescu AG.
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Journal of Clinical Endocrinology & Metabolism. , 2017 Apr 12.
[Journal Article]
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Context: Acromegaly has been associated with calcium-phosphate and bone turnover alterations. Controlled studies of these interactions are sparse.
Objective: To evaluate calcium and bone metabolism in active and treated acromegaly.
Design/Setting/Patients: We conducted a controlled prospective study at a tertiary referral center. We studied 22 patients with acromegaly referred for surgical or medical therapy (ACM) and 22 with nonfunctioning pituitary adenomas referred for surgery (control).
Main outcome measures: Calcium (serum and urine), phosphorus, PTH, 25-hydroxy- and 1,25-dihydroxy-vitamin D, bone turnover markers (serum C-terminal telopeptide type 1 collagen (CTX) and Procollagen type 1 N-terminal propeptide, (P1NP)), and cytokines (RANK-L and osteoprotegerin) at baseline and 3-6 months after treatment.
Results: At baseline, the ACM group had lower PTH levels than controls (36.3+/−13.9 vs 56.0+/−19.9 pg/ml) and higher phosphorus (4.34+/−0.71 vs 3.55+/−0.50 mg/dL) (p<0.01). Groups had similar levels of serum and urine calcium, 25-hydroxy- and 1,25-dihydroxy-vitamin D. The ACM group had higher bone turnover markers than control; P1NP and CTX were strongly correlated (R2 0.82, P<0.05). CTX was dependent on age and disease group, but not on gender or gonadal status. After treatment of acromegaly, serum calcium (9.52+/−0.43 to 9.26+/−0.28 mg/dL), phosphorus (4.34+/−0.71 to 3.90+/−0.80 mg/dL) and CTX (0.91+/−0.75 to 0.63+/−0.68 ng/ml) decreased, while PTH increased (36.3+/−13.9 to 48.9+/−16.7 pg/ml) (p 0.01). 25-hydroxyvitamin D, P1NP and RANK-L/ osteoprotegerin ratio did not change significantly.

Conclusion: Acromegaly patients exhibited PTH-independent calcium-phosphate alterations and enhanced coupled bone formation and resorption. Within 6 months of treatment, bone resorption decreased, while RANK-L/osteoprotegerin changes were inconsistent.

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Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in breast cancer patients.

Conte B; Del Mastro L.

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Since the survival of patients with cancer has significantly improved, chemotherapy-related premature ovarian failure (POF) in young cancer survivors has become a major issue in oncology. POF is associated with several health-related negative consequences, including menopausal symptoms, increased risk of cardiovascular diseases, osteoporosis, sexual disfunction, and infertility1-5. According to the major international guidelines, embryo/oocyte cryopreservation are the standard procedures for fertility preservation in young cancer women6,7. However, these techniques do not protect the whole ovarian function from the gonadotoxicity of anticancer therapies; indeed, they can only preserve fertility without preventing POF and related side effects. In recent years, temporary ovarian suppression during chemotherapy with lutening hormone-releasing hormone analogues (LHRHa) has emerged as an option to preserve both gonadal function and fertility. Despite temporary ovarian suppression with LHRHa showed to be an effective strategy to reduce the risk of treatment-related POF in several randomized clinical trials, its use as a standard procedure is still under debate. The present review will encompass the current evidences and controversies on the efficacy and safety of ovarian protection with LHRHa during chemotherapy for preservation of ovarian function and fertility in breast cancer patients, in light of the new data published.

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40.
Impact of Tryptophan Depletion on Executive System Function during Menopause is Moderated by Childhood Adversity.
Shanmugan S; Loughead J; Cao W; Sammel MD; Satterthwaite TD; Ruparel K; Gur RC; Epperson CN.
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Many healthy women with no history of cognitive dysfunction experience subjective executive difficulties during menopause. Preclinical literature suggests latent effects of early life adversity on serotonin function may play a role in this phenomenon. However, evidence in human participants regarding the mechanisms by which loss of estradiol contributes to this vulnerability is lacking. Here we examined the impact of tryptophan depletion (TD) and adverse childhood experiences (ACE) on brain activation during a working memory task in menopausal women. We hypothesized that an interactive effect between ACE and TD would be observed when women were hypogonadal, and that treatment with estradiol would attenuate this effect. Thirty-three women underwent functional imaging at four time points (123 total scans) in this double-blind, placebo controlled, cross-over study. The effects of TD, ACE, and TD x ACE were evaluated using a voxel-wise, mixed-effects, 2 x 2 ANOVA. In the absence of exogenous estradiol, a TD by ACE interaction was observed on BOLD signal in the right DLPFC such that TD increased activation in high ACE subjects but decreased activation in low ACE subjects. While a similar interaction was observed with placebo treatment, treatment with estradiol attenuated the effects of ACE and TD such that no between or within group differences were observed. Together, these results suggest that early life adversity may have a lasting impact on serotonergic circuits.
underlying executive function that are unmasked by loss of estradiol during menopause. Neuropsychopharmacology advance online publication, 12 April 2017; doi:10.1038/npp.2017.64.

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Efficacy of varicocelectomy in the treatment of hypogonadism in subfertile males with clinical varicocele: A meta-analysis.

Chen X; Yang D; Lin G; Bao J; Wang J; Tan W.

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To reassess the efficacy of varicocelectomy in the treatment of hypogonadism in subfertile males, we carried out a meta-analysis of clinical trials and retrospective studies that compared the pre-operative and postoperative serum testosterone. We searched Embase and PubMed (1980 to May 2016) for studies. Eight studies and 712 patients were included. The combined analysis of seven studies discovered that the mean serum testosterone of patients post-operation improved by 34.3 ng/dl (95% CI: 22.57-46.04, p < .00001, I2 = 0.0%) compared with their pre-operative levels. In subgroup analysis, testosterone improvements in the hypogonadal treated subgroup were more significant (improved by 123 ng/dl, 95% CI: 114.61-131.35, p < .00001, I2 = 37%) than in the eugonadal, or the untreated controls. In an analysis of surgery versus untreated control (three studies included), results showed that mean testosterone among hypogonadal increased by 105.65 ng/dl (95% CI: 77.99-133.32), favouring varicocelectomy, as the differences were significant (p < .00001). However, there were insignificant differences in eugonadal men with subfertility. Active surgical treatment of varicocele might have a benefit of maintaining healthy androgen levels in subfertile men.

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INTRODUCTION: Selective estrogen receptor modulators (SERMs) have been used off-label in men for more than 50 years. SERMs exert their action on the estrogen receptor agonistically or antagonistically. A fundamental knowledge of the complex molecular action and physiology of SERMs is important in understanding their use and future directions of study in men.

AIM: To review the basic science and mechanism of the action of estrogens, the estrogen receptor, and SERMs, and the existing clinical publications on the use of SERMs in men for infertility and hypogonadism with their strengths and weaknesses and to identify the need for future studies.
METHODS: After a review of publications on the basic science of estrogen receptors, a chronologic review of published evidence-based studies on the use of SERMs in men for infertility and hypogonadism was undertaken.

MAIN OUTCOME MEASURES: Clinical publications were assessed for type of study, inclusion criteria, outcome measurements, and results. Strengths and weaknesses of the publications were assessed and discussed.

RESULTS: Few prospective rigorously controlled trials have been undertaken on the use of SERMs in men. Most existing trials are largely retrospective anecdotal studies with inconsistent inclusion and end-point measurements. The SERMs are complex and at times can produce paradoxical results. Their action likely depends on the genetics of the individual, his tissue-specific composition of estrogen receptors, the molecular structure and pharmacodynamics of the SERMs, and their metabolism.

CONCLUSION: Rigorously controlled trials of the use of SERMs in men are needed to better identify their clinical benefit and long-term safety in infertile and hypogonadal men. Recent placebo-controlled pharmaceutical industry SERM trials have demonstrated short-term safety and efficacy in men with secondary hypogonadism and eventually might provide an alternative to exogenous testosterone replacement therapy in men with secondary hypogonadism. Helo S, Wynia B, McCullough A. "Cherchez La Femme": Modulation of Estrogen Receptor Function With Selective Modulators: Clinical Implications in the Field of Urology. Sex Med Rev 2017;X:XXX-XXX.

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Physical and social characteristics and support needs of adult female childhood cancer survivors who underwent hormone replacement therapy.

Tomioka A; Maru M; Kashimada K; Sakakibara H.

BACKGROUND: Female childhood cancer survivors who develop gonadal dysfunction require female hormone replacement therapy (HRT) from puberty until menopause. However, the support provided in such cases has not been studied. We investigated the physical and social characteristics and support needs of adult female childhood cancer survivors who underwent HRT.

METHODS: Forty-nine adult female childhood cancer survivors completed self-administered questionnaires. We compared the clinical characteristics, health status, and social conditions between a group that underwent HRT and a group that did not, and we surveyed support needs of the group that underwent HRT.

RESULTS: The median age of the subjects was 25.0 years (range 20-41). Twenty subjects (40.8%) underwent HRT. A significantly high number of those who underwent HRT also underwent radiation therapy (p < 0.01) and hematopoietic stem cell transplantation (p < 0.001), and none of them had a history of pregnancy or childbirth (p < 0.05). There were no significant differences in physical symptoms and social characteristics between the groups. Those who experienced anxiety regarding fertility required information about HRT, a platform to share their concerns, and psychological support and cooperation among healthcare providers.

CONCLUSIONS: Although the subjects of this survey exhibited good social adjustment regardless of whether or not they underwent HRT, they were anxious about fertility. It is important to understand the concerns and anxieties unique to female childhood cancer survivors and to enhance psychological support in addition to providing educational support so that HRT can be administered.
Hackett G.
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present Sexual Medicine Reviews. , 2017 Mar 21.

INTRODUCTION: Graham Jackson introduced the concept that erectile dysfunction (ED) is a marker for undiagnosed cardiovascular (CV) disease and future events. In the Princeton 3 guidelines, he recognized the important impact of testosterone deficiency (TD) on all-cause and CV mortality. Recent evidence suggests that testosterone therapy to target levels and for sufficient duration decreases CV events. Unfortunately, this had a modest impact on CV disease
management because ED is not incorporated into current risk calculators. This report is based on the Graham Jackson Memorial Lecture presented at the International Society for Sexual Medicine (ISSM) in Beijing in 2016.

AIM: To examine recent evidence as to whether ED should be upgraded to a risk factor, especially with the high predictive value in younger men, and to develop a case for TD to be considered an independent risk factor based on a large number of long-term studies during the past 5 years.

METHODS: A Medline search was undertaken to include articles on ED and TD and related terms from 1998 to 2016 during the preparation of ISSM guidelines on ED and TD.

MAIN OUTCOME MEASURES: A rational justification for ED and low testosterone to be considered risk factors for CV disease and be included in risk calculators.

RESULTS: The evidence for inclusion of ED and TD might be stronger than for accepted risk factors and have the advantages of being easily assessed, quantitative, symptomatic, and clinically relevant, especially in younger men. Because important studies are often published in endocrine, sexual medicine, urology, and cardiology journals, a multidisciplinary approach is needed.


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The steroid response to human chorionic gonadotropin (hCG) stimulation in men with Klinefelter syndrome does not change using immunoassay or mass spectrometry. Roli L; Santi D; Belli S; Tagliavini S; Cavalieri S; De Santis MC; Baraldi E; Fanelli F; Mezzullo M; Granata AR; Pagotto U; Pasquali R; Rochira V; Carani C; Simoni M; Trenti T. OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present Journal of Endocrinological Investigation. , 2017 Mar 21.

[Journal Article]

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PURPOSE: Liquid-chromatography tandem mass-spectrometry (LC-MS/MS) was developed in parallel to Immunoassays (IAs) and today is proposed as the "gold standard" for steroid assays. Leydig cells of men with Klinefelter syndrome (KS) are able to respond to human chorionic gonadotropin (hCG) stimulation, even if testosterone (T) production was impaired. The aim was to evaluate how results obtained by IAs and LC-MS/MS can differently impact on the outcome of a clinical research on gonadal steroidogenesis after hCG stimulation.

METHODS: A longitudinal, prospective, case-control clinical trial. (clinicaltrial.gov NCT02788136) was carried out, enrolling KS men and healthy age-matched controls, stimulated by hCG administration. Serum steroids were evaluated at baseline and for 5 days after intramuscular injection of 5000 IU hCG using both IAs and LC-MS/MS.

RESULTS: 13 KS patients (36+-9 years) not receiving T replacement therapy and 14 controls (32+-8 years) were enrolled. T, progesterone, cortisol, 17-hydroxy-progesterone (17OHP) and androstenedione, were significantly higher using IAs than LC-MS/MS. IAs and LC-MS/MS showed direct correlation for all five steroids, although the constant overestimation detected by IAs. Either methodology found the same 17OHP and T increasing profile after hCG stimulation, with equal areas under the curves (AUCs).

CONCLUSIONS: Although a linearity between IA and LC-MS/MS is demonstrated, LC-MS/MS is more sensitive and accurate, whereas IA shows a constant overestimation of sex steroid levels. This result suggests the need of reference intervals built on the specific assay. This fundamental difference between these two methodologies opens a deep reconsideration of what is needed to improve the accuracy of steroid hormone assays.

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46.
Evidence of Boldenone, Nandrolone, 5(10)-Estrene-3beta-17alpha-Diol and 4-Estrene-3,17-Dione as Minor Metabolites of Testosterone In Equine.
Wong JK; Leung DK; Curl P; Schiff PJ; Lam KK; Wan TS.
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The detection of boldenone, nandrolone, 5(10)-estrene-3beta,17alpha-diol and 4-estrene-3,17-dione in a urine sample collected from a gelding having been treated with testosterone (500mg "Testosterone Suspension 100", single dose, injected intramuscularly) in 2009 led the authors' laboratory to suspect that these 'testicular' steroids could be minor metabolites of testosterone in geldings. Administration trials on six castrated horses with "Testosterone Suspension 100" confirmed that low levels of boldenone, nandrolone, 5(10)-estrene-3beta,17alpha-diol and 4-estrene-3,17-dione could indeed be detected and confirmed in the early post-administration urine samples from all six geldings. Although boldenone has been reported to be present in urine after testosterone administration, there has been no direct evidence reported that boldenone,
nandrolone, 5(10)-estrene-3beta,17alpha-diol and 4-estrene-3,17-dione are metabolites of testosterone in geldings. Subsequent in vitro experiments involving the incubation of testosterone with horse liver microsomes, liver, adipose and muscle tissues, and adrenal cortex homogenates failed to provide evidence that these four substances are minor metabolites of testosterone. An administration trial using "Testosterone Suspension 100" supplemented with 13 C-labelled testosterone (500mg, 1:1 ratio, injected intramuscularly) was performed. The similarities of the excretion curves of 12 C-testosterone and 13 C-testosterone in urine suggest that there was minimal kinetic isotope effect. 13 C-Labelled boldenone, nandrolone and 4-estrene-3,17-dione were detected but not 5(10)-estrene-3beta,17alpha-diol and its 13 C-counterpart. This is the first unequivocal evidence of boldenone, nandrolone and 4-estrene-3,17-dione being metabolites of testosterone in geldings. In view of these results, caution should be exercised when interpreting findings of boldenone, nandrolone and/or 4-estrene-3,17-dione together with a relatively high level of testosterone in gelding urine.

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Serum Level of Zinc and Copper in Sudanese Women with Polycystic Ovarian Syndrome.
Sharif ME; Adam I; Ahmed MA; Rayis DA; Hamdan HZ.

The study aimed to evaluate the serum level of zinc and copper in women with polycystic ovarian syndrome (PCOS). A case-control study was conducted at Saad Abualila infertility center (Khartoum, Sudan). The cases were women who had a PCOS based on Rotterdam criteria. The controls were infertile women with no evidence of PCOS. The socio-demographic characteristics and medical history data were gathered using questionnaires. Zinc and copper levels were measured using atomic absorption spectrophotometer. While there was no difference in zinc and copper levels between the two groups (50 women in each arm), mean (SD) of body mass index (BMI) was significantly higher in women with PCOS compared to the controls [28.4 (4.2) vs. 25.6 (5.7) kg/m2; P = 0.006], respectively. There were no significant differences in the level of luteinizing hormone (LH), follicle stimulating hormone (FSH), LH/FSH, prolactin, testosterone, cholesterol, triglycerides and low-density lipoprotein (LDL) between the cases and the controls. In linear regression analyses, none of the investigated factors were associated with PCOS. Zinc and copper were not associated with PCOS in this setting.
Effects of Anabolic Androgenic Steroids on the Reproductive System of Athletes and Recreational Users: A Systematic Review and Meta-Analysis. [Review]
Christou MA; Christou PA; Markozannes G; Tsatsoulis A; Mastorakos G; Tigas S.
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BACKGROUND: Anabolic androgenic steroids (AAS) are testosterone derivatives used by athletes and recreational users to improve athletic performance and/or enhance appearance. Anabolic androgenic steroids use may have serious and potentially irreversible adverse effects on different organs and systems, including the reproductive system.
OBJECTIVE: This systematic review and meta-analysis aimed to critically assess the impact of AAS use on the reproductive system of athletes and recreational users.
METHODS: An electronic literature search was conducted using the databases MEDLINE, CENTRAL, and Google Scholar. Studies were included when the following criteria were fulfilled: participants were athletes or recreational users of any age, sex, level or type of sport; AAS use of any type, dose, form or duration; AAS effects on the reproductive system were assessed as stated by medical history, clinical examination, hormone and/or semen analysis. Random-effects meta-analysis was performed to assess the weighted mean difference (WMD) of serum
gonadotropin (luteinizing hormone, follicle-stimulating hormone) and testosterone levels compared with baseline, during the period of AAS use, as well as following AAS discontinuation.

RESULTS: Thirty-three studies (three randomized clinical trials, 11 cohort, 18 cross-sectional, and one non-randomized parallel clinical trial) were included in the systematic review (3879 participants; 1766 AAS users and 2113 non-AAS users). The majority of the participants were men; only six studies provided data for female athletes. A meta-analysis (11 studies) was conducted of studies evaluating serum gonadotropin and testosterone levels in male subjects: (1) prior to, and during AAS use (six studies, n = 65 AAS users; seven studies, n = 59, evaluating gonadotropin and testosterone levels respectively); (2) during AAS use and following AAS discontinuation (four studies, n = 35; six studies, n = 39, respectively); as well as (3) prior to AAS use and following AAS discontinuation (three studies, n = 17; five studies, n = 27, respectively). During AAS intake, significant reductions in luteinizing hormone [weighted mean difference (WMD) -3.37 IU/L, 95% confidence interval (CI) -5.05 to -1.70, p < 0.001], follicle-stimulating hormone (WMD -1.73 IU/L, 95% CI -2.67 to -0.79, p < 0.001), and endogenous testosterone levels (WMD -10.75 nmol/L, 95% CI -15.01 to -6.49, p < 0.001) were reported. Following AAS discontinuation, serum gonadotropin levels gradually returned to baseline values within 13-24 weeks, whereas serum testosterone levels remained lower as compared with baseline (WMD -9.40 nmol/L, 95% CI -14.38 to -4.42, p < 0.001). Serum testosterone levels remained reduced at 16 weeks following discontinuation of AAS. In addition, AAS abuse resulted in structural and functional sperm changes, a reduction in testicular volume, gynecomastia, as well as clitoromegaly, menstrual irregularities, and subfertility.

CONCLUSION: The majority of AAS users demonstrated hypogonadism with persistently low gonadotropin and testosterone levels, lasting for several weeks to months after AAS withdrawal. Anabolic androgenic steroid use results in profound and prolonged effects on the reproductive system of athletes and recreational users and potentially on fertility.
Nandrolone decanoate interferes with testosterone biosynthesis altering blood-testis barrier components.

Barone R; Pitruzzella A; Marino Gammazza A; Rappa F; Salerno M; Barone F; Sangiorgi C; D'Amico D; Locorotondo N; Di Gaudio F; Cipolloni L; Di Felice V; Schiavone S; Rapisarda V; Sani G; Tambo A; Cappello F; Turillazzi E; Pomara C.

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The aim of this study was to investigate whether nandrolone decanoate (ND) use affects testosterone production and testicular morphology in a model of trained and sedentary mice. A group of mice underwent endurance training while another set led a sedentary lifestyle and were freely mobile within cages. All experimental groups were treated with either ND or peanut oil at different doses for 6 weeks. Testosterone serum levels were measured via liquid chromatography-mass spectrometry. Western blot analysis and quantitative real-time PCR were utilized to determine gene and protein expression levels of the primary enzymes implicated in
testosterone biosynthesis and gene expression levels of the blood-testis barrier (BTB) components. Immunohistochemistry and immunofluorescence were conducted for testicular morphological evaluation. The study demonstrated that moderate to high doses of ND induced a diminished serum testosterone level and altered the expression level of the key steroidogenic enzymes involved in testosterone biosynthesis. At the morphological level, ND induced degradation of the BTB by targeting the tight junction protein-1 (TJP1). ND stimulation deregulated metalloproteinase-9, metalloproteinase-2 (MMP-2) and the tissue inhibitor of MMP-2. Moreover, ND administration resulted in a mislocalization of mucin-1. In conclusion, ND abuse induces a decline in testosterone production that is unable to regulate the internalization and redistribution of TJP1 and may induce the deregulation of other BTB constituents via the inhibition of MMP-2. ND may well be considered as both a potential inducer of male infertility and a potential risk factor to a low endogenous bioavailable testosterone.

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Testicular responses to hCG stimulation at varying doses in men with spinal cord injury.

Bauman WA; La Fountaine MF; Cirnigliaro CM; Kirshblum SC; Spungen AM.

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STUDY DESIGN: Prospective.

OBJECTIVES: To test whether provocative stimulation of the testes identifies men with chronic spinal cord injury (SCI), a population in which serum testosterone concentrations are often depressed, possibly due to gonadal dysfunction. To accomplish this objective, conventional and lower than the conventional doses of human chorionic gonadotropin (hCG) were administered.

METHODS: Thirty men with chronic SCI (duration of injury >1 year; 18 and 65 years old; 16 eugonadal (>12.1nmol/l) and 14 hypogonadal (12.1nmol/l)) or able-bodied (AB) men (11 eugonadal and 27 hypogonadal) were recruited for the study. Stimulation tests were performed to quantify testicular responses to the intramuscular administration of hCG at three dose concentrations (i.e., 400, 2000 and 4000IU). The hCG was administered on two consecutive days, and blood was collected for serum testosterone in the early morning prior to each of the two injections; subjects returned on day 3 for a final blood sample collection.

RESULTS: The average gonadal response in the SCI and AB groups to each dose of hCG was not significantly different in the hypogonadal or eugonadal subjects, with the mean serum testosterone concentrations in all groups demonstrating an adequate response.
CONCLUSIONS: This work confirmed the absence of primary testicular dysfunction without additional benefit demonstrated of provocative stimulation of the testes with lower than conventional doses of hCG. Our findings support prior work that suggested a secondary testicular dysfunction that occurs in a majority of those with SCI and depressed serum testosterone concentrations. Spinal Cord advance online publication, 21 February 2017; doi:10.1038/sc.2017.8.
Reproductive dysfunction and associated pathology in women undergoing military training.

[Review]

Gifford RM; Reynolds RM; Greeves J; Anderson RA; Woods DR.
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INTRODUCTION: Evidence from civilian athletes raises the question of whether reproductive dysfunction may be seen in female soldiers as a result of military training. Such reproductive dysfunction consists of impaired ovulation with or without long-term subfertility.

METHODS: A critical review of pertinent evidence following an extensive literature search.

RESULTS: The evidence points towards reduced energy availability as the most likely explanation for exercise-induced reproductive dysfunction. Evidence also suggests that reproductive dysfunction is mediated by activation of the hypothalamic-pituitary-adrenal axis and suppression of the hypothalamic-pituitary-gonadal axis, with elevated ghrelin and reduced leptin likely to play an important role. The observed reproductive dysfunction exists as part of a female athletic triad, together with osteopenia and disordered eating. If this phenomenon was shown to exist with UK military training, this would be of significant concern. We hypothesise that the nature of military training and possibly field exercises may contribute to greater risk of reproductive dysfunction among female military trainees compared with exercising civilian controls. We discuss the features of military training and its participants, such as energy availability, age at recruitment, body phenotype, type of physical training, psychogenic stressors, altered sleep pattern and elemental exposure as contributors to reproductive dysfunction.

CONCLUSIONS: We identify lines of future research to more fully characterise reproductive dysfunction in military women and suggest possible interventions that, if indicated, could improve their future well-being.
52.

Gonadal and Sexual Dysfunction in Childhood Cancer Survivors.

Yoon JY; Park HJ; Ju HY; Yoon JH; Chung JS; Hwang SH; Lee DO; Shim HY; Park BK.

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Cancer Research & Treatment. , 2017 Jan 25.

[Journal Article]
Purpose: Few studies have addressed gonadal and sexual dysfunctions in childhood cancer survivors. We evaluated the prevalence rates and risk factors for gonadal failure among adolescent/young adult childhood cancer survivors and their sexual function.

Materials and Methods: Subjects were childhood cancer survivors aged 15-29 years who had completed therapy more than two years ago. Demographic and medical characteristics were obtained from the patients' medical records. In addition, hormonal evaluation and semen analysis were performed and sexual function was evaluated via questionnaire.

Results: The study included 105 survivors (57 males, 48 females), of which 61 were adults (age>19 years) and 44 were adolescents. In both males and females, the proportion of survivors with low sex hormone levels did not differ among age groups or follow-up period. Thirteen female subjects (27.1%) needed sex hormone replacement, while five males subjects (8.8%) were suspected of having hypogonadism, but none were receiving sex hormone replacement. Of 27 semen samples, 14 showed azo- or oligospermia. The proportion of normospermia was lower in the high cyclophosphamide equivalent dose (CED) group (CED >= 8,000 mg/m2) than the low CED group (27.3% vs 62.5%, P = 0.047). Among adults, none were married and only 10 men (35.7%) and eight women (34.3%) were in a romantic relationship. Though a significant proportion (12.0% of males and 5.3% of females) of adolescent survivors had experienced sexual activity, 13.6% had not experienced sex education.

Conclusion: The childhood cancer survivors in this study showed a high prevalence of gonadal/sexual dysfunction; accordingly, proper strategies are needed to manage these complications.
Effect of supplements during the cold season on the reproductive system in prepubertal Tibetan sheep ewes.

Jing X; Peng Q; Hu R; Wang H; Yu X; Degen A; Zou H; Bao S; Zhao S; Wang Z.

OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present


We examined the development of the reproductive system in prepubertal Tibetan sheep ewes when fed only oat hay (CON) or supplemented with either lick blocks (BS) or concentrate feed (CS) during the cold season. The average daily gain of the CS ewes was greater than that of the BS ewes (P < 0.05), which was greater than that of the CON ewes. The same pattern was observed in the number of ovarian follicles (P < 0.001), that is, CS > BS > CON. Serum concentrations of gonadotropin-releasing hormone, follicle-stimulating hormone, luteotrophic hormone, estradiol and progesterone in the CS and BS groups were higher than in the CON group (P < 0.05). The messenger RNA (mRNA) expression of KiSS-1, GPR54 (G protein-coupled receptor 54), ERalpha (estradiol receptor alpha) in the hypothalamic anteroventral periventricular area of the CS group were higher than in both the BS and CON groups (P < 0.05), while the BS group was higher than in the CON group (P < 0.05). Similar differences among groups were observed for gonadotropin-releasing hormone receptor mRNA expression in the pituitary, follicle-stimulating hormone receptor and luteinizing hormone receptor mRNA expression in the ovary. These results indicated that the KiSS1/GPR54 system was more active with nutrition or trace mineral supplementation during the cold season. The system stimulated the hypothalamic-pituitary-gonadal axis and enhanced follicular development in prepubertal Tibetan sheep ewes. We
concluded that energy, protein and trace minerals supplements could improve the reproductive performance of Tibetan sheep on the Qinghai-Tibetan plateau.

Sustanon induces dose-independent hypertrophy and satellite cell proliferation in slow oxidative fibers of avian skeletal muscle.
Sustanon is a well-known anabolic drug that is used to treat hypogonadism and restore muscle mass and bone density. As research to date has been limited to its effects in glycolytic fibers, this study aimed to investigate the dose-related effects of Sustanon on the oxidative fibers of avian skeletal muscle. Adult female chickens were randomly divided into 4 groups: control (C), received a dose of 100 μl normal saline per injection; and Sustanon-1, -2, and -3 (S1, S2, and S3), that received a dose of 12.5, 25, or 50 mg/kg Sustanon per injection, respectively. Each bird received 4 injections at weekly intervals (1 injection/week). Robust histochemical and immunofluorescent techniques along with morphometric analyses were applied to determine the oxidative activity and morphological variations of the oxidative muscle fibers in all groups. Sustanon-treated groups exhibited significant increases in fiber size and numbers of satellite cells and myonuclei compared to the control group. However, no significant variations were found between Sustanon-treated groups in the aforementioned indices. In conclusion, Sustanon induced oxidative fiber hypertrophy that was associated with satellite cell proliferation and myonuclear accretion in avian skeletal muscle. Furthermore, the effects of Sustanon appeared to be dose-independent.
Microsurgical Subinguinal Varicocele Repair of Grade II-III Lesions Associated with Improvements of Testosterone Levels.

Elzanaty S; Johansen C.

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[Journal Article]

UI: 28559777

INTRODUCTION: The results of reports on the association between varicocele repair and testosterone levels were conflicting. The aim of the present study is, therefore, to investigate the impact of varicocele repair on testosterone levels.

MATERIALS AND METHODS: The study is based on 20 men who experienced microsurgical subinguinal varicoceles repair because of chronic dull scrotal pain. All hormonal profiles available in the clinical records were reviewed. Follow-up evaluation was done at 1 and 12 months after surgery. Men were classified into groups based on the preoperative testosterone levels: euogonadal (serum levels of testosterone > 12 nmol/l), hypogonadal men (serum levels of testosterone <= 12 nmol/l).

RESULTS: Microsurgical subinguinal varicocele repair was associated with a significant improvements of testosterone levels at 1 and 12 months after surgery as compared to the preoperative levels (13 nmol/l vs. 18 nmol/l, p = 0.03; 13 nmol/l vs. 15 nmol/l, p = 0.01). The same trend was seen in men who were classified as being hypogonadal (7.0 nmol/l vs. 15 nmol/l, p = 0.01; 7.0 nmol/l vs. 10 nmol/l, p = 0.02). No significant improvements in testosterone levels were observed in euogonadal men (p > 0.05).

CONCLUSION: Microsurgical subinguinal varicocele repair was associated with a significant improvements of testosterone levels in men with grade II-III lesions and low preoperative testosterone values.
56.
Association between Serum Testosterone and PSA Levels in Middle-Aged Healthy Men from the General Population.
Elzanaty S; Rezanezhad B; Dohle G.
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[Journal Article]
UI: 28559776

INTRODUCTION: The aim of the present study was to evaluate the association between serum testosterone and PSA levels in middle-aged healthy men from the general population.
MATERIALS AND METHODS: Based on 119 healthy men from the general population, total testosterone and PSA levels were measured. Demographic data regarding BMI, waist-to-hip ratio, smoking, and alcohol consumption were also collected. Men were classified into two groups according to testosterone levels; hypogonadal (testosterone <= 12 nmol/l), and eugonadal (testosterone > 12 nmol/l).
RESULTS: The mean age of the subjects was 55 years (range 46-60 years). No significant correlation between serum testosterone and PSA levels was found (p = 0.60). PSA levels were similar when compared between hypogonadal and eugonadal men (1.4 micro g/l vs. 1.4 micro g/l, p = 0.90). When using a multivariate analysis model adjusted for the age of the subjects, BMI, waist-to-hip ratio, smoking, and alcohol consumption, a positive significant association between testosterone and PSA levels was found (beta = 0.03, 95 % CI = 0.003-0.062, p = 0.03).
CONCLUSION: Only after adjusted multivariate analysis, our results indicated that testosterone was associated with PSA levels in middle-aged healthy men.
Primary retroperitoneal mature cystic teratoma (dermoid cyst) in a 51-year-old male: Case report and historical literature review.

Tiu A; Sovani V; Khan N; Hooda S.

OBJECTIVES: Primary retroperitoneal mature cystic teratomas are exceedingly uncommon in males aged 50 years and above, and only seven cases have been reported in the literature so far. They usually occur in infants less than 6 months and young females. The aim of this article is to present a rare case of a 51-year-old male with a primary retroperitoneal mature cystic teratoma located in the right infrarenal area adherent to the psoas muscle and to discuss a historical literature review.

METHODS: An incidental hypoechoic, solid appearing 8.2 x 7.6 x 7.8 cm3 mass arising off the inferior pole of the right kidney was found on abdominal ultrasound during evaluation for a history
of alcoholism. Computerized tomography (CT) scan revealed small calcifications in the lower part of the cystic mass. Laparotomy with excision of the retroperitoneal mass was performed.

RESULTS: On gross examination, the specimen consisted of a cyst filled with pale yellow greasy material with entrapped hair. Histopathologic examination revealed a dermoid cyst with focal chronic inflammation, dystrophic calcification, and foreign-body giant cell reaction.

CONCLUSIONS: Retroperitoneal mature cystic teratoma in an older male is extremely rare. Primary gonadal teratoma with retroperitoneal metastasis should be excluded first. Evaluation of age and location of tumor are critical for its prognosis. Complete excision of tumor is necessary to evaluate whether there are immature and solid elements which need long-term follow up due to the increased risk of malignancy.

Status
In-Data-Review

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58.
Comparison of the Ratio of the Length of the Second and Fourth Digits in Subgroups of Fertile and Infertile Cases.
Akinsal EC; Demirtas A; Ekmekcioglu O.
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[Journal Article]
UI: 28537047
PURPOSE: To identify any relationship between known reasons of male infertility and 2D:4D ratio.

MATERIALS AND METHODS: A total of 371 males were included in the study. The cases were grouped into 6 groups including sperm count < 5 million/mL, sperm count &ge; 5 million/mL, Klinefelter Syndrome, hypogonadotropic hypogonadism, vasal agenesis and control. Groups were compared with each other in terms of 2D:4D ratios and groups with a 2D:4D ratios below 1 and equal/above 1 were compared.

RESULTS: The greatest ratios were in the vasal agenesis and hypogonadotropic hypogonadism groups and analysis of the data with logistic regression analysis showed that there was a significant difference in terms of 2D:4D ratios for these groups when comparing with control group. The other groups showed no statistically significant differences.

CONCLUSION: The results of the present study showed some significant difference between 2D:4D ratios for the subgroups of the fertile and infertile cases. Although, 2D:4D ratio is not an unaccompanied parameter to reveal causes of male infertility, it can be associated with some situations that are related with male infertility.

Status
In-Process

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59.
Acute vs chronic exposure to high fat diet leads to distinct regulation of PKA.
London E; Nesterova M; Stratakis CA.
The cAMP-dependent protein kinase (PKA) is an essential regulator of lipid and glucose metabolism that plays a critical role in energy homeostasis. The impact of diet on PKA signaling has not been defined, although perturbations in individual PKA subunits are associated with changes in adiposity, physical activity and energy intake in mice and humans. We hypothesized that a high fat diet (HFD) would elicit peripheral and central alterations in the PKA system that would differ depending on length of exposure to HFD; these differences could protect against or promote diet-induced obesity (DIO). 12-week-old C57Bl/6J mice were randomly assigned to a regular diet or HFD and weighed weekly throughout the feeding studies (4 days, 14 weeks; respectively), and during killing. PKA activity and subunit expression were measured in liver, gonadal adipose tissue (AT) and brain. Acute HFD-feeding suppressed basal hepatic PKA activity. In contrast, hepatic and hypothalamic PKA activities were significantly increased after chronic HFD-feeding. Changes in AT were more subtle, and overall, altered PKA regulation in response to chronic HFD exposure was more profound in female mice. The suppression of hepatic PKA activity after 4 day HFD-feeding was indicative of a protective peripheral effect against obesity in the context of overnutrition. In response to chronic HFD-feeding, and with the development of DIO, dysregulated hepatic and hypothalamic PKA signaling was a signature of obesity that is likely to promote further metabolic dysfunction in mice.

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Stratakis, Constantine A. Section on Endocrinology and GeneticsProgram on Developmental Endocrinology and Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA.
Effect of sexual excitation on testosterone and nitric oxide levels of water buffalo bulls (Bubalus bubalis) with different categories of sexual behavior and their correlation with each other.

Swelum AA; Saadeldin IM; Zaher HA; Alsharifi SAM; Alowaimer AN.

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[Journal Article]
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We studied the effect of sexual excitation on serum testosterone and nitric oxide (NO) levels in water buffalo bulls with different categories of sexual behavior and their correlation with each other. Buffalo bulls were classified according to their sexual behavior (including reaction time, sexual aggressiveness and mating ability): acceptable (good to excellent) (n=5), fair (n=5), and unacceptable (poor) (n=5) sexual behavior. Blood samples were collected from all animals immediately before and after sexual teasing and/or mounting to estimate the testosterone and NO levels using a commercial radioimmunoassay kit and Griess reaction test, respectively. Comparisons among groups were evaluated using a mixed-design analysis of variance. Pearson's correlation coefficients were calculated to determine the relationship between testosterone and NO levels before and after sexual excitation besides sexual behavior. The level of testosterone before sexual excitation was higher (p<=0.05) in bulls with acceptable and fair sexual behavior than in bulls with unacceptable sexual behavior (0.86 +/- 0.01, 0.69 +/- 0.02, and 0.29 +/- 0.02ng/mL, respectively). The level of NO was higher (p<=0.05) in bulls with acceptable and fair sexual behavior than in bulls with unacceptable sexual behavior (8.00 +/- 0.03, 7.66 +/- 0.19, and 6.29 +/- 0.33muM, respectively). Sexual excitation significantly (p<0.05) increase testosterone and NO levels in bulls with acceptable (1.45 +/- 0.01ng/mL and 19.04 +/- 0.32muM, respectively) or fair (0.92 +/- 0.02ng/mL and 14.95 +/- 0.34muM, respectively) sexual behavior, but not in bulls with unacceptable sexual behavior. The unacceptable sexual behavior bulls had significantly lower testosterone and NO levels than the other bulls. There was a strong correlation
and association between serum testosterone and NO levels besides sexual behavior of buffalo bulls. In conclusion, the alteration in the testosterone and NO levels after sexual excitation depends on the sexual behavior category of buffalo-bull. Testosterone and NO can be used to create a sexual behavior score. The testosterone and NO levels of can be predicted via evaluation of sexual behavior of buffalo bull.

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Status
In-Process

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20170507

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61. Causal relationship between obesity and serum testosterone status in men: A bi-directional mendelian randomization analysis.
Eriksson J; Haring R; Grarup N; Vandenput L; Wallaschofski H; Lorentzen E; Hansen T; Mellstrom D; Pedersen O; Nauck M; Lorentzon M; Nystrup Husemoen LL; Volzke H; Karlsson M; Baumeister SE; Linneberg A; Ohlsson C.

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[Journal Article]
UI: 28448539

CONTEXT: Obesity in men is associated with low serum testosterone and both are associated with several diseases and increased mortality.

OBJECTIVES: Examine the direction and causality of the relationship between body mass index (BMI) and serum testosterone.

DESIGN: Bi-directional Mendelian randomization (MR) analysis on prospective cohorts.

SETTING: Five cohorts from Denmark, Germany and Sweden (Inter99, SHIP, SHIP Trend, GOOD and MrOS Sweden).

PARTICIPANTS: 7446 Caucasian men, genotyped for 97 BMI-associated SNPs and three testosterone-associated SNPs.

MAIN OUTCOME MEASURES: BMI and serum testosterone adjusted for age, smoking, time of blood sampling and site.

RESULTS: 1 SD genetically instrumented increase in BMI was associated with a 0.25 SD decrease in serum testosterone (IV ratio: -0.25, 95% CI: -0.42--0.09, p = 2.8*10^-3). For a body weight reduction altering the BMI from 30 to 25 kg/m2, the effect would equal a 13% increase in serum testosterone. No association was seen for genetically instrumented testosterone with BMI, a finding that was confirmed using large-scale data from the GIANT consortium (n = 104349).

CONCLUSIONS: Our results suggest that there is a causal effect of BMI on serum testosterone in men. Population level interventions to reduce BMI are expected to increase serum testosterone in men.

Status
In-Process

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Mullerian dysgenesis: a critical review of the literature. [Review]
Choussein S; Nasioudis D; Schizas D; Economopoulos KP.
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MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
[Journal Article. Review]
UI: 28434104
PURPOSE: To present an update of the genetic, clinical, diagnostic, and therapeutic aspects of Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome.
METHODS: Studies were considered eligible if they have evaluated patients with MRKH syndrome. Eligible articles were identified by a search of MEDLINE bibliographical database from 1950 to August 2016. A purely descriptive approach was adopted concerning all outcomes examined by the individual studies.
RESULTS: MRKH syndrome is defined as congenital aplasia of the upper vagina and impairment of uterine development in normal 46XX females. Accounting for 1:4500 women, MRKH is the second most common cause of primary amenorrhea following gonadal dysgenesis. Potential association of MRKH syndrome to specific genes has been the focus of recent research. Null-association results of HOXA genes and Wnt5a, Wnt7a, and Wnt9a have been reported, while point mutations of the WNT4 gene point mutations have been associated with an MRKH-like
syndrome characterized by Mullerian duct regression and hyperandrogenism. Ultrasound and Magnetic Resonance Imaging (MRI) are the main techniques to establish an accurate diagnosis of the syndrome. Several non-surgical and surgical procedures have been reported for the creation of a functional neovagina; in general, non-surgical treatment should be the first initially pursued. Along with psychological support, recent developments in assisted reproductive technologies of IVF techniques and the availability of gestational surrogacy, as well as the recent breakthrough of successful uterus transplantation, enable women with MRKH syndrome to attain their own genetic child.

CONCLUSION(S): MRKH syndrome is a medical modality with important social, legal, and ethical projections that require a multi-disciplinary approach.

Status
In-Process

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2017
Normalization of Testosterone Levels After Testosterone Replacement Therapy Is Associated With Decreased Incidence of Atrial Fibrillation.

Sharma R; Oni OA; Gupta K; Sharma M; Sharma R; Singh V; Parashara D; Kamalakar S; Dawn B; Chen G; Ambrose JA; Barua RS.

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Journal of the American Heart Association. 6(5), 2017 May 09.
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BACKGROUND: Atrial fibrillation (AF) is the most common cardiac dysrhythmia associated with significant morbidity and mortality. Several small studies have reported that low serum total testosterone (TT) levels were associated with a higher incidence of AF. In contrast, it is also reported that anabolic steroid use is associated with an increase in the risk of AF. To date, no study has explored the effect of testosterone normalization on new incidence of AF after testosterone replacement therapy (TRT) in patients with low testosterone.

METHODS AND RESULTS: Using data from the Veterans Administrations Corporate Data Warehouse, we identified a national cohort of 76 639 veterans with low TT levels and divided them into 3 groups. Group 1 had TRT resulting in normalization of TT levels (normalized TRT), group 2 had TRT without normalization of TT levels (nonnormalized TRT), and group 3 did not receive TRT (no TRT). Propensity score-weighted stabilized inverse probability of treatment weighting Cox proportional hazard methods were used for analysis of the data from these groups to determine the association between post-TRT levels of TT and the incidence of AF. Group 1 (40 856 patients, median age 66 years) had significantly lower risk of AF than group 2 (23 939 patients, median age 65 years; hazard ratio 0.90, 95% CI 0.81-0.99, P=0.0255) and group 3 (11 853 patients, median age 67 years; hazard ratio 0.79, 95% CI 0.70-0.89, P=0.0001). There was no statistical difference between groups 2 and 3 (hazard ratio 0.89, 95% CI 0.78-1.0009, P=0.0675) in incidence of AF.

CONCLUSIONS: These novel results suggest that normalization of TT levels after TRT is associated with a significant decrease in the incidence of AF.

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Status
In-Process
Effect of extracellular matrix on testosterone production during in vitro culture of bovine testicular cells.

Akbarinejad V; Tajik P; Movahedin M; Youssefi R.

Testosterone is believed to play a significant role in spermatogenesis, but its contribution to the process of spermatogenesis is not completely understood. Given that extracellular matrix (ECM) facilitates differentiation of spermatogonial stem cells (SSCs) during culture, the present study was conducted to elucidate whether testosterone contribute to the permissive effect of ECM on SSCs differentiation. In experiment 1, testosterone production was measured in testicular cells cultured for 12 days on ECM or plastic (control). In experiment 2, testosterone production was assessed in testicular cells cultured on ECM or plastic (control) and exposed to different concentrations of hCG. In experiment 3, the gene expression of factors involved in testosterone production was analyzed. Testosterone concentration was lower in ECM than in the control group in experiment 1 (p < 0.05). In experiment 2, testosterone concentration was increased in response to hCG in both groups but cells cultured on ECM were more responsive to hCG than those cultured on plastic (p < 0.05). In the experiment 3, qRT-PCR revealed the inhibitory effect of ECM on the gene expression of steroidogenic acute regulatory protein (STAR) (p < 0.05). Nevertheless, the expression of LH receptor was greater in ECM-exposed than in unexposed cells (p < 0.05). In conclusion, the present study showed that inhibiting the expression of STAR, ECM could lower testosterone production by Leydig cells during in vitro culture. In addition, the results indicated that ECM could augment the responsiveness of Leydig cells to hCG through stimulating the expression of LH receptor.
INTRODUCTION: Infertility affects 50 to 80 million (between 8 and 12% of couples). Male factor is a cause of infertility in almost half of the cases, mainly due to oligoasthenoteratozoospermia. DNA fragmentation is now considered an important factor in the aetiology of male infertility. We studied the effects on semen analysis and on DNA fragmentation of in vivo administration of Myo-Inositol and Tribulus Terrestris plus Alga Ecklonia plus Biovis (Tradafertil; Tradapharma Sagl, Switzerland) in men with previously diagnosed male infertility.

MATERIALS AND METHODS: Sixty patients were enrolled in the present study and were randomized into two subgroups: the group A who received Myo-inositol 1000 mg, Tribulus Terrestris 300 mg, Alga Ecklonia Bicyclis 200 mg and Biovis one tablet a day for 90 days, and the group B (placebo group) who received one placebo tablet a day for 90 days. The primary efficacy outcome was the improvement of semen characteristics after 3 months’ therapy and the secondary outcome was the reduction of the DNA fragmentation after treatment.
RESULTS: The groups were homogenous for age, hormonal levels, sperm concentration and all parameters of sperm analysis. Sperm concentration and progressive motility improved after treatment with Tradafertil (3.82 Mil/ml vs. 1.71 Mil/ml; p<0.05; 4.86% vs. 1.00%; p<0.05) as well as the DNA fragmentation (-1.64% vs -0.39%, p<0.001). No side effects were revealed.

CONCLUSIONS: In conclusion, we can affirm that Tradafertil is safe and tolerable. It is a new phytotherapeutic approach to Oligoasthenoteratospermia (OAT) syndrome that could lead to good results without interacting with hypothalamic-pituitary-gonadal axis.

Status
In-Process

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66.
Male Hypogonadism and Osteoporosis: The Effects, Clinical Consequences, and Treatment of Testosterone Deficiency in Bone Health. [Review]
Golds G; Houdek D; Arnason T.
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It is well recognized that bone loss accelerates in hypogonadal states, with female menopause being the classic example of sex hormones affecting the regulation of bone metabolism. Underrepresented is our knowledge of the clinical and metabolic consequences of overt male hypogonadism, as well as the more subtle age-related decline in testosterone on bone quality. While menopause and estrogen deficiency are well-known risk factors for osteoporosis in women, the effects of age-related testosterone decline in men on bone health are less well known. Much of our knowledge comes from observational studies and retrospective analysis on small groups of men with variable causes of primary or secondary hypogonadism and mild to overt testosterone deficiencies. This review aims to present the current knowledge of the consequences of adult male hypogonadism on bone metabolism. The direct and indirect effects of testosterone on bone cells will be explored as well as the important differences in male osteoporosis and assessment as compared to that in females. The clinical consequence of both primary and secondary hypogonadism, as well as testosterone decline in older males, on bone density and fracture risk in men will be summarized. Finally, the therapeutic options and their efficacy in male osteoporosis and hypogonadism will be discussed.

Status
In-Data-Review

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Reproductive hormonal variations and adenohypophyseal lesions in pre-pubertal buffalo heifers inoculated with Pasteurella multocida type B: 2 and its immunogens.

Jesse FF; Ibrahim HH; Abba Y; Chung EL; Marza AD; Mazlan M; Zamri-Saad M; Omar AR; Zakaria MZ; Saharee AA; Haron AW; Lila MA.

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[Journal Article]

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BACKGROUND: Hemorrhagic septicemia is a fatal disease of cattle and buffaloes caused by P. multocida. Although the pathogenesis of the bacteria has been well established in literature, there is a paucity of information on the possible role of the bacteria and its immunogens; lipopolysaccharide (LPS) and outer membrane proteins (OMPs) on the reproductive capacity of buffalo heifers.

METHODS: In this study, twenty one healthy prepubertal female buffaloes aged 8 months were divided into seven groups of 3 buffaloes each (G1-G7). Group 1 (G1) served as the negative control group and were inoculated orally with 10 mL sterile Phosphate Buffer Saline (PBS), groups 2 (G2) and 3 (G3) were inoculated orally and subcutaneously with 10 mL of 1012 colony forming unit (cfu) of P.multocida type B: 2, while groups 4 (G4) and 5 (G5) received 10 mL of bacterial LPS orally and intravenously, respectively. Lastly, groups 6 (G6) and 7 (G7) were orally and subcutaneously inoculated with 10 mL of bacterial OMPs. Whole blood was collected in EDTA vials at stipulated time points (0, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 120, 168, 216, 264, 312, 360, 408, 456 and 504 h), while tissue sections of the pituitary glands were collected and transported to the histopathology laboratory in 10% buffered formalin for processing and Hematoxylin and eosin staining. Plasma levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), progesterone (PG), estradiol (EST) and gonadotrophin releasing hormone (GnRH) were determined.

RESULTS: The histopathological lesions observed in the pituitary gland included hemorrhage, congestion, inflammatory cell infiltration, hydropic degeneration, necrosis and edema. These changes were higher (p < 0.05) in distribution and severity in G3, G6 and G7. Hormonal concentrations of LH, FSH, PG, EST and GnRH declined in all inoculation groups as time elapsed and were lower (p < 0.05) than that of the control group.
CONCLUSION: Based on these findings, P. multocida B: 2 and its immunogens can be said to negatively affect the hypothalamic-pituitary-gonadal axis, resulting in decreased levels of reproductive hormones which may predispose to infertility in buffalo heifers.

Status
In-Process

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68.
Modifications of anxiety-like behavior in prenatally stressed male offspring with imbalance of androgens.
Fedotova J; Akulova V; Pivina S; Dragasek J; Caprnda M; Kruzliak P.
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present American Journal Of Translational Research. 9(3):1448-1459, 2017.
[Journal Article]
UI: 28386370
Gonadal hormones have been well-known to affect brain regions known to be involved in the modulation of mood and affective-related behavior. Prenatal stress might alter hypothalamic-pituitary-gonadal axis, it could be a target for development of affective-related disorders in male offspring. The present study was designed to examine an anxiety-like behavior in the adult male offspring with low levels of endogenous androgens delivered from pregnant dams exposed to prenatal stress from gestation day 15 to gestation day 19. The non-stressed and prenatally stressed intact, gonadectomized (GDX) and GDX male offspring treated with oil solvent or testosterone propionate (TP, 0.5 mg/kg, s.c., 14 days, once daily) were used in all experiments. Anxiety-like behavior was assessed in the elevated plus maze (EPM) and the open field test (OFT), respectively. Also, testosterone levels in the blood serum were measured in all experimental groups of offspring. Prenatally stressed GDX offspring demonstrated a significant decrease for time spent into the open arms and increase for time spent into the closed arms as compared to the non-stressed offspring. Administration of TP to the prenatally stressed GDX offspring resulted in a more markedly decrease of the time spent into the open arms and significantly raised the time spent into the closed arms as compared to the non-stressed GDX
offspring treated with TP, non-stressed/prenatally stressed GDX offspring. Prenatally stressed GDX offspring showed a significant increase of crossing, rearing, grooming and defecation as compared to the prenatally stressed control offspring. On the contrary, administration of TP to the prenatally stressed GDX offspring significantly decreased crossing behavior, frequency of rearing and grooming behavior as compared to the non-stressed GDX offspring treated with TP, non-stressed/prenatally stressed GDX offspring. Prenatally stressed GDX offspring demonstrated a significant decrease of testosterone levels as compared to the non-stressed/prenatally stressed intact offspring, as well as non-stressed GDX offspring. Administration of TP significantly increased testosterone levels when prenatally stressed GDX offspring were compared with the prenatally stressed intact offspring, non-stressed/prenatally stressed GDX offspring. Thus, the results of the study clearly suggest that gonadectomy and TP supplementation profoundly changed an anxiety-related behavior in prenatally stressed male offspring in the EPM. Our current findings suggest that androgen deficiency in the prenatally stressed male offspring produces the high anxiety level and induces a marked anxious-like state. TP supplementation provokes development of profoundly anxious-like state in the prenatally stressed male offspring. Furthermore, this is the first study to show anxiogenic-like effect of TP administration on anxiety-related states in prenatally stressed male offspring with androgen deficiency.

Status
PubMed-not-MEDLINE
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Response to ovarian stimulation is not impacted by a breast cancer diagnosis.
Quinn MM; Cakmak H; Letourneau JM; Cedars MI; Rosen MP.
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid
MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
[Journal Article]
Ui: 28122888

STUDY QUESTION: Does a breast cancer diagnosis impact ovarian function in the setting of fertility preservation?

SUMMARY ANSWER: Ovarian reserve and ovarian stimulation outcomes are similar in patients with a new diagnosis of breast cancer and patients undergoing elective fertility preservation.

WHAT IS KNOWN ALREADY: Prior studies, with small study populations, lack of controlling for individual differences in ovarian reserve and infertile controls, have reported conflicting outcomes for cancer patients undergoing ovarian stimulation for fertility preservation.

STUDY DESIGN, SIZE, DURATION: This retrospective cohort analysis included 589 patients undergoing ovarian stimulation for fertility preservation between 2009 and 2015.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women with a recent breast cancer diagnosis (n = 191) and women desiring elective fertility preservation (n = 398) underwent ovarian stimulation with an antagonist protocol at an academic medical center. The aromatase inhibitor letrozole was administered to breast cancer patients with estrogen-sensitive disease.

MAIN RESULTS AND THE ROLE OF CHANCE: Baseline antral follicle count (AFC) was not different between the breast cancer patients and controls (15.4 +/- 10.4 [mean +/- SD] vs 15.4 +/- 10.0, P = NS), even after categorization by age. Total (19.4 +/- 0.9 [mean +/- SEM] vs 17.0 +/- 0.5, P = NS) and mature (MII) oocytes retrieved (13.7 +/- 0.7 vs 13.2 +/- 0.4, P = NS), adjusted
for age, BMI and total gonadotropin dose, were also similar between the two groups. Letrozole use was associated with a decreased maturity rate (MII/total oocytes retrieved) compared to elective cryopreservation (0.71 +/- 0.01 vs 0.77 +/- 0.01, P < 0.001), although the mature oocyte yield [MII/AFC] was comparable (1.01 +/- 0.06 vs 0.93 +/- 0.03, P = NS).

LIMITATIONS, REASONS FOR CAUTION: The single center design may impact generalizability. Additionally, the lack of subsequent embryo and pregnancy data is an inherent weakness.

WIDER IMPLICATIONS OF THE FINDINGS: In females, a breast cancer diagnosis does not impact gonadal function as measured by AFC or ovarian stimulation outcomes. Breast cancer patients should be counseled that their response to ovarian stimulation for fertility preservation is similar to that of patients undergoing elective oocyte cryopreservation.

STUDY FUNDING/COMPETING INTEREST(S): None.

TRIAL REGISTRATION NUMBER: N/A.

Status
In-Data-Review

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20170126

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2017
Expanding the genetic spectrum of ANOS1 mutations in patients with congenital hypogonadotropic hypogonadism.

Goncalves CI; Fonseca F; Borges T; Cunha F; Lemos MC.

OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present


[Journal Article]

UI: 28122887

STUDY QUESTION: What is the prevalence and functional consequence of ANOS1 (KAL1) mutations in a group of men with congenital hypogonadotropic hypogonadism (CHH)?

SUMMARY ANSWER: Three of forty-two (7.1%) patients presented ANOS1 mutations, including a novel splice site mutation leading to exon skipping and a novel contiguous gene deletion associated with ichthyosis.

WHAT IS KNOWN ALREADY: CHH is characterized by lack of pubertal development and infertility, due to deficient production, secretion or action of GnRH, and can be associated with anosmia/hyposmia (Kallmann syndrome, KS) or with a normal sense of smell (normosmic CHH). Mutations in the anosmin-1 (ANOS1) gene are responsible for the X-linked recessive form of KS.

STUDY DESIGN, SIZE, DURATION: This cross-sectional study included 42 unrelated men with CHH (20 with KS and 22 with normosmic CHH).

PARTICIPANTS/MATERIALS, SETTING, METHODS: Patients were screened for mutations in the ANOS1 gene by DNA sequencing. Identified mutations were further investigated by RT-PCR analysis and multiplex ligation-dependent probe amplification (MLPA) analysis.

MAIN RESULTS AND THE ROLE OF CHANCE: Hemizygous mutations were identified in three (7.1%) KS cases: a novel splice acceptor site mutation (c.542-1G>C), leading to skipping of exon 5 in the ANOS1 transcript in a patient with self-reported normosmia (but hyposmic upon testing); a recurrent nonsense mutation (c.571C>T, p.Arg191*); and a novel 4.8 Mb deletion involving ANOS1 and eight other genes (VCX3B, VCX2, PNPLA4, VCX, STS, HDHD1, VCX3A and NLGN4X) in KS associated with ichthyosis.

LIMITATIONS, REASONS FOR CAUTION: Objective olfactory testing was not performed in all cases of self-reported normosmia and this may have underestimated the olfactory deficits.

WIDER IMPLICATIONS OF THE FINDINGS: This study further expands the spectrum of known genetic defects associated with CHH and suggests that patients with self-reported normal olfactory function should not be excluded from ANOS1 genetic testing.

STUDY FUNDING/COMPETING INTEREST(S): This study was funded by the Portuguese Foundation for Science and Technology. The authors have no conflicts of interest.

TRIAL REGISTRATION NUMBER: N/A.
71.
State-of-the-Art: a Review of Cardiovascular Effects of Testosterone Replacement Therapy in Adult Males. [Review]
Elsherbiny A; Tricomi M; Bhatt D; Dandapantula HK.
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
[Journal Article. Review]
UI: 28361372
PURPOSE OF REVIEW: According to an Endocrine Society Clinical Practice Guideline published in June 2010, testosterone replacement therapy (TRT) should be administered only to men who are hypogonadal with documented low testosterone level on two morning measurements. This recommendation was based on previous studies that did not show an increased risk in cardiovascular events with TRT. In contrast, recent studies did show an increased risk which prompted the FDA to investigate further.
RECENT FINDINGS: Multiple studies suggested an increased risk in cardiovascular events among groups of men prescribed TRT. There is recent evidence that TRT can be associated with higher cardiovascular risks, while these risks are still not well established, and more well-designed trials are needed. Physicians should always be cautious when prescribing TRT to their patients. Potential risks should be discussed with each patient, and TRT requires regular monitoring to help minimize side effects.

Status
In-Data-Review

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20170331

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2017

72.
Birth Weight in Different Etiologies of Disorders of Sex Development.
Poyrazoglu S; Darendeliler F; Ahmed SF; Hughes I; Bryce J; Jiang J; Rodie M; Hiort O; Hannema SE; Bertelloni S; Lisa L; Guran T; Cools M; Desloovere A; Claahsen-van der Grinten HL; Nordenstrom A; Holterhus PM; Kohler B; Niedziela M; Krone N. OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present Journal of Clinical Endocrinology & Metabolism. 102(3):1044-1050, 2017 Mar 01. [Journal Article]
UI: 28359094
Context: It is well established that boys are heavier than girls at birth. Although the cause of birth weight (BW) difference is unknown, it has been proposed that it could be generated from prenatal androgen action.

Objective: The aim of the current study was to determine the BW of children with disorders of sex development (DSD) of different etiologies and to evaluate the effects of androgen action on BW.

Methods: Data regarding diagnosis, BW, gestational age, karyotype, and concomitant conditions were collected from the International Disorders of Sex Development (I-DSD) Registry (www.i-dsd). BW standard deviation score was calculated according to gestational age. Cases were evaluated according to disorder classification in I-DSD (i.e., disorders of gonadal development, androgen excess, androgen synthesis, androgen action, nonspecific disorder of undermasculinization groups, and Leydig cell defect).

Results: A total of 533 cases were available; 400 (75%) cases were 46,XY, and 133 (25%) cases were 46,XX. Eighty cases (15%) were born small for gestational age (SGA). Frequency of SGA was higher in the 46,XY group (17.8%) than in the 46,XX (6.7%) group (P = 0.001). Mean BW standard deviation scores of cases with androgen excess and androgen deficiency [in disorders of gonadal development, androgen synthesis, and Leydig cell defect groups and androgen receptor gene (AR) mutation-positive cases in disorders of androgen action groups] were similar to normal children with the same karyotype. SGA birth frequency was higher in the AR mutation-negative cases in disorders of androgen action group and in the nonspecific disorders of the undermasculinization group.

Conclusions: BW dimorphism is unlikely to be explained by fetal androgen action per se. 46,XY DSDs due to nonspecific disorders of undermasculinization are more frequently associated with fetal growth restriction, SGA, and concomitant conditions.

Status
In-Data-Review

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Poyrazoglu, Sukran; Darendeliler, Feyza; Ahmed, S Faisal; Hughes, Ieuan; Bryce, Jillian; Jiang, Jipu; Rodie, Martina; Hiort, Olaf; Hannema, Sabine E; Bertelloni, Silvano; Lisa, Lidka; Guran, Tulay; Cools, Martine; Desloovere, An; Claahsen-van der Grinten, Hedi L; Nordenstrom, Anna; Holterhus, Paul-Martin; Kohler, Birgit; Niedziela, Marek; Krone, Nils.

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20170330
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2017

73.
Pregnancy and Delivery in the Sequel of Kidney Transplantation: Single-Center Study of 8 Years' Experience.
Yuksel Y; Tekin S; Yuksel D; Duman I; Sarier M; Yucetin L; Turan E; Celep H; Ugurlu T; Inal MM; Asuman YH; Demirbas A.
BACKGROUND: Depending on hypothalamic, hypophyseal, and gonadal axis dysfunction, anovulatory irregular cycles occur and the probability of pregnancy decreases in the patients with chronic kidney disease (CKD). Maternal mortality and morbidity rates are increased in CKD patients; the risk of premature delivery is 70% and the risk of preeclampsia is 40% more than normal among those with a creatine level of >2.5 mg/dL.

METHODS: If a pregnancy is expected in the sequel of kidney transplantation (KT), a multidisciplinary team approach should be adopted and both the gynecologist and the nephrologist should follow the patient simultaneously. Among 3883 patients who underwent KT at Antalya Medical Park Hospital Transplantion Department between November 2009 and October 2016, the records of 550 female patients between the ages of 18 and 40 years were examined retrospectively; 31 patients who complied with these criteria were included in the study group. In 6 of these patients who had an unplanned pregnancy, medical abortion was performed after the families were informed about the possible fetal anomalies caused by the use of everolimus in the first trimester, and they were excluded from the study (pregnant group). The control group consisted of 43 patients who had a KT and became pregnant, and of those who had recently undergone KT and shared similarities regarding age, CKD etiology, duration of dialysis, and number of transplants.

RESULTS: In both groups, the ages of the patients, their follow-up span and dialysis duration, tissue compatibility, age of the donor, and time elapsed until the pregnancy was analyzed, whereas in the control group, creatinine levels in the first, second, third, and fourth years after the KT were reviewed. Additionally, in the pregnant group, creatinine levels of the first, second, and third trimesters; delivery week; birth weight of the baby; APGAR scores of the first minute; postnatal creatinine levels of first, second, and third years; and prenatal, maternal, and postnatal acute rejections were reviewed. We measured the creatine clearance by use of the Cockcroft-Gault formula in the pregnancy group before pregnancy and during delivery [Cockcroft-Gault formula: (140 - age) x body weight (kg)/72 x plasma creatine level (mg/dL) x 0.85].

CONCLUSIONS: Pregnancy after KT is risky both for the mother and the baby; however, if planned and followed in coordination within an experienced center, both the pregnancy period and the birth process can occur without distress.

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Status
In-Process
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20170325

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2017

74.
Treatment of Hypogonadism: Current and Future Therapies. [Review]
Thirumalai A; Berkseth KE; Amory JK.
The treatment of hypogonadism in men is of great interest to both patients and providers. There are a number of testosterone formulations currently available and several additional formulations under development. In addition, there are some lesser-used alternative therapies for the management of male hypogonadism, which may have advantages for certain patient groups. The future of hypogonadism therapy may lie in the development of selective androgen receptor modulators that allow the benefits of androgens whilst minimizing unwanted side effects.

Status
In-Data-Review

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20170202

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2017

75.
Short-term buserelin administration induces apoptosis and morphological changes in adult rat testes.
Khadivi B; Peirouvi T; Javanmardl MZ; Rasmi Y.
PURPOSE: To investigate the effect of buserelin on gonadal structure and function in adult male rats.

METHODS: Twenty-four adult Wistar male rats were divided into three groups: two treated groups and controls. The first and second treated groups received 300 (low dose) and 500 (high dose) micro g/kg buserelin, respectively, and the control group received normal saline. All groups were treated subcutaneously for five days.

RESULTS: The seminiferous tubular epithelial thickness was significant decreased in the treated groups compared with those in the control. There was a significant increase in apoptotic cell death in high dose treated group compared with low dose treated and control groups. No significant difference in serum testosterone level was observed after one month in the three groups.

CONCLUSION: Buserelin induces apoptotic cell death and decreased diameter and epithelium thickness of seminiferous tubules in the adult rat testes.
An open-label clinical trial to investigate the efficacy and safety of corifollitropin alfa combined with hCG in adult men with hypogonadotropic hypogonadism.

Nieschlag E; Bouloux PG; Stegmann BJ; Shankar RR; Guan Y; Tzontcheva A; McCrary Sisk C; Behre HM.


[Journal Article]
UI: 28270212

BACKGROUND: Hypogonadotropic hypogonadism (HH) in men results in insufficient testicular function and deficiencies in testosterone and spermatogenesis. Combinations of human chorionic gonadotropin (hCG) and recombinant follicle-stimulating hormone (recFSH) have been successful in the treatment of HH. Corifollitropin alfa is a long-acting FSH-analog with demonstrated action in women seeking infertility care. The aim of this study was to investigate the efficacy and safety of corifollitropin alfa combined with hCG to increase testicular volume and induce spermatogenesis in men with HH.

METHODS: This was a Phase III, multi-center, open-label, single-arm trial of corifollitropin alfa in azoospermic men aged 18 to 50 years with HH. After 16 weeks of pretreatment of 23 subjects with hCG alone, 18 subjects with normalized testosterone (T) levels who remained azoospermic entered the 52-week combined treatment phase with hCG twice-weekly and 150 mug corifollitropin alfa every other week. The increase in testicular volume (primary efficacy endpoint) and induction of spermatogenesis resulting in a sperm count >=1x10^6/mL (key secondary efficacy endpoint) during 52 weeks of combined treatment were assessed. Safety was evaluated by the presence of anti-corifollitropin alfa antibodies and the occurrence of adverse events (AEs).

RESULTS: Mean (+/-SD) testicular volume increased from 8.6 (+/-6.09) mL to 17.8 (+/-8.93) mL (geometric mean fold increase, 2.30 [95% CI: 2.03, 2.62]); 14 (77.8%) subjects reached a sperm count >=1x10^6/mL. No subject developed confirmed anti-corifollitropin alfa antibodies during the trial. Treatment was generally well tolerated.

CONCLUSIONS: Corifollitropin alfa 150 mug administrated every other week combined with twice-weekly hCG for 52 weeks increased testicular volume significantly, and induced spermatogenesis in >75% of men with HH who had remained azoospermic after hCG treatment alone.

TRIAL REGISTRATION: ClinicalTrials.gov: NCT01709331.
77.
Effects of environmentally relevant concentrations of the anti-inflammatory drug diclofenac in freshwater fish Rhamdia quelen.
Guioski IC; Stein Piancini LD; Dagostim AC; de Morais Calado SL; Favaro LF; Boschen SL; Cestari MM; da Cunha C; Silva de Assis HC.
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Ecotoxicology & Environmental Safety. 139:291-300, 2017 May.
[Journal Article]
UI: 28167441
The presence of pharmaceuticals in the aquatic environment and its impact on humans and the ecosystem are emerging issues in environmental health. This study evaluated the potential biochemical, genetic and reproductive effects of the diclofenac by waterborne exposure, in a semi-static bioassay for 21 days. The fish Rhamdia quelen were exposed to environmental concentrations of diclofenac (0, 0.2, 2 and 20 micro g/L). The results showed that in the liver, diclofenac reduced the catalase and ethoxyresorufin-O-deethylase activities in fish exposed to 2 micro g/L, and superoxide dismutase in all exposed groups. The levels of reduced glutathione and glutathione S-transferase (GST) activity increased at all tested concentrations. Lipid peroxidation (LPO) was reduced in the groups exposed to 0.2 and 20 micro g/L of diclofenac, but there was no protein oxidation. In the testis, the concentration of 0.2 micro g/L caused major changes as inhibition of SOD, glutathione peroxidase and GST activities and also LPO decrease. Diclofenac was not genotoxic and not altered plasma testosterone and estradiol levels and testicular morphology. In brain, there was a reduction of dopamine and its metabolite DOPAC (3, 4-dihydroxyphenylacetic acid) in exposure to diclofenac, but this not disrupted the hypothalamic-pituitary-gonadal axis.

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Status
In-Process

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78.
Estrogens regulate glycosylation of IgG in women and men.
Ercan A; Kohrt WM; Cui J; Deane KD; Pezer M; Yu EW; Hausmann JS; Campbell H; Kaiser UB; Rudd PM; Lauc G; Wilson JF; Finkelstein JS; Nigrovic PA.
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[Journal Article]
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The immunologic potency of IgG is modulated by glycosylation, but mechanisms regulating this process are undefined. A role for sex hormones is suggested by differences in IgG glycans between women and men, most prominently with respect to galactose. We therefore assessed IgG galactosylation in 713 healthy adults from 2 cohorts as well as in 159 subjects from 4 randomized controlled studies of endocrine manipulation: postmenopausal women receiving conjugated estrogens, raloxifene, or placebo; premenopausal women deprived of gonadal hormones with leuprolide and treated with estradiol or placebo; men deprived of gonadal hormones with goserelin and given testosterone or placebo; and men deprived of gonadal hormones with goserelin and given testosterone or placebo together with anastrozole to block conversion of testosterone to estradiol. Menopause was associated with an increase in agalactosylated IgG glycans, particularly in the most abundant fucosylated nonbisected (G0F) glycoform. Conjugated estrogens and raloxifene reduced G0F glycans in postmenopausal women, while in premenopausal women leuprolide increased G0F glycans in a manner reversed
by estradiol. Among men, goserelin increased G0F glycans, an effect blocked by testosterone through conversion to estradiol. These results establish estrogens as an in vivo modulator of IgG galactosylation in both women and men, defining a pathway by which sex modulates immunity.

Status
In-Data-Review

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Nesfatin-1 modulates murine gastric vagal afferent mechanosensitivity in a nutritional state dependent manner.

Kentish SJ; Li H; Frisby CL; Page AJ.

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[Journal Article]
UI: 28087413

Food intake is regulated by vagal afferent signals from the stomach. Nesfatin-1 is an anorexigenic peptide produced within the gastrointestinal tract and has well defined central effects. We aimed to determine if nesfatin-1 can modulate gastric vagal afferent signals in the periphery and further whether this is altered in different nutritional states. Female C57BL/6J mice were fed either a standard laboratory diet (SLD) or a high fat diet (HFD) for 12 weeks or fasted overnight. Plasma nucleobindin-2 (NUCB2; nesfatin-1 precursor)/nesfatin-1 levels were assayed, the expression of NUCB2 in the gastric mucosa and adipose tissue was assessed using real-time quantitative reverse-transcription polymerase chain reaction. An in vitro preparation was used to determine the effect of nesfatin-1 on gastric vagal afferent mechanosensitivity. HFD mice exhibited an increased body weight and adiposity. Plasma NUCB2/nesfatin-1 levels were unchanged between any of the groups of mice. NUCB2 mRNA was detected in the gastric mucosa and gonadal fat of SLD, HFD and fasted mice with no difference in mRNA abundance between groups in either
tissue. In SLD and fasted mice nesfatin-1 potentiated mucosal receptor mechanosensitivity, an effect not observed in HFD mice. Tension receptor mechanosensitivity was unaffected by nesfatin-1 in SLD and fasted mice, but was inhibited in HFD mice. In conclusion, Nesfatin-1 modulates gastric vagal afferent mechanosensitivity in a nutritional state dependent manner.

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In-Data-Review
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Effects of two-year testosterone replacement therapy on cognition, emotions and quality of life in young and middle-aged hypogonadal men.
Lasaite L; Ceponis J; Preiksa RT; Zilaitiene B.
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Andrologia. 49(3), 2017 Apr.
[Clinical Trial. Journal Article]
UI: 27545990
The aim of the study was to examine the effects of two-year testosterone replacement therapy on cognitive functioning, emotional state and quality of life in young and middle-aged men with hypogonadotropic hypogonadism. Nineteen males diagnosed with hypogonadotropic hypogonadism participated in the study. Cognitive functions were assessed by Trail Making Test and Digit Span Test of Wechsler Adult Intelligence Scale. Emotional state was evaluated by Profile of Mood States. Quality of life was evaluated by WHO Brief Quality of Life Questionnaire. Changes after two-year testosterone replacement therapy were detected in Trail Making A (42.9 +/- 22.3 vs. 36.2 +/- 22.5, p = .050) and B (90.6 +/- 55.3 vs. 65.6 +/- 21.4, p = .025) tests, showing improvement in attention and visual scanning abilities, executive function and psychomotor speed, as well as in Digit Span Test forward score (5.4 +/- 2.0 vs. 6.1 +/- 2.6, p = .046), showing improvement in attention capacity and psychomotor speed. No significant differences were observed in emotional state and quality of life. In conclusion, beneficial effect in cognitive functioning (improved attention and visual scanning ability, executive function and psychomotor speed), but not in emotional state and quality of life, was observed in young and middle-aged hypogonadal men after two-year testosterone replacement therapy. Copyright © 2016 Blackwell Verlag GmbH.
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Date Created
The Clinical Characteristics of Obese Patients with Acanthosis Nigricans and Its Independent Risk Factors.
Huang Y; Chen J; Wang X; Li Y; Yang S; Qu S.
[Clinical Trial. Journal Article]
UI: 28081576
Objective: This study aimed to investigate the clinical characteristics and risk factors for acanthosis nigricans (AN) in obese patients. Methods: 80 obese patients without AN (OB group) and 128 obese patients with AN (AN group) were included in this study. Clinical data for each patient were collected. Serum levels of leptin were measured by ELISA. Results: Body mass index (BMI), uric acid (UA) levels, fasting insulin, and HOMA-IR were higher in AN than OB (P<0.05). The levels of leptin were significantly higher in AN than OB (P<0.001) after adjustment for BMI and gender. In male patients, AN showed lower serum levels of testosterone than OB (P<0.001). Multiple Logistic-regression analysis demonstrated that UA (OR 4.627, 95%CI 2.443-8.762, P<0.001) and Leptin (OR 4.098, 95%CI 1.237-13.581, P=0.021) were independent risk factors for AN. In addition, low testosterone level was an independent risk factor for AN in male obese patients (OR 39.062, 95%CI 5.523-283.808, P<0.001). Conclusions: AN is associated with more severe hyperinsulinemia and hyperuricemia in obese patients, as well as lower serum testosterone levels in male patients. UA and Leptin were independent risk factors for AN in obese patients. Low testosterone may be a valuable predictor of AN in male obese patients.
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Status
MEDLINE
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Huang, Yueye; Chen, Jiaqi; Wang, Xingchun; Li, Yan; Yang, Shezhen; Qu, Shen.
Institution
Lipid Accumulation Product (LAP) as an Index of Metabolic and Hormonal Disorders in Aging Men.

Rotter I; Ryl A; Szyllinska A; Pawlukowska W; Lubkowska A; Laszczynska M.

Lipid accumulation product (LAP) is an index used for evaluating lipid overaccumulation in adults. Our study aimed at assessing associations between LAP and metabolic syndrome (MetS) and its components, age-related testosterone deficiency syndrome (TDS), low-density cholesterol (LDL), as well as HOMA-IR (insulin resistance ratio), insulin level in non-diabetics and total testosterone (TT), estradiol E2, dehydroepiandrosterone sulphate (DHEAs) and sex hormone-binding globulin (SHBG) in aging men. 313 men aged 50-75 were surveyed with regard to the prevalence of diabetes (T2DM) and hypertension (HT). Anthropometric measurements, including waist circumference and arterial pressure, were performed. We also determined the levels of fasting
plasma glucose (FPG), total cholesterol (TC), high-density cholesterol (HDL), low-density cholesterol (LDL), triglyceride (TG), insulin, TT, SHBG, DHEAs, and E2. Patients with diagnosed MetS, T2DM, HT, obesity, overweight and TDS had a significantly higher LAP compared to those without these conditions. LAP was significantly positively correlated with serum TC, FPG, insulin, DHEAs, as well as APB-systolic concentration, and negatively correlated with HDL, TT, and SHBG. LAP may then be used as a simple and inexpensive biomarker of metabolic disorders, and in risk assessment related to testosterone deficiency in aging men.

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83.

Sex steroids in relation to cardiac structure and function in men. [Review]
De Smet MA; Lapauw B; De Backer T.
The prevalence of testosterone substitution as well as of androgen deprivation therapy in men is increasing. This review aims to summarise available knowledge of the effects of sex steroids on cardiac structure and function in men. MEDLINE was searched through PubMed. Original studies, systematic reviews and meta-analyses, and relevant citations were screened. A short-term hormonal intervention study in healthy young men with respect to echocardiographic parameters of structure and function was performed. Preclinical research provides sufficient evidence for the heart as a substrate for sex hormones. In animals, administration of oestradiol appears to have beneficial effects on cardiac structure and function, whereas administration of testosterone to noncastrated animals adversely affects cardiac function. However, the effects of sex steroids on cardiac function and structure appear more heterogeneous in human observational studies while comparative, prospective studies in humans are lacking. It is concluded that although effects of testosterone substitution as well as of androgen deprivation on cardiac structure and function can be expected based on pre-clinical research, there exists an important knowledge gap of the effects of hormonal intervention in men. As such, there is a need to address this question in future prospective intervention trials.

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84.

Effects of two-year testosterone replacement therapy on cognition, emotions and quality of life in young and middle-aged hypogonadal men.

Lasaite L; Ceponis J; Preiksa RT; Zilaitiene B.

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Andrologia. 49(3), 2017 Apr.

[Clinical Trial. Journal Article]

UI: 27545990

The aim of the study was to examine the effects of two-year testosterone replacement therapy on cognitive functioning, emotional state and quality of life in young and middle-aged men with hypogonadotropic hypogonadism. Nineteen males diagnosed with hypogonadotropic hypogonadism participated in the study. Cognitive functions were assessed by Trail Making Test and Digit Span Test of Wechsler Adult Intelligence Scale. Emotional state was evaluated by Profile of Mood States. Quality of life was evaluated by WHO Brief Quality of Life Questionnaire.

Changes after two-year testosterone replacement therapy were detected in Trail Making A (42.9 +/- 22.3 vs. 36.2 +/- 22.5, p = .050) and B (90.6 +/- 55.3 vs. 65.6 +/- 21.4, p = .025) tests, showing improvement in attention and visual scanning abilities, executive function and psychomotor speed, as well as in Digit Span Test forward score (5.4 +/- 2.0 vs. 6.1 +/- 2.6, p = .046), showing improvement in attention capacity and psychomotor speed. No significant differences were observed in emotional state and quality of life. In conclusion, beneficial effect in cognitive functioning (improved attention and visual scanning ability, executive function and psychomotor speed), but not in emotional state and quality of life, was observed in young and middle-aged hypogonadal men after two-year testosterone replacement therapy.

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Sex steroids in relation to cardiac structure and function in men. [Review]
De Smet MA; Lapauw B; De Backer T.
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Andrologia. 49(2), 2017 Mar.
[Journal Article. Review]
Ui: 27135437
The prevalence of testosterone substitution as well as of androgen deprivation therapy in men is increasing. This review aims to summarise available knowledge of the effects of sex steroids on cardiac structure and function in men. MEDLINE was searched through PubMed. Original studies, systematic reviews and meta-analyses, and relevant citations were screened. A short-term hormonal intervention study in healthy young men with respect to echocardiographic parameters of structure and function was performed. Preclinical research provides sufficient evidence for the heart as a substrate for sex hormones. In animals, administration of oestradiol appears to have beneficial effects on cardiac structure and function, whereas administration of testosterone to noncastrated animals adversely affects cardiac function. However, the effects of sex steroids on cardiac function and structure appear more heterogeneous in human observational studies while comparative, prospective studies in humans are lacking. It is concluded that although effects of testosterone substitution as well as of androgen deprivation on cardiac structure and function can be expected based on pre-clinical research, there exists an important knowledge gap of the effects of hormonal intervention in men. As such, there is a need to address this question in future prospective intervention trials.
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Status
MEDLINE
Association between sex and speech auditory brainstem responses in adults, and relationship to sex hormone levels.

Background: The aim of this study was to investigate the association between sex and speech-ABR in adults, and its relationship to sex hormone levels. Material/Methods: Speech-ABR were elicited with the consonant-vowel syllable (/da/) in a total of 35 adults. Reproductive hormone levels were also measured. Results: The transient response of the speech-ABR (waves V, A, and O) in females show a shorter latency (waves V, A and O) and a larger amplitude (waves V and A) than in males (P<0.05), except for the amplitude of peak O (P>0.05). The sustained response of females exhibited a larger amplitude (wave F, P<0.05) and a shorter latency (wave D, E, and F, P<0.05) than in males, except for the amplitude of peak D and E (P>0.05). The latencies of speech-ABR were positively correlated with testosterone level (P<0.05), and were negatively correlated with estradiol (E2) levels (P<0.05), except for wave E (P>0.05). The E2 showed a positive correlation with the absolute value of amplitude of the speech-ABR (P < 0.05). On the contrary, total testosterone showed a negative correlation with the absolute value of amplitude the speech-ABR (P<0.05), except for wave D and wave O (P>0.05). Conclusions: Sex differences in speech-ABR are significant in adults. The latencies and amplitude of the speech-ABR waves
were correlated with the E2 concentration and testosterone level. The sex hormones likely affect speech encoding in the brainstem.

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Status
EMBASE

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87.
Oxidative stress status in congenital hypogonadism: an appraisal.
Haymana C., Aydogdu A., Soykut B., Erdem O., Ibrahimov T., Dinc M., Meric C., Basaran Y., Sonmez A., Azal O.

Embase

[Article]
AN: 615879469

Patients with hypogonadism are at increased risk of cardiac and metabolic diseases. However, the pathogenesis of increased cardiometabolic risk in patients with hypogonadism is not clear. Oxidative stress plays an important role in the pathogenesis of cardiometabolic diseases. This study aimed to investigate possible differences in oxidative stress conditions between patients with hypogonadism and healthy controls. In this study, 38 male patients with congenital hypogonadotrophic hypogonadism (CHH) (mean age: 21.7 +/- 1.6 years) and 44 healthy male controls (mean age: 22.3 +/- 1.4 years) with almost equal body mass index were enrolled. The demographic parameters, follicle-stimulating hormone (FSH), luteinizing hormone (LH), total and free testosterone, homeostatic model assessment of insulin resistance (HOMA-IR) and oxidative
stress parameters, such as superoxide dismutase, catalase (CAT), glutathione peroxidase (GPx) and malondialdehyde (MDA), were compared between both groups. Compared to the healthy controls, triglycerides (p = .02), insulin levels, HOMA-IR values, CAT activities and MDA levels (p < .001 for all) were significantly higher and HDL cholesterol (p = .04), total and free testosterone, FSH, LH levels and GPx activity were significantly lower (p < .001 for all) in patients with CHH. There were significant correlations between total testosterone levels and CAT activity (r = -.33 p = .01), GPx activity (r = .36 p = .007) and MDA (r = -.47 p < .001) levels. The results of this study showed that young and treatment-naive patients with congenital hypogonadism had an increased status of oxidative stress.

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Normalization of testosterone levels after testosterone replacement therapy is associated with decreased incidence of atrial fibrillation.


Embase
Background-Atrial fibrillation (AF) is the most common cardiac dysrhythmia associated with significant morbidity and mortality. Several small studies have reported that low serum total testosterone (TT) levels were associated with a higher incidence of AF. In contrast, it is also reported that anabolic steroid use is associated with an increase in the risk of AF. To date, no study has explored the effect of testosterone normalization on new incidence of AF after testosterone replacement therapy (TRT) in patients with low testosterone.

Methods and Results-Using data from the Veterans Administrations Corporate Data Warehouse, we identified a national cohort of 76 639 veterans with low TT levels and divided them into 3 groups. Group 1 had TRT resulting in normalization of TT levels (normalized TRT), group 2 had TRT without normalization of TT levels (nonnormalized TRT), and group 3 did not receive TRT (no TRT). Propensity score-weighted stabilized inverse probability of treatment weighting Cox proportional hazard methods were used for analysis of the data from these groups to determine the association between post-TRT levels of TT and the incidence of AF. Group 1 (40 856 patients, median age 66 years) had significantly lower risk of AF than group 2 (23 939 patients, median age 65 years; hazard ratio 0.90, 95% CI 0.81-0.99, P = 0.0255) and group 3 (11 853 patients, median age 67 years; hazard ratio 0.79, 95% CI 0.70-0.89, P = 0.0001). There was no statistical difference between groups 2 and 3 (hazard ratio 0.89, 95% CI 0.78-1.0009, P = 0.0675) in incidence of AF. Conclusions-These novel results suggest that normalization of TT levels after TRT is associated with a significant decrease in the incidence of AF.

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Status

EMBASE

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89.
Evidence-based management of systemic sclerosis: Navigating recommendations and guidelines.
Pellar R.E., Pope J.E.
Embase Seminars in Arthritis and Rheumatism. 46 (6) (pp 767-774), 2017. Date of Publication: June 2017.
[Review]
AN: 614109369
Objectives Systemic sclerosis (SSc) is a rare heterogeneous connective tissue disease.
Recommendations addressing the major issues in the management of SSc including screening and treatment of organ complications are needed. Methods The updated European League Against Rheumatism/European Scleroderma Trial and Research (EULAR/EUSTAR) and the British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guidelines were compared and contrasted. Results The updated EULAR/EUSTAR guidelines focus specifically on the management of SSc features and include data on newer therapeutic modalities and mention a research agenda. These recommendations are pharmacologic, with few guidelines regarding investigations and non-pharmacologic management. Recommendations from BSR/BHPR are similar to the organ manifestations mentioned in the EULAR/EUSTAR recommendations, and expand on several domains of treatment, including general measures, non-pharmacologic treatment, cardiac involvement, calcinosis, and musculoskeletal features. The guidelines usually agree with one another. Limitations include the lack of guidance for combination or second-line therapy, algorithmic suggestions, the absence of evidence-based recommendations regarding the treatment of specific complications (i.e., gastric antral ectasia and erectile dysfunction). Consensus for when to treat interstitial lung disease in SSc is lacking. There are differences between Europe and North American experts due to access and indications for certain therapies. Conclusions Care gaps in SSc have been demonstrated so the
EULAR/EUSTAR and BSR/BHP guidelines can promote best practices. Certain complications warrant active investigation to further improve outcomes in SSc and future updates of these recommendations. Care gaps in SSc have been demonstrated so the EULAR/EUSTAR and BSR/BHP guidelines can promote best practices. Certain complications warrant active investigation to further improve outcomes in SSc.

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90.
Comparison of the clinical parameters of benign prostate hyperplasia in diabetic and non diabetic patients.
Ozcan L., Besiroglu H., Dursun M., Polat E.C., Otunctemur A., Ozbek E.
Embase
[Article]
AN: 616229795
Objective: We evaluated the correlation between benign prostate hyperplasia (BPH) measures and diabetes mellitus in men with benign prostate hyperplasia in a prospective study. Materials and methods: Between 2008-2012, 100 diabetic and 200 non diabetic patients undergoing surgery due to benign prostate hyperplasia were enrolled in the study. The parameters evaluated for each patients included prostate volume, fasting blood glucose, HbA1c, total testosterone, total prostatic specific antigen (T-PSA), triglycerides, total cholesterol and body mass index (BMI). A questionnaire including international prostate symptom score (IPSS) was administered and
uroflow test measuring the peak urinary flow rate was performed to appreciate the complaints of
the patients objectively. Results: Diabetic patients are more likely to have larger prostate volume.
The symptom score evaluated by IPSS and post micturition residual volume were also
significantly higher in diabetic groups. The other statistically significant different parameter
between two groups was total testosterone that diabetic patients tend to have lower levels.
Diabetic counterparts were established to have higher BMI. No statistically significant
differentiation was observed about triglyceride and total cholesterol levels and uroflow rates.
Conclusions: Our study suggests a positive correlation between high prostate volume and
diagnosis of diabetes mellitus in patients with benign prostatic hyperplasia. We also observed a
positive correlation between symptom scores and post micturion residual volumes and diagnosis
of diabetes mellitus suggesting that the presence of diabetes is related to both static and dynamic
components of benign prostate hyperplasia. Additionally testosterone levels were lower in
diabetic patients. Further studies need to confirm these relationship in a larger population.

91.
Genotoxic effect of iron overload and disease complications in transfused beta thalassaemic
patients.

Embase
In previously reported studies, we observed significantly high genotoxicity biomarkers in regularly transfused thalassaemic patients, thus, in this study, we better investigated the genotoxic effect of iron overload and of thalassaemia complications, including their drug treatments. The assessment was performed in 64 regularly transfused thalassaemic patients using cytokinesis-block micronucleus and comet assays. All patients were splenectomised and undergoing iron chelation therapy. To reduce hypoxia-induced oxidative damage, the patients with haemoglobin levels <9.5 g/dL were excluded. Serum concentrations of ferritin, iron, transferrin and the percentage of transferrin saturation, as well as cardiac and hepatic T2* magnetic resonance imaging, were considered to evaluate serum and organ siderosis. All genotoxic biomarkers significantly differed between patients and healthy subjects. Iron intake via blood transfusions was inversely related to percentage of DNA in tail. The disease complications affecting endpoints were active Hepatitis C virus infection, drug therapy for osteoporosis (i.e. bisphosphonates) and hormone replacement therapy for hypogonadism. The results, highlighting the combined effect of iron overload and, mainly, disease complications, including their respective pharmacological treatments, confirmed the increased cancer risk in thalassaemic patients.

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Paracetamol causes endocrine disruption and hepatotoxicity in male fish Rhamdia quelen after subchronic exposure.


Embase
Environmental Toxicology and Pharmacology. 53 (pp 111-120), 2017. Date of Publication: July 2017.

[Article]
AN: 616313480

Paracetamol is one of the most widely sold non-prescription drugs. This study aimed to evaluate the effects of the paracetamol on reproductive, biochemical, genetic, histopathological and hematological biomarkers by waterborne exposure. Male fish of Rhamdia quelen were exposed to environmental concentrations of paracetamol (0, 0.25, 2.5 mug/L) in a semi-static bioassay for 21 days. Hemoglobin and hematocrit were reduced upon exposure to 0.25 mug/L of paracetamol. Leukocytes and thrombocytes increased after paracetamol exposure. Paracetamol reduced testosterone levels in all exposed groups and increased estradiol levels at higher concentration. Serotonin and dopamine levels increased at exposure to 0.25 mug/L. Paracetamol also caused protein carbonyls and increased SOD activity in fish exposed to 2.5 mug/L and in addition led to an inhibition of EROD and GST activities in both concentrations. Hepatic genotoxicity occurred at the 0.25 mug/L concentration. Hepatic tissues of exposed fish showed mild blood congestion and leucocytes infiltration. The results showed that paracetamol disrupted the hypothalamic-pituitary-gonadal axis, changed hematological parameters and caused hepatotoxicity in Rhamdia quelen. The findings suggest that this drug merits attention relative to its potential endocrine disrupter effect and hepatotoxicity, even at concentrations found in the aquatic environment.

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Effects of transdermal testosterone gel or an aromatase inhibitor on serum concentration and pulsatility of growth hormone in older men with age-related low testosterone.

Dias J.P., Veldhuis J.D., Carlson O., Shardell M., Chia C.W., Melvin D., Egan J.M., Basaria S.

Embase
Metabolism: Clinical and Experimental. 69 (pp 143-147), 2017. Date of Publication: 01 Apr 2017. [Article]
AN: 614237419

Growth hormone is the major regulator of growth and body composition. Pulsatile GH secretion declines exponentially with age. Testosterone replacement is being increasingly offered to older men with age-related low testosterone. Testosterone administration has been shown to stimulate GH secretion. However, little is known about the effect of testosterone aromatization to estradiol on GH pulsatility and its impact on IGF-1 in older men. Objective This randomized controlled proof-of-concept trial investigated the relative effects of testosterone and estradiol on GH pulsatility and IGF-1 in older men with low testosterone. Design Thirty-seven men, >= 65 years with total testosterone < 350 ng/dL were randomized to 5 g transdermal testosterone gel (TT), 1 mg oral aromatase inhibitor (AI) or placebo daily for 12 months. Primary outcome was deconvolution and approximate entropy analyses of pulsatile including basal and entropic modes of secretion performed at baseline and 3 months. Secondary outcomes included IGF-1 evaluated at baseline, 3 and 6 months. Results At 3 months, mean GH and in IGF-1 were similar between the three groups. At 6 months, IGF-1 significantly increased by DELTA 15.3 +/- 10.3 ng/ml in the TT-group compared to placebo (P = 0.03). Both intervention groups significantly increased GH pulse frequency (TT-group, P = 0.04; AI-group, P = 0.05) compared to placebo. The GH secretory-burst mode (duration) significantly decreased in the TT-group (P = 0.0018) compared to placebo while it remained unchanged in the AI-group (P = 0.059). Conclusions In older men,
testosterone increases GH pulse frequency while the aromatization to estradiol is involved in the rise of IGF-1 levels.

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2017

94.
Physiological and psychological effects of testosterone during severe energy deficit and recovery: A study protocol for a randomized, placebo-controlled trial for Optimizing Performance for Soldiers (OPS).

Embase

Contemporary Clinical Trials. 58 (pp 47-57), 2017. Date of Publication: 01 Jul 2017.

[Article]
AN: 615989391
Background The physiological consequences of severe energy deficit include hypogonadism and the loss of fat-free mass. Prolonged energy deficit also impacts physical performance, mood, attentiveness, and decision-making capabilities. This study will determine whether maintaining a eugonadal state during severe, sustained energy deficit attenuates physiological decrements and maintains mental performance. This study will also assess the effects of normalizing testosterone levels during severe energy deficit and recovery on gut health and appetite regulation. Methods Fifty physically active men will participate in a 3-phase, randomized, placebo-controlled study. After completing a 14-d, energy-adequate, diet acclimation phase (protein: 1.6 g . kg\(^{-1}\) . d\(^{-1}\); fat: 30% total energy intake), participants will be randomized to undergo a 28-d, 55% energy deficit phase with (DEF + TEST: 200 mg testosterone enanthate per week) or without (DEF) exogenous testosterone. Diet and physical activity will be rigorously controlled. Recovery from the energy deficit (ad libitum diet, no testosterone) will be assessed until body mass has been recovered within +/- 2.5% of initial body mass. Body composition, stable isotope methodologies, proteomics, muscle biopsies, whole-room calorimetry, molecular biology, activity/sleep monitoring, personality and cognitive function assessments, functional MRI, and comprehensive biochemistries will be used to assess physiological and psychological responses to energy restriction and recovery feeding while volunteers are in an expected hypogonadal versus eugonadal state. Discussion The Optimizing Performance for Soldiers (OPS) study aims to determine whether preventing hypogonadism will mitigate declines in physical and mental function that typically occur during prolonged energy deficit, and the efficacy of testosterone replacement on recovery from severe underfeeding. Trial Registration: NCT02734238.

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We investigated the effects of testosterone replacement therapy (TRT) on metabolic factors among hypogonadal men with a metabolic syndrome. From the study population of the EARTH study, which was a randomised controlled study in Japan, 65 hypogonadal patients with a metabolic syndrome, comprising the TRT group (n = 32) and controls (n = 33), were included in this study analysis. The TRT group was administered 250mg of testosterone enanthate as an intramuscular injection every 4 weeks for 12 months. Waist circumference, body mass index, body fat volume and blood pressure were measured in all patients at baseline and at 12 months. In addition, blood biochemical data, including total cholesterol, triglyceride (TG), HDL cholesterol, fasting plasma glucose (FPG) and haemoglobin A1c (HbA1c) levels, were also evaluated. Changes in these categories from baseline to 12 months were compared between the TRT and control groups, with significant differences observed in waist circumference, body fat percentage, FPG, TG and HbA1c levels. No significant differences were observed in other parameters. TRT for 1 year was associated with improvements in some metabolic factors among Japanese men with hypogonadism and metabolic syndrome.
96.
Final adult height in long-term growth hormone-treated achondroplasia patients.

Harada D., Namba N., Hanioka Y., Ueyama K., Sakamoto N., Nakano Y., Izui M., Nagamatsu Y.,
Kashiwagi H., Yamamuro M., Ishiura Y., Ogitani A., Seino Y.

Embase
[Article In Press]
AN: 616187150

The objective of this study was to evaluate the gain in final height of achondroplasia (ACH) patients with long-term growth hormone (GH) treatment. We analyzed medical data of 22 adult patients (8 males and 14 females) treated with GH at a dose of 0.05 mg/kg/day. Optionally, tibial lengthening (TL) was performed with the Ilizalov method in 15 patients and TL as well as femoral lengthening (FL) in 6 patients. Concomitant gonadal suppression therapy with buserelin acetate was applied in 13 patients. The mean treatment periods with GH were 10.7 +/- 4.0 and 9.3 +/- 2.5 years for males and females, respectively. GH treatment augmented the final height +0.60 +/- 0.52 SD (+3.5 cm) and +0.51 +/- 1.29 SD (+2.8 cm) in males and females compared to non-treated ACH patients, respectively. Final height of ACH patients that underwent GH and TL increased +1.72 +/- 0.72 SD (+10.0 cm) and +1.95 +/- 1.34 SD (+9.8 cm) in males and females, respectively. GH, TL, and FL increased their final height +2.97 SD (+17.2 cm) and +3.41 +/- 1.63
SD (+17.3 cm) in males and females, respectively. Gonadal suppression therapy had no impact on final height. Conclusions: Long-term GH treatment contributes to 2.6 and 2.1% of final adult height in male and female ACH patients, respectively.

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97.
The testosterone status in overweight young adults of peshawar.

Embase

[Article]
AN: 615948501

Objective: To see whether obesity decreases the testosterone concentration in young male adults, who have no other cause of decreased testosterone. Material & Methods: This was a comparative, case control and cross sectional study conducted in the Department of Biochemistry, Khyber Medical College, Peshawar - Pakistan. The study period was from January 2016 to December 2016, consisting of two groups, A and B, each having 32 subjects. Group A had BMI of >25 Kg/m2 while the control group B had BMI of < 25 Kg/m2. Their testosterone concentrations were compared keeping other confounding factors like age, sex, educational
status and socioeconomic conditions constant. The weight in Kg and height in meters were measured for each subject and then BMI was calculated. A blood sample of approximately 5-ml was collected from each participant. The sera were prepared and stored in labeled tubes which were then properly sealed, placed in racks and were stored in a freezer at -20degreeC till further analysis. The samples were analyzed for serum Testosterone level by Radioimmunoassay (RIA) method. Results: Group A had 32 obese subjects having a BMI 26.9 Kg/m2 with a SD of 1.501. The testosterone concentration of group A is compared with that of control group B having a normal BMI of 21.7 with a SD of 1.557. Testosterone concentrations of the two study groups revealed a significant difference (P< 0.001) when compared by the independent sample t-test. Conclusion: The increase trend of obesity in elderly people and now in young adults should be prevented as it lower serum testosterone concentrations, apart from other hazards like diabetes, hypertension, CVD and osteoarthritis.

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98.
Western-style diet, sex steroids and metabolism.
Varlamov O.
Embase
[Article]
AN: 610761020
The evolutionary transition from hunting to farming was associated with introduction of carbohydrate-rich diets. Today, the increased consumption of simple sugars and high-fat food brought about by Western-style diet and physical inactivity are leading causes of the growing obesity epidemic in the Western society. The extension of human lifespan far beyond reproductive age increased the burden of metabolic disorders associated with overnutrition and age-related hypogonadism. Sex steroids are essential regulators of both reproductive function and energy metabolism, whereas their imbalance causes infertility, obesity, glucose intolerance, dyslipidemia, and increased appetite. Clinical and translational studies suggest that dietary restriction and weight control can improve metabolic and reproductive outcomes of sex hormone-related pathologies, including testosterone deficiency in men and natural menopause and hyperandrogenemia in women. Minimizing metabolic and reproductive decline through rationally designed diet and exercise can help extend human reproductive age and promote healthy aging.

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99.
POEMS Syndrome: an Enigma.
Warsame R., Yanamandra U., Kapoor P.

Embase
Current Hematologic Malignancy Reports. 12 (2) (pp 85-95), 2017. Date of Publication: 01 Apr 2017.
POEMS syndrome is a paraneoplastic disorder secondary to an underlying plasma cell dyscrasia. By definition, all patients with POEMS syndrome must display polyneuropathy and monoclonal plasma cell disorder. In addition, at least one major criterion (Castleman's disease, sclerotic bone lesions, or vascular endothelial growth factor elevation) and one minor criterion (organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema, thrombocytosis, or polycythemia) are required for diagnosis. Treatment is based on extent of the disease. Radiotherapy is used for localized disease. Systemic therapy is required for disseminated disease, with bone marrow involvement by clonal plasma cells, or in patients who progress shortly after radiation. Upfront autologous stem cell transplantation is the treatment of choice for transplant-eligible patients. Outcomes are typically superior to that of standard myeloma. Herein, using a case vignette, we outline the latest evidence regarding the prognostication and management of POEMS syndrome, with a focus on its relapsing-remitting course.


100.
The steroid response to human chorionic gonadotropin (hCG) stimulation in men with Klinefelter syndrome does not change using immunoassay or mass spectrometry.

Embase
AN: 616101211

Purpose: Liquid-chromatography tandem mass-spectrometry (LC-MS/MS) was developed in parallel to Immunoassays (IAs) and today is proposed as the "gold standard" for steroid assays. Leydig cells of men with Klinefelter syndrome (KS) are able to respond to human chorionic gonadotropin (hCG) stimulation, even if testosterone (T) production was impaired. The aim was to evaluate how results obtained by IAs and LC-MS/MS can differently impact on the outcome of a clinical research on gonadal steroidogenesis after hCG stimulation. Methods: A longitudinal, prospective, case-control clinical trial. (clinicaltrial.gov NCT02788136) was carried out, enrolling KS men and healthy age-matched controls, stimulated by hCG administration. Serum steroids were evaluated at baseline and for 5 days after intramuscular injection of 5000 IU hCG using both IAs and LC-MS/MS. Results: 13 KS patients (36 +/- 9 years) not receiving T replacement therapy and 14 controls (32 +/- 8 years) were enrolled. T, progesterone, cortisol, 17-hydroxy-progesterone (17OHP) and androstenedione, were significantly higher using IAs than LC-MS/MS. IAs and LC-MS/MS showed direct correlation for all five steroids, although the constant overestimation detected by IAs. Either methodology found the same 17OHP and T increasing profile after hCG stimulation, with equal areas under the curves (AUCs). Conclusions: Although a linearity between IA and LC-MS/MS is demonstrated, LC-MS/MS is more sensitive and accurate, whereas IA shows a constant overestimation of sex steroid levels. This result suggests the need of reference intervals built on the specific assay. This fundamental difference between these two methodologies opens a deep reconsideration of what is needed to improve the accuracy of steroid hormone assays.

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Fluid intelligence, traits of personality and personality disorders in a cohort of adult KS patients with the classic 47, XXY karyotype.

Liberato D., Granato S., Grimaldi D., Rossi F.M., Tahani N., Gianfrilli D., Anzuini A., Lenzi A., Cavaggioni G., Radicioni A.F.

Purpose: Klinefelter's syndrome (KS) is associated with specific neurobehavioral features and personality traits. The aim of our study was to investigate fluid intelligence, personality traits and personality disorders (PD) and possible correlations with testosterone in a cohort of adult KS patients. Methods: We analyzed 58 adult KS patients with the classic 47, XXY karyotype. The Structured Clinical Interview for axis II disorders was used to assess DSM IV personality disorders. Personality traits were assessed using MMPI-2. Fluid intelligence was tested by using Raven's Standard Progressive Matrices (SPM) Test. Testosterone blood concentration was measured by CMIA. Results: PD prevalence was 31%. Four altered MMPI scales (Social Responsibility, Dominance, Ego Strength and Repression) were found in more than 40% of patients. Overcontrolled hostility and MacAndrew Alcoholism Scale-Revised scales were altered in the PD- group only. Biz-Odd Thinking and Post-Traumatic Stress Disorder scale were
associated with the presence of personality disorder. The raw SPM score was 44 +/- 10.8 without any significant correlation with testosterone. No significant difference in mean age, SPM raw score and MMPI score was observed between eugonadal, hypogonadal and treated patients.

Conclusions: Most KS patients had average fluid intelligence. PD prevalence was higher than in the general population. Testosterone was not correlated with fluid intelligence, personality traits or PD, but a reduction in marital distress was observed in treated patients. This could suggest that testosterone therapy can improve physical symptoms and this effect could also improve relationship abilities and wellness awareness.

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102.

BH4 improves postprandial endothelial function after a high-fat meal in men and postmenopausal women.

Shah Y., Bass L., Davison G.W., Seigler N., Pollock J.S., Thomas J., Harris R.A.

Embase

[Article]
Objective: The timing and duration of menopause is important when evaluating the risk for cardiovascular disease in postmenopausal women, likely related in part to nitric oxide (NO) bioavailability. The flow-mediated dilation (FMD) test is a noninvasive assessment of NO bioavailability in humans, and tetrahydrobiopterin (BH4) is essential for NO synthesis. A high-fat meal (HFM) has been used to increase lipemia and reduce NO bioavailability. Thus, this study sought to determine if menopausal transition has any impact on the postprandial endothelial function response to a HFM, and evaluate the effect of BH4 on postprandial endothelial function in postmenopausal women and men. Methods: Utilizing a randomized, double-blind, placebo-controlled design, sex-steroid hormones and FMD were determined in 30 older adults (10 postmenopausal women aged below 3 y [W < 3], 10 postmenopausal women aged above 10 y [W > 10], and 10 men) at baseline and 4 hours after the ingestion of a HFM alone or a HFM with BH4 (HFM + BH4; 5 mg/kg). Results: Data are presented as mean +/- SEM. Independent of treatment, postprandial testosterone was significantly (P < 0.05) decreased in men (- 64 +/- 11 ng/dL), whereas no changes were observed in W < 3 or W > 10 group. In addition, concentrations of progesterone were higher (P = 0.019) and the testosterone/estradiol ratio was lower (P = 0.026) in all groups after the ingestion of HFM + BH4 compared with the ingestion of HFM alone. Overall, an increase in FMD was observed after the ingestion of HFM + BH4 (DELTA 1.9% +/- 0.6%), whereas no change in FMD was observed after the ingestion of HFM alone (DELTA - 0.7% +/- 0.6%). Conclusions: Coingestion of BH4 with a HFM not only alters the sex-steroid hormone ratio, it improves postprandial FMD after a HFM regardless of postmenopause status or sex.
Diagnostic utility of testosterone priming prior to dynamic tests to differentiate constitutional delay in puberty from isolated hypogonadotropic hypogonadism.

Sukumar S.P., Bhansali A., Sachdeva N., Ahuja C.K., Gorsi U., Jarial K.D.S., Walia R.

Embase
[Article]
AN: 615295888

Context: Differentiation between constitutional delay in puberty (CDP) and isolated hypogonadotropic hypogonadism (IHH) during adolescence is a great clinical challenge, and the available diagnostic tests are of limited value. Objective: To study the effect of withdrawal of short-term, low-dose testosterone therapy (testosterone priming) on the discriminatory power of dynamic tests for hypothalmo-pituitary-testicular axis to differentiate CDP from IHH. Design: A prospective study (n = 30) consisting of 20 boys with delayed puberty (group A) and 10 patients with IHH (group B). Intervention: Patients in groups A and B underwent Triptorelin and hCG stimulation tests, prior to and 2 months after withdrawal of 'testosterone priming' (100 mg intramuscularly 4 weekly for 3 months) and were followed up until the onset of puberty or 18 years of age, whichever was earlier. Results: At baseline, Triptorelin-stimulated 4 h LH, with a cut-off of 2.8 IU/l, and hCG-stimulated day 7 testosterone with a cut-off of 3.8 nmol/l had sensitivities of 80% each, and specificities of 93% and 87%, respectively, to diagnose CDP. After withdrawal of testosterone, a 4 h LH cut-off of 14.7 IU/l and day 7 testosterone cut-off of 10.3 nmol/l had sensitivities of 93% and 88% respectively, and specificity and positive predictive value of 100% each. A basal inhibin B > 94.7 ng/l was discriminatory for diagnosing CDP after withdrawal of testosterone priming. Conclusions: Inhibin B levels or 4 h LH after Triptorelin stimulation are the best discriminatory tests to differentiate CDP from IHH, when performed after withdrawal of 'testosterone priming'.

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The effectiveness of zinc supplementation in men with isolated hypogonadotropic hypogonadism.


A multicenter, open-label, randomized, controlled superiority trial with 18 months of follow-up was conducted to investigate whether oral zinc supplementation could further promote spermatogenesis in males with isolated hypogonadotropic hypogonadism (IHH) receiving sequential purified urinary follicular-stimulating hormone/human chorionic gonadotropin (uFSH/hCG) replacement. Sixty-seven Chinese male IHH patients were recruited from the Departments of Endocrinology in eight tertiary hospitals and randomly allocated into the sequential uFSH/hCG group (Group A, n = 34) or the sequential uFSH plus zinc supplementation group (Group B, n = 33). In Group A, patients received sequential uFSH (75 U, three times a week every other 3 months) and hCG (2000 U, twice a week) treatments. In Group B, patients received oral zinc supplementation (40 mg day-1) in addition to the sequential uFSH/hCG treatment given to patients in Group A. The primary outcome was the proportion of patients with a sperm concentration \( \geq 1.0 \times 106 \) ml-1 during the 18 months. The comparison of efficacy between Groups A and B was analyzed. Nineteen of 34 (55.9\%) patients receiving sequential uFSH/hCG and 20 of 33 (60.6\%) patients receiving sequential uFSH/hCG plus zinc supplementation
achieved sperm concentrations \(\geq 1.0 \times 10^6\) ml\(^{-1}\) by intention to treat analyses. No differences between Group A and Group B were observed as far as the efficacy of inducing spermatogenesis (\(P = 0.69\)). We concluded that the sequential uFSH/hCG plus zinc supplementation regimen had a similar efficacy to the sequential uFSH/hCG treatment alone. The additional improvement of 40 mg day\(^{-1}\) oral zinc supplementation on spermatogenesis and masculinization in male IHH patients is very subtle.

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Apostolidis A., Rantell A., Anding R., Kirschner-Hermanns R., Cardozo L.

Embase
Neurourology and Urodynamics. 36 (4) (pp 869-875), 2017. Date of Publication: April 2017.

[Review]

AN: 615708517

AIM: To discuss available data on the links between LUTD and sexual dysfunction, what is still unknown about the causative effect of disease processes on sexual function (SF), and to suggest proposals for further research. METHODS: At the 2015 International Consultation on Incontinence-Research Society (ICI-RS), a multi-disciplinary group presented a literature search of what is known about the effect of LUTD on SF in men and women. Wider discussions regarding knowledge gaps, and ideal research methodology ensued and are presented.

RESULTS: The underlying mechanisms of the impact of LUTD on SF remain largely unknown. Risk factors for the metabolic syndrome may cause both LUTS and ED in men, and their improvement may improve both conditions. In women, neurovascular changes may be common in LUTD and FSD. Successful LUTS management results in FSD improvement, but the mechanisms are ill understood. Gaps in standardization of sexual dysfunction terminology, variations of assessment, and treatment in clinical practice and research make most studies not comparable. The sensitive knowledge and subjective nature of the problem present challenges and often result in neglecting it. CONCLUSION: Neurovascular and hormonal factors, but also indirect effects may link LUTD to SD in both sexes, but the evidence is not robust and the mechanisms unclear. There is a need for defining the terminology and standardizing outcomes assessed in clinical trials. The multifactorial nature of SF in both sexes makes trial design challenging and "real world" studies may prove more beneficial for patients' outcomes and clinicians' understanding.

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Publisher
Testosterone replacement therapy improves health-related quality of life for patients with late-onset hypogonadism: a meta-analysis of randomized controlled trials.


Embase
Andrologia. 49 (4) (no pagination), 2017. Article Number: e12630. Date of Publication: 01 May 2017.

[Article]
AN: 611239040

Although testosterone replacement therapy can restore serum testosterone concentrations to normal level in late-onset hypogonadism patients, whether it can improve patients' quality of life remains uncertain. Therefore, we perform a meta-analysis of randomized controlled trials on this issue. Five randomized controlled trials total 1,212 patients were included. Fixed-effect model was used to calculate the weighted mean difference of score of Aging Males’ Symptom rating scale. Our result reveals that testosterone replacement therapy improves patients' health-related quality of life in terms of the decrease in the AMS total score [WMD = -2.96 (-4.21, -1.71), p < .00001] and the psychological [WMD = -0.89 (-1.41, -0.37), p = .0008], somatic [WMD = -0.89 (-1.41, -0.37), p = .0008] and sexual [WMD = -1.29 (-1.75, -0.83), p < .00001] subscale score.

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Li Y., Zhang M., Liu X., Cui W., Rampersad S., Li F., Lin Z., Yang P., Li H., Sheng C., Cheng X., Qu S.
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This study aims to compare the prevalence of hypogonadism between male patients with early-onset type 2 diabetes mellitus (T2DM) and late-onset type 2 diabetes. A total of 122 male patients with early-onset T2DM (diagnosis age <=40 years) and 100 male patients with late-onset T2DM (diagnosis age >40 years) were recruited from our in-patient department between 1 January 2013 and 28 December 2015. Serum FSH, LH, testosterone, lipid profile, uric acid, HbA1c, and beta-cell function were determined in blood samples. The diagnosis of hypogonadism was based on the levels of LH, FSH, and total testosterone. The mean onset age was 29.86 +/- 6.31 and 54.47 +/- 9.97 years old in the early-onset group and late-onset group, respectively. Compared with late-onset T2DM, those with early-onset T2DM had a higher proportion of new-onset diabetes, were more likely to be obese, and had worse glycemic control, lipid control, and lower sex hormone-binding globulin (SHBG). The prevalence of hypogonadism was much higher in the early-onset group than in the late-onset group (48.0% vs. 26.7%, p < 0.05). The rate of secondary hypogonadism in the early-onset group and late-onset group were 44.3% and 25.0%, respectively (p < 0.05). Obesity, waist circumference, and SHBG were significantly associated with serum total testosterone level in all, early-onset, and late-onset T2DM. Both all and early-onset T2DM groups had positive correlations between total testosterone and fasting C-peptide, total cholesterol, triglycerides, and uric acid. Our results indicate that in a population of admission to a large urban hospital in China, the prevalence of hypogonadism was higher in the patients with
early-onset T2DM than that of late-onset T2DM. This prevalence might be attributable to greater obesity, worse lipid control, and lower SHBG levels in those patients. Copyright © 2017 American Society of Andrology and European Academy of Andrology.

108.
Fertility preservation in women with CNS tumors.
Tosoni A., Balestrini D., Brandes A.A.

Embase
[Review]
AN: 615607772

Introduction: Fertility impairment due to treatments is a major concern for adolescents and young adult patients who survived cancer. Areas covered: Chemotherapy may determine a detrimental effect on ovary function, leading to infertility, and premature ovarian failure. Embryo and oocyte cryopreservation is a standard strategy for fertility preservation; other strategies, such as gonadal tissue cryopreservation and the use of gonadotropin-releasing hormone agonist, are still considered experimental. There are few data available regarding the effect of pregnancy on glioma, which indicates tumor progression during pregnancy in 33-45% of patients. Expert commentary: Glioma patients need to be advised about the risk of tumor progression during
pregnancy, and about the possible, even if not proven, interaction between hormone stimulation and tumor growth. Copyright © 2017 Informa UK Limited, trading as Taylor & Francis Group.

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109.
Testosterone replacement therapy: The Emperor's new clothes.
Sansone A., Sansone M., Lenzi A., Romanelli F.
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AN: 614486462
The mean age of the world population has steadily increased in the last decades, as a result of increased life expectancy and reduced birth rate. Global aging has led to a greater worldwide cost for healthcare: hormonal alterations contribute to the pathogenesis of several conditions and might cause a significant reduction in the perceived sense of well-being. Menopause is archetypal of hormonal alterations occurring during aging: in males, sex hormones do not decrease abruptly, yet testosterone levels decrease steadily and continuously during aging, ultimately resulting in late-onset hypogonadism. Treatment of this condition might mitigate most symptoms; however, testosterone replacement therapy (TRT) should be prescribed only in selected patients and it should not be considered as an antiaging treatment. In recent years, different authors have questioned health risks associated with testosterone treatment; while position statements from many scientific societies seem to be reassuring, the Food and Drug Administration has issued a
warning in regard to the possible side effects of this therapy. We aim to review recent
controversies and discoveries in regard to TRT.

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2017

110.
Bone quality in beta-thalassemia intermedia: relationships with bone quantity and endocrine and
hematologic variables.

Baldini M., Marcon A., Ulivieri F.M., Seghezzi S., Cassin R., Messina C., Cappellini M.D.,
Graziadei G.

Embase

[Article]
AN: 615688651

We report the first evaluation of bone quality in 70 thalassemia intermedia (TI) patients (37 males,
33 females, age 41 +/- 12 years). Thirty-three patients (47%) had been transfused, 34 (49%) had
been splenectomized, 39 (56%) were on iron chelation therapy, and 11 (16%) were on
hydroxyurea. Mean hemoglobin was 9.2 +/- 1.5 g/dl, median ferritin 537 ng/dl (range 14-4893),
and mean liver iron concentration 7.6 +/- 6.4 mg Fe/g dw. Fifteen patients (21%) had
endocrinopathies, and 29 (41%) had vitamin D deficiency. Bone quantity (bone mineral density,
BMD) and bone quality (trabecular bone score, TBS) were evaluated by densitometry. In 53/70
patients (76%), osteopathy was found (osteoporosis in 26/53, osteopenia in 27/53). BMD values were higher in the never-transfused patients and in the not-chelated group. A highly significant correlation was found between splenectomy and BMD at all the sites, with lower values in the splenectomized patients. TBS values were significantly lower in TI patients than in 65 non-thalassemic controls (1.22 vs 1.36, p < 0.01), mainly in those splenectomized and in the transfused and chelated groups (p < 0.01). TBS did not correlate with liver iron concentration values. Our data disclose the major role of non-invasive bone quality evaluation in TI patients, especially those with the worst health state, to obtain a comprehensive assessment of fracture risk. Splenectomy seems to play a major part in bone complications. Copyright © 2017, Springer-Verlag Berlin Heidelberg.

Statin, testosterone and phosphodiesterase 5-inhibitor treatments and age related mortality in diabetes.
Hackett G., Jones P.W., Strange R.C., Ramachandran S.
AIM To determine how statins, testosterone (T) replacement therapy (TRT) and phosphodiesterase 5-inhibitors (PDE5I) influence age related mortality in diabetic men.

METHODS We studied 857 diabetic men screened for the BLAST study, stratifying them (mean follow-up = 3.8 years) into: (1) Normal T levels/untreated (total T > 12 nmol/L and free T > 0.25 nmol/L), Low T/untreated and Low T/treated; (2) PDE5I/untreated and PDE5I/treated; and (3) statin/untreated and statin/treated groups. The relationship between age and mortality, alone and with T/TRT, statin and PDE5I treatment was studied using logistic regression. Mortality probability and 95%CI were calculated from the above models for each individual. RESULTS Age was associated with mortality (logistic regression, OR = 1.10, 95%CI: 1.08-1.13, P < 0.001). With all factors included, age (OR = 1.08, 95%CI: 1.06-1.11, P < 0.001), Low T/treated (OR = 0.38, 95%CI: 0.15-0.92, P = 0.033), PDE5I/treated (OR = 0.17, 95%CI: 0.053-0.56, P = 0.004) and statin/treated (OR = 0.59, 95%CI: 0.36-0.97, P = 0.038) were associated with lower mortality. Age related mortality was as described by Gompertz, r² = 0.881 when Ln (mortality) was plotted against age. The probability of mortality and 95%CI (from logistic regression) of individuals, treated/untreated with the drugs, alone and in combination was plotted against age. Overlap of 95%CI lines was evident with statins and TRT. No overlap was evident with PDE5I alone and with statins and TRT, this suggesting a change in the relationship between age and mortality.

CONCLUSION We show that statins, PDE5I and TRT reduce mortality in diabetes. PDE5I, alone and with the other treatments significantly alter age related mortality in diabetic men. Copyright © The Author(s) 2017. Published by Baishideng Publishing Group Inc.
Endogenous sex hormone levels and coronary heart disease risk in postmenopausal women: A meta-analysis of prospective studies.
Wang H., Li Y., Wang X., Bu J., Yan G., Lou D.
Embase
[Article]
AN: 615726783
Background: Low testosterone levels have been associated with coronary heart disease (CHD) morbidity and mortality in men, but the influence of hormones in postmenopausal women is unclear. This meta-analysis aimed to examine whether there is an association between endogenous sex hormones and CHD risk in postmenopausal women. Methods: A systematic search of the PubMed and EMBASE databases from 1966 to 30 November 2016 was performed for prospective studies that reported an association between endogenous sex hormones and CHD in postmenopausal women. Summary relative risks (RRs) and 95% confidence intervals (CIs) were combined by using a random-effects model. Results: A total of 13 publications (12 studies, including six prospective cohort and six nested case-control studies) were included. The summary RRs for CHD were 1.01 (95% CI 0.77-1.31) comparing the highest versus lowest tertile of total testosterone, with evidence of high heterogeneity (I²=80.7%). In subgroup and meta-regression analyses, none of the variables were identified as contributing to significant heterogeneity. Based on a comparison of the highest versus lowest tertile models, the summary RRs (95% CIs) for CHD were 0.88 (0.63-1.23, I²=48.7%) for free testosterone, 1.16 (0.82-1.63, I²=47.8%) for estradiol, 0.98 (0.90-1.07, I²=3.2%) for sex hormone-binding globulin and 1.19 (0.89-1.58, I²=0) for dehydroepiandrosterone. Conclusion: There is limited evidence to suggest that endogenous levels of sex hormones are not significantly associated with CHD risk in postmenopausal women. Copyright © The European Society of Cardiology 2016.
Clinical Risk Factors Associated With Urethral Atrophy.
Morey A.F.
Embase
[Article]
AN: 614080567
Objective To analyze a series of clinical risk factors associated with pretreatment urethral
atrophy. Methods We retrospectively reviewed 301 patients who underwent artificial urinary
sphincter (AUS) placement between September 2009 and November 2015; of these, 60 (19.9%)
transcorporal cuff patients were excluded. Patients were stratified into 2 groups based on
intraoperative spongiosal circumference measurements. Men with urethral atrophy (3.5cm cuff
size) were compared to controls (>=4cm cuff size). Chi-square test, Mann-Whitney U test, and
logistic regression analyses were performed to determine risk factors for urethral atrophy. Results
Among 241 AUS patients analyzed, urethral atrophy was present in 151 patients (62.7%) compared to 90 patients (37.3%) who received larger cuffs (range 4-5.5cm). Patients with urethral
atrophy were older (71.1years vs 68.3 years; P<.02), more likely to have received radiation
(52.9% vs. 33.3%; P<.007), and had a longer time interval between prostate cancer treatment
and AUS surgery (8.9 years vs. 6.6 years; P<.033). On multivariable analysis, radiation therapy
was independently associated with risk of urethral atrophy (odds ratio 1.77, 95% confidence interval: 1.01-3.13; P=.046), whereas greater time between cancer therapy and incontinence surgery approached clinical significance (odds ratio 1.05, 95% confidence interval 1.00-1.09; P=.05). Conclusion History of radiation therapy and increasing length of time from prostate cancer treatment are associated with urethral atrophy before AUS placement. Copyright © 2016 Elsevier Inc.

Testosterone level and endothelial dysfunction in patients with vasculogenic erectile dysfunction.
Omar Y.A., Younis S.E., Ismail I.Y., El-Sakka A.I.

Embase
Andrology. 5 (3) (pp 527-534), 2017. Date of Publication: May 2017.
[Article]
AN: 615423899

The association between endothelial dysfunction and late onset hypogonadism (LOH) in patients with vasculogenic erectile dysfunction (ED) is not yet well settled. Our objective was to assess the association between LOH and endothelial dysfunction in patients with vasculogenic ED. Throughout 2014-2015 a total of 90 men were enrolled in this cross-sectional observational study. Of them 60 patients with a clinical diagnosis of ED were further subdivided into two equal groups: patients with vasculogenic ED and LOH (A); patients with vasculogenic ED and euogonadal (B). Thirty age-matched men with no ED or hypogonadism were enrolled as control group (C). All
patients were subjected to detailed medical and sexual history, total testosterone (TT), calculated free (FT) and bioavailable testosterone (BT), flow cytometric evaluation for endothelial progenitor cells (EPCs) (CD45negative/CD34positive/CD144positive) and endothelial microparticles (EMPs) (CD45negative/CD144positive/annexin V positive). The mean age +/- SD of the three groups A, B and C were 51.3 +/- 11.1, 53.6 +/- 10.6 and 48.3 +/- 5 years, respectively, with insignificant age differences (p = 0.089). The diagnostic criteria of LOH were adapted according to European male aging study, 2010. The means of TT(ng/mL) were 2.32 +/- 0.21, 6.43 +/- 0.36 and 5.37 +/- 0.30 in groups A, B and C, respectively. There were highly significant differences between group A and groups B and C (p < 0.001 for each). The means of EPCs were 0.43 +/- 0.070, 0.22 +/- 0.05 and 0.032 +/- 0.013 in groups A, B and C, respectively. The means of EMPs were 0.15 +/- 0.029, 0.056 +/- 0.013 and 0.014 +/- 0.002 in groups A, B and C, respectively. There were significant differences between group C and groups A and B (p < 0.05 for each). This study clearly demonstrated that there is a significant association between LOH and the higher expression of EPCs and EMPs in patients with vasculogenic ED. Copyright © 2017 American Society of Andrology and European Academy of Andrology


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115.
Causal relationship between obesity and serum testosterone status in men: A bidirectional mendelian randomization analysis.
Context Obesity in men is associated with low serum testosterone and both are associated with several diseases and increased mortality. Objectives Examine the direction and causality of the relationship between body mass index (BMI) and serum testosterone. Design Bi-directional Mendelian randomization (MR) analysis on prospective cohorts. Setting Five cohorts from Denmark, Germany and Sweden (Inter99, SHIP, SHIP Trend, GOOD and MrOS Sweden). Participants 7446 Caucasian men, genotyped for 97 BMI-associated SNPs and three testosterone-associated SNPs. Main outcome measures BMI and serum testosterone adjusted for age, smoking, time of blood sampling and site. Results 1 SD genetically instrumented increase in BMI was associated with a 0.25 SD decrease in serum testosterone (IV ratio: -0.25, 95% CI: -0.42-0.09, p = 2.8*10^-3). For a body weight reduction altering the BMI from 30 to 25 kg/m2, the effect would equal a 13% increase in serum testosterone. No association was seen for genetically instrumented testosterone with BMI, a finding that was confirmed using large-scale data from the GIANT consortium (n = 104349). Conclusions Our results suggest that there is a causal effect of BMI on serum testosterone in men. Population level interventions to reduce BMI are expected to increase serum testosterone in men. Copyright © 2017 Eriksson et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Influences of flavones on cell viability and cAMP-dependent steroidogenic gene regulation in MA-10 Leydig cells.

Cormier M., Ghouili F., Roumaud P., Bauer W., Touaibia M., Martin L.J.

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Cell Biology and Toxicology. (pp 1-16), 2017. Date of Publication: 28 Apr 2017.
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AN: 615772951

Testicular Leydig cells are major contributors of androgen synthesis and secretion, which play an important role in testis development, normal masculinization, maintenance of spermatogenesis, and general male fertility. The rate-limiting step in testosterone biosynthesis involves the transfer
of cholesterol to the mitochondrial inner membrane by the steroidogenic acute regulatory (Star) protein, a critical factor in steroid hormone biosynthesis. Once inside the mitochondria, cholesterol is metabolized by the steroidogenic enzyme Cyp11a1 to pregnenolone, which is further converted to testosterone by the action of other steroidogenic enzymes. Interestingly, the Star protein level declines during Leydig cell aging, resulting in defective mitochondrial cholesterol transfer and lower testosterone production. It is possible to delay the age-related decline in testosterone production by increasing Star and/or Cyp11a1 gene expression using supplementation with flavonoids, a group of polyphenolic compounds widely distributed in fruits and vegetables. In this study, we examined whether the distribution of hydroxyl groups among flavones could influence their potency to stimulate steroidogenesis within Leydig cells. Low levels of apigenin, luteolin, chrysine, and baicalein (10 μM) stimulated cAMP-dependent Star, Cyp11a1, and Fdx1 promoters’ activation and may increase steroidogenesis within Leydig cells. Indeed, luteolin effectively increased cAMP-dependent accumulation of progesterone from MA-10 Leydig cells, possibly through activation of Star and Fdx1 transcription. Thus, dietary luteolin could be potentially effective to maintain steroid production within aging males. Copyright © 2017 Springer Science+Business Media Dordrecht

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Springer Netherlands

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20170503

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2017

117.

Reduction of calprotectin and phosphate during testosterone therapy in aging men: a randomized controlled trial.

Pedersen L., Christensen L.L., Pedersen S.M., Andersen M.
Objectives: To investigate the effect of testosterone treatment on biomarkers calprotectin, fibroblast growth factor 23 (FGF23), soluble Klotho, phosphate, calcium, parathyroid hormone, creatinine and estimated glomerular filtration rate. Design: Randomized, double-blinded, placebo-controlled study. Setting: Odense Androgen Study-the effect of Testim and training in hypogonadal men. Participants: Men aged 60-78 years old with a low normal concentration of free of bioavailable testosterone <7.3 nmol/L and waist circumference >94 cm recruited from 2008 to 2009 (N = 48) by advertisement. Intervention: Participants were randomized to receive 5-10 g gel/50-100 mg testosterone (Testim, Ipsen, France) or 5-10 g gel/placebo. Results: The plasma levels of calprotectin and phosphate were significantly reduced in the group receiving testosterone therapy (gel) compared to the placebo group (p < 0.05). Testosterone treatment did not have any significant effect on plasma levels of FGF23 or soluble Klotho. The reduction in phosphate levels was inversely associated with bioavailable testosterone. Conclusion: Compared to the placebo group, 6 months of testosterone therapy (gel) reduced calprotectin and phosphate levels suggesting decreased inflammation and decreased cardiovascular risk. Copyright © 2016, Italian Society of Endocrinology (SIE).
Effect of triclosan on anuran development and growth in a larval amphibian growth and development assay.

Fort D.J., Mathis M.B., Pawlowski S., Wolf J.C., Peter R., Champ S.

Embase

Journal of Applied Toxicology. (no pagination), 2017. Date of Publication: 2017. [Article In Press]

AN: 615677115

A larval amphibian growth and development assay was performed to evaluate the potential effects of environmentally-relevant concentrations of triclosan (TCS) on amphibian development and growth. Xenopus laevis were exposed to TCS 0.0 (control), 6.3, 12.5 and 25.0 mug l-1 (estimated maximum tolerable concentration) until 10 weeks post-metamorphosis. At median metamorphosis time (Nieuwkoop and Faber stage 62), five larvae per replicate were collected for snout-vent length, hind limb length and body weight measurements, and histopathological examination of thyroid glands. Endpoints evaluated at test termination were based on draft guidance (USEPA, ) and included: survival; snout-vent length; body weight; gender; nuptial pad development (males); and liver, kidney, gonad and gonadal ducts histopathology. Exposure to TCS did not decrease survival, induce general signs of toxicity, affect median metamorphosis time or alter sex ratios. Exposure to TCS 12.5 and 25 mug l-1 increased growth during the metamorphic stages relative to the control, but did not influence growth during the post-metamorphic phase. Overall, several statistically significant findings were found in larvae exposed to TCS, such as a decrease in the prevalence of stage 3 Mullerian ducts in the anterior trunk sections of TCS 25.0 mug l-1 dose group females as compared to controls; most were not considered toxicologically relevant. Copyright © 2017 John Wiley & Sons, Ltd.

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20170428
Introduction: It has been described among the literature the close relationship that exists between dysgenetic gonads with positive Y chromosome and the risk of developing gonadoblastoma. However, it is still uncertain the relationship with stromal tumors and there is not much information about this topic. In this paper is presented the case of a patient with Turner syndrome mosaicism 45X(8)/46,XY(92) and sex cord tumor with annular tubule pattern. Materials and methods: A search was conducted in Embase, Ovid, Ebsco and PubMed databases with the terms "(Turner syndrome) and sex cord stromal tumor". However, only in PubMed we were able to find an article that meets the search criteria and it is considered the first case report in the literature that refers to the relationship between Turner syndrome and sex cord stromal tumor. Conclusions: There is little evidence that exists for cases like this, so the management of these patients is still uncertain and controversial, especially by the different perspectives in-between specialties. Specifically, with this patient it is still uncertain the relationship between the risk and the benefit of the management with growth hormone after the finding of neoplasm. Copyright © 2017 Sociedad Colombiana de Urologia.

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Association of testosterone levels with anemia in older men a controlled clinical trial.
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JAMA Internal Medicine. 177 (4) (pp 480-490), 2017. Date of Publication: 01 Apr 2017.
[Article]
AN: 615586520
IMPORTANCE In one-third of older men with anemia, no recognized cause can be found.
OBJECTIVE To determine if testosterone treatment of men 65 years or older with unequivocally low testosterone levels and unexplained anemia would increase their hemoglobin concentration.
DESIGN, SETTING, AND PARTICIPANTS A double-blinded, placebo-controlled trial with treatment allocation by minimization using 788 men 65 years or older who have average testosterone levels of less than 275 ng/dL. Of 788 participants, 126 were anemic (hemoglobin >=12.7 g/dL), 62 of whom had no known cause. The trial was conducted in 12 academic medical centers in the United States from June 2010 to June 2014. INTERVENTIONS Testosterone gel, the dose adjusted to maintain the testosterone levels normal for young men, or placebo gel for 12 months. MAIN OUTCOMES AND MEASURES The percent of men with unexplained anemia whose month 12 hemoglobin levels had increased by 1.0 g/dL or more in response to testosterone compared with placebo. The statistical analysis was intent-to-treat by a logistic mixed effects model adjusted for balancing factors. RESULTS The men had a mean age of 74.8 years and body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) of 30.7; 84.9% were white. Testosterone treatment resulted in a greater percentage of men with unexplained anemia whose month 12 hemoglobin levels had increased by 1.0 g/dL or more over baseline (54%) than did placebo (15%) (adjusted OR, 31.5; 95%CI, 3.7-277.8; P = .002) and a greater percentage of men who at month 12 were no longer anemic (58.3%) compared with placebo (22.2%) (adjusted OR, 17.0; 95%CI, 2.8-104.0; P = .002). Testosterone treatment also resulted in a greater percentage of men with anemia of known cause whose month 12 hemoglobin levels had increased by 1.0 g/dL or more (52%) than did placebo (19%) (adjusted OR, 8.2; 95%CI, 2.1-
31.9; P = .003). Testosterone treatment resulted in a hemoglobin concentration of more than 17.5 g/dL in 6 men who had not been anemic at baseline. CONCLUSIONS AND RELEVANCE Among older men with low testosterone levels, testosterone treatment significantly increased the hemoglobin levels of those with unexplained anemia as well as those with anemia from known causes. These increases may be of clinical value, as suggested by the magnitude of the changes and the correction of anemia in most men, but the overall health benefits remain to be established. Measurement of testosterone levels might be considered in men 65 years or older who have unexplained anemia and symptoms of low testosterone levels. Copyright © 2017 American Medical Association.

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Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone a controlled clinical trial.

IMPORTANCE As men age, they experience decreased serum testosterone concentrations, decreased bone mineral density (BMD), and increased risk of fracture. OBJECTIVE To determine whether testosterone treatment of older men with low testosterone increases volumetric BMD (vBMD) and estimated bone strength. DESIGN, SETTING, AND PARTICIPANTS Placebo-controlled, double-blind trial with treatment allocation by minimization at 9 US academic medical centers of men 65 years or older with 2 testosterone concentrations averaging less than 275 ng/L participating in the Testosterone Trials from December 2011 to June 2014. The analysis was a modified intent-to-treat comparison of treatment groups by multivariable linear regression adjusted for balancing factors as required by minimization. INTERVENTIONS Testosterone gel, adjusted to maintain the testosterone level within the normal range for young men, or placebo gel for 1 year. MAIN OUTCOMES AND MEASURES Spine and hip vBMD was determined by quantitative computed tomography at baseline and 12 months. Bone strength was estimated by finite element analysis of quantitative computed tomography data. Areal BMD was assessed by dual energy x-ray absorptiometry at baseline and 12 months. RESULTS There were 211 participants (mean [SD] age, 72.3 [5.9] years; 86% white; mean [SD] body mass index, 31.2 [3.4]). Testosterone treatment was associated with significantly greater increases than placebo in mean spine trabecular vBMD (7.5%; 95%CI, 4.8% to 10.3% vs 0.8%; 95%CI, -1.9% to 3.4%; treatment effect, 6.8%; 95%CI, 4.8% - 8.7%; P < .001), spine peripheral vBMD, hip trabecular and peripheral vBMD, and mean estimated strength of spine trabecular bone (10.8%; 95%CI, 7.4% to 14.3% vs 2.4%; 95%CI, -1.0% to 5.7%; treatment effect, 8.5%; 95%CI, 6.0% - 10.9%; P < .001), spine peripheral bone, and hip trabecular and peripheral bone. The estimated strength increases were greater in trabecular than peripheral bone and greater in the spine than hip. Testosterone treatment increased spine areal BMD but less than vBMD. CONCLUSIONS AND RELEVANCE Testosterone treatment for 1 year of older men with low testosterone significantly increased vBMD and estimated bone strength, more in trabecular than peripheral bone and more in the spine than hip. A larger, longer trial could determine whether this treatment also reduces fracture risk. Copyright © 2017 American Medical Association.
Meta-analysis of Results of Testosterone Therapy on Sexual Function Based on International Index of Erectile Function Scores.

Corona G., Rastrelli G., Morgentaler A., Sforza A., Mannucci E., Maggi M.

Embase


[Article In Press]

AN: 615612217

Context: The interpretation of available clinical evidence related to the effect of testosterone (T) treatment (TTh) on sexual function has been inconsistent, in part due to the use of different and self-reported measures to assess outcomes. The International Index of Erectile Function (IIEF) is the most frequently used validated tool to assess male sexual function. Objective: To perform a meta-analysis of available data evaluating the effect of TTh on male sexual function using IIEF as the primary outcome. Evidence acquisition: An extensive Medline, Embase, and Cochrane search was performed including all placebo-controlled randomized clinical trials enrolling men comparing the effect of TTh on sexual function. Evidence synthesis: Out of 137 retrieved articles, 14 were included in the study enrolling 2298 participants, with a mean follow-up of 40.1 wk and mean age of 60.2. +/- 6.5 yr. Using IIEF-erectile function domain (IIEF-EFD) as the outcome, we found that TTh significantly improved erectile function compared with placebo (mean difference = 2.31 [1.41;3.22] IIEF-EFD score, p < 0.0001). Patients with more severe hypogonadism (total T. < 8 nmol/l) reported greater changes in final IIEF-EFD score when compared with those with a milder T deficiency (total T. < 12 nmol/l; 1.47 [0.90;2.03] and 2.95 [1.86;4.03] for total T. < 12 nmol/l and <8 nmol/l, respectively, Q = 5.61, p = 0.02). The magnitude of the effect was lower in the presence of metabolic derangements, such as diabetes and obesity. Other aspects of sexual function, as evaluated by IIEF subdomains, were also improved with TTh including libido, intercourse satisfaction, orgasm, and overall sexual satisfaction. Conclusions: TTh significantly improves erectile function and other sexual parameters as measured by IIEF in hypogonadal men. These results argue that sexual dysfunction should be considered a hallmark manifestation of T deficiency, since those symptoms can be significantly improved with normalization of serum T. In addition, these results suggest that TTh alone may be considered a reasonable treatment for hypogonadal men with milder degrees of erectile dysfunction, whereas the addition of other
treatments, such as phosphodiesterase type 5 inhibitors, may be more appropriate for men with more severe erectile dysfunction. Patient summary: We investigated the effect of testosterone treatment on sexual function by performing a meta-analysis of all available studies that used the most frequently used assessment tool, the International Index of Erectile Function. We found that testosterone treatment significantly improves erectile dysfunction, as well as other aspects of sexual function, in men with testosterone deficiency. This treatment may be all that is required for hypogonadal men with milder erectile dysfunction; however, additional treatments may be necessary in more severe cases. The present meta-analysis investigates the effect of testosterone treatment (TTh) on sexual function over placebo considering the International Index of Erectile Function (IIEF) as final outcome. Our data indicate that TTh significantly improves erectile function and other sexual parameters as measured by IIEF. The effects of TTh on erectile dysfunction are greater in patients with lower testosterone levels at baseline and lower in the presence of metabolic derangements, such as diabetes and obesity. The observed mean 2.3-point increase in IIEF-erectile function domain score is clinically meaningful, suggesting that TTh alone may be a reasonable treatment option in men with milder form of erectile dysfunction whereas the addition of other treatments, such as phosphodiesterase type 5 inhibitors, may be more appropriate for men with more severe erectile dysfunction. Copyright © 2017.
Purpose We sought to determine the role of sex hormone-binding globulin in patients with male infertility. Materials and Methods We retrospectively reviewed the records of 168 males seen at a fertility clinic from 2012 to 2014 to investigate the accuracy of total testosterone in the biochemical diagnosis of hypogonadism using calculated bioavailable testosterone as the reference value. We used multivariable analysis to assess sex hormone-binding globulin as an independent predictor of infertility. Results Computations using calculated bioavailable testosterone as a standard in the measurement of definitive biochemical hypogonadism (less than 156 ng/dl) revealed 81% sensitivity, 83% specificity, 81% positive predictive value and 82% negative predictive value for diagnosing hypogonadism with total testosterone alone. Of the 90 men with total testosterone greater than 300 ng/dl, 20% had low bioavailable testosterone less than 156 ng/dl, 52% had borderline low bioavailable testosterone less than 210 ng/dl and only 48% could be considered biochemically eugonadal according to calculated bioavailable testosterone. Of the 80 patients with total testosterone less than 300 ng/dl, 19% had free testosterone levels greater than 6.5 ng/dl and, thus, could be considered to be eugonadal. By a magnitude similar to that of follicle-stimulating hormone, sex hormone-binding globulin independently predicted decreased sperm concentration (p = 0.0027) and motility (p = 0.0447). After excluding men with azoospermia, only sex hormone-binding globulin levels differed significantly in classically hypogonadal men (group 1-total testosterone less than 300 ng/dl) and those missed but hypogonadal (group 2-calculated bioavailable testosterone less than 210 ng/dl) (p = 0.0001). At a more stringent cutoff of calculated bioavailable testosterone less than 156 ng/dl, sperm motility was significantly different for groups 1 and 2 (p = 0.014). Conclusions Adding sex hormone-binding globulin to total testosterone serum testing facilitates more accurate diagnosis with free testosterone and calculated bioavailable testosterone, and clinical implications of decreased semen parameters to a magnitude similar to that of follicle-stimulating hormone. This warrants further study of the role of sex hormone-binding globulin in male infertility.
125.
Early weight loss predicts the reduction of obesity in men with erectile dysfunction and hypogonadism undergoing long-term testosterone replacement therapy.
Salman M., Yassin D.-J., Shoukfeh H., Nettleship J.E., Yassin A.
Embase
Aging Male. 20 (1) (pp 45-48), 2017. Date of Publication: 02 Jan 2017.
[Article]
AN: 614212785
We and others have previously shown that testosterone replacement therapy (TRT) results in sustained weight loss in the majority of middle-aged hypogonadal men. Previously, however, a small proportion failed to lose at least 5% of their baseline weight. The reason for this is not yet understood. In the present study, we sought to identify early indicators that may predict successful long-term weight loss, defined as a reduction of at least 5% of total body weight relative to baseline weight (T0), in men with hypogonadism undergoing TRT. Eight parameters measured were assessed as potential predictors of sustained weight loss: loss of 3% or more of baseline weight after 1 year of TRT; severe hypogonadism, BMI, waist circumference, International Prostate Symptom Score (IPSS), glycated hemoglobin (HbA1C), age and use of vardenafil. Among the eight measured parameters, three factors were significantly associated with sustained weight loss over the entire period of TRT treatment: (1) a loss of 3% of the baseline body weight after 1 year of TRT; (2) baseline BMI over 30; and (3) a waist circumference >102
cm. Age was not a predictor of weight loss. Copyright © 2017 Informa UK Limited, trading as Taylor & Francis Group.

Non-targeted LC-MS based metabolomics analysis of the urinary steroidal profile.
Palermo A., Botre F., de la Torre X., Zamboni N.
Embase
Analytica Chimica Acta. 964 (pp 112-122), 2017. Date of Publication: 29 Apr 2017.
[Article]
AN: 614305067
The urinary steroidal fraction has been extensively explored as non-invasive alternative to monitor pathological conditions as well as to unveil the illicit intake of pseudo-endogenous anabolic steroids in sport. However, the majority of previous approaches involved the a priori selection of potentially relevant target analytes. Here we describe the non-targeted analysis of the urinary steroidal profiles. The workflow includes minimal sample pretreatment and normalization according to the specific gravity of urine, a 20 min reverse phase ultra-performance liquid chromatographic separation hyphenated to electrospray time-of-flight mass spectrometry. As initial validation, we analyzed a set of quality control urines spiked with glucurono- and sulfo-conjugated steroids at physiological ranges. We then applied the method for the analysis of
samples collected after single transdermal administration of testosterone in hypogonadal men. The method allowed profiling of approximately three thousand metabolic features, including steroids of clinical and forensic relevance. It successfully identified metabolic pathways mostly responsible for groups clustering even in the context of high inter-individual variability and allowed the detection of currently unknown metabolic features correlating with testosterone administration. These outcomes set the stage for future studies aimed at implementing currently monitored urinary steroidal markers both in clinical and forensic analysis. Copyright © 2017 Elsevier B.V.

127.
Xeroderma pigmentosum-Cockayne syndrome complex.
Natale V., Raquer H.
Embase
[Review]
AN: 615118749
Xeroderma pigmentosum-Cockayne syndrome complex is a very rare multisystem degenerative disorder (Orpha: 220295; OMIM: 278730, 278760, 278780, 610651). Published information on XP-CS is mostly scattered throughout the literature. We compiled statistics related to symptom prevalence in XP-CS and have written a clinical description of the syndrome. We also drew on clinical practices used in XP and in Cockayne syndrome without XP to aid management of XP-CS. Extensive searches of the literature identified 43 XP-CS patients. The diagnosis had been confirmed with molecular or biochemical methods in 42 of them. Clinical features of each patient were summarized in spreadsheets and summary statistics were generated from this data. XP patients are classified into complementation groups according to the gene that is mutated. There are four groups in XP-CS, and classification was available for 42 patients. Twenty-one were in the XP-G complementation group, 13 in XP-D, 5 in XP-B, and 3 in XP-F. Overall, the clinical features of XP-CS are very similar to those of CS without XP, with the exception of skin cancers in XP-CS. However, one intriguing finding was that cancer incidence was lower in XP-CS compared to XP alone or XP-neurological disorder. The cancer rate in XP-CS was higher than in CS without XP, an unsurprising finding. There is preliminary evidence for the existence of severity groups in XP-CS, as is the case in CS. Although health problems in XP-CS vary both in severity and in when they the first occur, there was overall homogeneity between all complementation groups and putative severity groups. Severely affected patients met fewer milestones and died at younger ages compared to more mildly affected patients. Copyright © 2017 The Author(s).
Low serum testosterone is associated with impaired graft function early after heart transplantation.

Poglajen G., Jensterle M., Kravos N., Janez A., Vrtovec B.

Embase


[Article In Press]
AN: 615431401

Background: We sought to investigate a correlation between serum testosterone levels and graft function early after heart transplantation. Methods: In a cross-sectional study, we measured serum testosterone levels 4 weeks after heart transplantation in 49 consecutive male recipients. Echocardiography was carried out to evaluate graft function. Low serum testosterone was defined as <11 nmol/L. Results: Low serum testosterone was present in 21 (43%) recipients (Group A), and 28 (57%) had normal testosterone levels (Group B). The two groups did not differ in age and presence of renal dysfunction, arterial hypertension, diabetes, or hyperlipidemia. Donor age and allograft ischemic time were not different between the two groups. Both groups had comparable tacrolimus trough levels, dose of mycophenolate mofetil, and methylprednisolone. Patients in Group A had significantly lower LVEF (58+/−5% vs 65+/−6% vs Group B, P=.001) and TAPSE (1.3+/−0.3 cm vs 1.6+/−0.3 cm in Group B, P=.01). In comparison with Group B, more patients in Group A were found to have low grade (1R) rejection (25% vs 3%; P=.02). Conclusion: Low serum testosterone levels appear to be associated with impaired graft function and an increased incidence of low-grade rejection episodes early after heart transplantation. Copyright © 2017 John Wiley & Sons A/S.

Status
ARTICLE IN PRESS

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High Prevalence of Low Serum Biologically Active Testosterone in Older Male Veterans.
Conover C.F., Yarrow J.F., Garrett T.J., Ye F., Quinlivan E.P., Cannady D.F., Peterson M.D., Borst S.E.
Embase
[Article]
AN: 614440730
Objectives Assess the prevalence of hypogonadism in older male Veterans by comparing direct measurements of total testosterone (T) and bioavailable testosterone (BioT) versus indirect BioT values derived from existing and newly developed regression analyses. Design Cohort study. Setting Malcom Randall VA Medical Center, Gainesville, FL. Participants Community-dwelling male Veterans aged 60 and older (n = 203). Measurements Total T, BioT, albumin, sex hormone-binding globulin (SHBG), and body mass index were evaluated. Blood values were assessed via liquid chromatography-tandem mass spectrometry (LC-MS/MS) and clinical or commercially available immunoassays to compare accuracy among assessment techniques. Existing and newly developed multiple regression analyses were evaluated to assess accuracy in predicting BioT. Results Total T was 13.80 +/- 6.25 nmol/L (398 +/- 180 ng/dL) and was low (<=10.4 nmol/L or <=300 ng/dL) in 34% of participants. SHBG was 58 +/- 35 nmol/L and elevated (>=62 nmol/L) in 36% of participants. BioT was 1.94 +/- 0.97 nmol/L (56 +/- 28 ng/dL), with 72% of participants below the clinical cutoff (<=2.43 nmol/L or <=70 ng/dL). Albumin was within the normal clinical range. Total T and BioT measured via immunoassay and LC-MS/MS were moderately to highly correlated, with no differences between assessment methods. Several existing predictive equations overestimated BioT by 74% to 166% within our cohort (P < .001). A newly developed regression model that included total T, SHBG, albumin, and age more accurately predicted BioT, with values correlated (r = 0.508, P < .001) and comparable to LC-MS/MS. Conclusion In our cohort, the prevalence of low total T was higher and low BioT was markedly higher than reported in the general age-matched population, indicating a greater incidence of hypogonadism in older male Veterans. In addition, existing empiric formulae, derived from other populations produced BioT values that were considerably greater than those directly measured, whereas our newly developed regression analysis provides improved predictive capabilities for older male Veterans. Copyright © 2016
Status
Introduction The prevalence of metabolic syndrome (MetS) is rapidly increasing in the United States and, because of its strong association with male hypogonadism, has become a significant topic of interest in the sexual medicine community. At the center of this conversation is the...
efficacy and safety of testosterone replacement therapy (TRT) as a therapeutic option for HG and MetS. 

Aim To provide a review of the current literature pertaining to TRT and MetS. 

Methods A thorough literature review was performed to review the relation between TRT and MetS using the PubMed online database from 1976 through 2016 with the keywords testosterone, hypogonadism, metabolic syndrome, and testosterone therapy. 

Main Outcome Measures 

Outcomes pertaining to MetS including weight, waist circumference, body mass index, blood glucose control, cholesterol parameters, blood pressure, and quality of life.

Results From the plethora of contrasting literature on the efficacy and safety of TRT, it is increasingly clear that more well-defined studies are needed to clarify the efficacy and safety of TRT. Although most of the current literature shows that TRT has the potential to significantly lower the studied outcome variables associated with MetS, several studies provide more mixed results.

Conclusion TRT has the potential to alleviate some of the morbidity associated with hypogonadism and MetS. Larger multicenter well-designed studies are needed to better describe and quantify the relation between MetS and TRT.


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20170418

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2017
Purpose of Review: According to an Endocrine Society Clinical Practice Guideline published in June 2010, testosterone replacement therapy (TRT) should be administered only to men who are hypogonadal with documented low testosterone level on two morning measurements. This recommendation was based on previous studies that did not show an increased risk in cardiovascular events with TRT. In contrast, recent studies did show an increased risk which prompted the FDA to investigate further. Recent Findings: Multiple studies suggested an increased risk in cardiovascular events among groups of men prescribed TRT. Summary: There is recent evidence that TRT can be associated with higher cardiovascular risks, while these risks are still not well established, and more well-designed trials are needed. Physicians should always be cautious when prescribing TRT to their patients. Potential risks should be discussed with each patient, and TRT requires regular monitoring to help minimize side effects. Copyright © 2017, Springer Science+Business Media New York.
Novel perspectives on hypothalamic-pituitary dysfunction as a risk factor for non-alcoholic fatty liver disease.

Hoffmann A., Muller H.L.

Embase

Minerva Endocrinologica. 42 (2) (pp 132-144), 2017. Date of Publication: June 2017.

[Review]

AN: 615321550

Non-alcoholic fatty liver disease (NAFLD) presents a disease with a wide spectrum spanning from benign steatosis to steatohepatitis with fibrosis and scarring that can lead to cirrhosis. With increasing prevalence, NAFLD is developing into the leading indication for liver transplantation worldwide. Disturbances in endocrine, hypothalamic-pituitary axes have been associated with NAFLD, including GH deficiency, hypothyroidism, hypercortisolemia, and hypogonadism. In this review, we examine the published data (search: PUBMED, 1990-2016) suggesting a link between endocrine abnormalities of hypothalamic-pituitary axes and NAFLD and summarize the clinical data on risk factors for NAFLD in specific diseases involving hypothalamic-pituitary axes. Hormonal substitution of endocrine deficiencies has been shown to have beneficial effects at least in some instances. While the association between type 2 diabetes and NAFLD is well known, there is rather limited appreciation of the condition among common endocrine diseases involving hypothalamic-pituitary axes. In diseases involving hypothalamic-pituitary areas and manifesting clinically with endocrine deficiencies of hypothalamic-pituitary axes such as childhood-onset craniopharyngioma NAFLD is a frequent sequela of hypothalamic obesity.

Copyright © 2016 Edizioni Minerva Medica.
Hypogonadal men with type 2 diabetes mellitus have smaller bone size and lower bone turnover. Colleluori G., Aguirre L., Dorin R., Robbins D., Blevins D., Barnouin Y., Chen R., Qualls C., Villareal D.T., Armamento-Villareal R.

Bone. 99 (pp 14-19), 2017. Date of Publication: 01 Jun 2017.

AN: 614951098

Introduction Both hypogonadism and type 2 diabetes mellitus (T2D) are associated with increased fracture risk. Emerging data support the negative effect of low testosterone on glucose metabolism, however, there is little information on the bone health of hypogonadal men with diabetes. We evaluated the bone mineral density (BMD), bone geometry and bone turnover of hypogonadal men with T2D compared to hypogonadal men without diabetes. Materials and Methods Cross-sectional study, men 40-74 years old, with average morning testosterone (done twice) of < 300 ng/dl. Areal BMD (aBMD) was measured by DXA; volumetric BMD (vBMD) and bone geometry by peripheral-quantitative-computed-tomography; serum C-telopeptide (CTX), osteocalcin, sclerostin and sex hormone-binding globulin (SHBG) by ELISA, testosterone and 25-hydroxyvitamin D (25OHD) by automated immunoassay and estradiol by liquid-chromatography/mass-spectrometry. Groups were compared by ANOVA adjusted for covariates.

Results One-hundred five men, 49 with and 56 without diabetes were enrolled. Adjusted vBMD at 38% tibia was higher in diabetic than non-diabetic men (857.3 +/- 69.0 mg/cm3 vs. 828.7 +/- 96.7 mg/cm3, p = 0.02). Endosteal (43.9 +/- 5.8 mm vs. 47.1 +/- 7.8 mm, p = 0.04) and periosteal (78.4 +/- 5.0 mm vs. 81.3 +/- 6.5 mm, p = 0.02) circumferences and total area (491.0 +/- 61.0 mm2 vs. 527.7 +/- 87.2 mm2, p = 0.02) at 38% tibia, were lower in diabetic men even after adjustments for covariates. CTX (0.25 +/- 0.14 ng/ml vs. 0.40 +/- 0.19 ng/ml, p < 0.001) and osteocalcin (4.8 +/- 2.8 ng/ml vs. 6.8 +/- 3.5 ng/ml, p = 0.006) were lower in diabetic men; there were no differences in sclerostin and 25OHD. Circulating gonadal hormones were comparable between the groups. Conclusion Among hypogonadal men, those with T2D have higher BMD, poorer bone geometry and relatively suppressed bone turnover. Studies with larger sample size are needed to verify our findings and possible even greater risk for fractures among hypogonadal diabetic men. Copyright © 2017
134.
Non-Sexual Implications of Phosphodiesterase Type 5 Inhibitors.
Mostafa T.
Embase
Sexual Medicine Reviews. 5 (2) (pp 170-199), 2017. Date of Publication: 01 Apr 2017.
[Review]
AN: 614940799
Introduction Phosphodiesterase type 5 (PDE5) hydrolyses cyclic guanylate monophosphate specifically to 5' guanylate monophosphate, promoting corporeal vascular relaxation and penile
erection in response to sexual stimulation. Oral PDE5 inhibitors (PDE5-Is) have afforded effective and well-tolerated treatment for erectile dysfunction. In addition, PDE5-Is have stimulated academic and clinical interest for their potential benefits in diverse non-sexual applications. Aim To highlight possible potential non-sexual implications of PDE5-Is. Methods A systematic review was conducted until January 2016 based on a search of all relevant articles in Medline Medical Subject Heading, Scopus, Cochrane Library, EMBASE, and CINAHL databases without language restriction. Key words used to assess outcome and estimates for the relevant associations were PDE5 inhibitors, sildenafil, tadalafil, vardenafil, and avanafil. Main Outcome Measures Different non-sexual implications for PDE5-Is. Results PDE5-Is demonstrated beneficial effects in different medical applications with possible widespread implications for cardiovascular, pulmonary, cutaneous, gastrointestinal, urogenital, cellular, musculoskeletal, neurologic, and reproductive disorders. However, most applications were carried out experimentally in preclinical studies of off-label indications. Conclusion PDE5-Is are a conceptually attractive therapeutic class of agents with pleiotropic effects. Exploring PDE5-Is for their possible implications seems to be valuable in different medical disorders. However, well-designed clinical trials are needed before these agents can be recommended for selected applications. Mostafa T. Non-Sexual Implications of Phosphodiesterase Type 5 Inhibitors. Sex Med Rev 2017;5:170-199. Copyright © 2016 International Society for Sexual Medicine

135.

Male Hypogonadism and Osteoporosis: The Effects, Clinical Consequences, and Treatment of Testosterone Deficiency in Bone Health.
It is well recognized that bone loss accelerates in hypogonadal states, with female menopause being the classic example of sex hormones affecting the regulation of bone metabolism. Underrepresented is our knowledge of the clinical and metabolic consequences of overt male hypogonadism, as well as the more subtle age-related decline in testosterone on bone quality. While menopause and estrogen deficiency are well-known risk factors for osteoporosis in women, the effects of age-related testosterone decline in men on bone health are less well known. Much of our knowledge comes from observational studies and retrospective analysis on small groups of men with variable causes of primary or secondary hypogonadism and mild to overt testosterone deficiencies. This review aims to present the current knowledge of the consequences of adult male hypogonadism on bone metabolism. The direct and indirect effects of testosterone on bone cells will be explored as well as the important differences in male osteoporosis and assessment as compared to that in females. The clinical consequence of both primary and secondary hypogonadism, as well as testosterone decline in older males, on bone density and fracture risk in men will be summarized. Finally, the therapeutic options and their efficacy in male osteoporosis and hypogonadism will be discussed. Copyright © 2017 Gary Golds et al.
Mortality in adults with hypopituitarism: a systematic review and meta-analysis.


Embase
Endocrine. 56 (1) (pp 33-42), 2017. Date of Publication: 01 Apr 2017.

[Article]

AN: 613129881

Purpose: Hypopituitarism is a rare disorder with significant morbidity. To study the evidence on the association of premature mortality and hypopituitarism. Methods: A comprehensive search of multiple databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus was conducted through August, 2015. Eligible studies that evaluated patients with hypopituitarism and reported mortality estimates were selected following a predefined protocol. Reviewers, independently and in duplicate, extracted data and assessed the risk of bias. Results: We included 12 studies (published 1996-2015) that reported on 23,515 patients. Compared to the general population, hypopituitarism was associated with an overall excess mortality (weighted SMR of 1.55; 95 % CI 1.14-2.11), I² = 97.8 %, P = 0.000. Risk factors for increased mortality included younger age at diagnosis, female gender, diagnosis of craniopharyngioma, radiation therapy, transcranial surgery, diabetes insipidus and hypogonadism. Conclusion: Hypopituitarism may be associated with premature mortality in adults. Risk is particularly higher in women and those diagnosed at a younger age.


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Efficacy of varicocelectomy in the treatment of hypogonadism in subfertile males with clinical varicocele: A meta-analysis.
Embase
[Article In Press]
AN: 615331072
To reassess the efficacy of varicocelectomy in the treatment of hypogonadism in subfertile males, we carried out a meta-analysis of clinical trials and retrospective studies that compared the pre-operative and postoperative serum testosterone. We searched Embase and PubMed (1980 to May 2016) for studies. Eight studies and 712 patients were included. The combined analysis of seven studies discovered that the mean serum testosterone of patients post-operation improved by 34.3 ng/dl (95% CI: 22.57-46.04, p < .00001, I² = 0.0%) compared with their pre-operative levels. In subgroup analysis, testosterone improvements in the hypogonadal treated subgroup were more significant (improved by 123 ng/dl, 95% CI: 114.61-131.35, p < .00001, I² = 37%) than in the eugonadal, or the untreated controls. In an analysis of surgery versus untreated control (three studies included), results showed that mean testosterone among hypogonadal increased by 105.65 ng/dl (95% CI: 77.99-133.32), favouring varicocelectomy, as the differences were significant (p < .00001). However, there were insignificant differences in eugonadal (p = .36). In conclusion, varicocelectomy significantly improved testosterone in hypogonadal men with subfertility. Active surgical treatment of varicocele might have a benefit of maintaining healthy androgen levels in subfertile men. Copyright © 2017 Blackwell Verlag GmbH.
Status
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Association between asthma and female sex hormones. <Associacao entre asma e hormonios sexuais femininos.>
Baldacara R.P.C., Silva I.
Embase

**CONTEXT AND OBJECTIVE:** The relationship between sex hormones and asthma has been evaluated in several studies. The aim of this review article was to investigate the association between asthma and female sex hormones, under different conditions (premenstrual asthma, use of oral contraceptives, menopause, hormone replacement therapy and pregnancy).

**DESIGN AND SETTING:** Narrative review of the medical literature, Universidade Federal do Tocantins (UFT) and Universidade Federal de Sao Paulo (Unifesp).

**METHODS:** We searched the CAPES journal portal, a Brazilian platform that provides access to articles in the MEDLINE, PubMed, SciELO, and LILACS databases. The following keywords were used based on Medical Subject Headings: asthma, sex hormones, women and use of oral contraceptives.

**RESULTS:** The associations between sex hormones and asthma remain obscure. In adults, asthma is more common in women than in men. In addition, mortality due to asthma is significantly higher among females. The immune system is influenced by sex hormones: either because progesterone stimulates progesterone-induced blocking factor and Th2 cytokines or because contraceptives derived from progesterone and estrogen stimulate the transcription factor GATA-3.

**CONCLUSIONS:** The associations between asthma and female sex hormones remain obscure. We speculate that estrogen fluctuations are responsible for asthma exacerbations that occur in women. Because of the anti-inflammatory action of estrogen, it decreases TNF-alpha production, interferon-gamma expression and NK cell activity. We suggest that further studies that highlight the underlying physiopathological mechanisms contributing towards these interactions should be conducted.

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139.
Pharmacokinetics of testosterone cream applied to scrotal skin.
Iyer R., Mok S.F., Savkovic S., Turner L., Fraser G., Desai R., Jayadev V., Conway A.J.,
Handelsman D.J.
Embase
[Article In Press]
AN: 615246433
Scrotal skin is thin and has high steroid permeability, but the pharmacokinetics of testosterone via
the scrotal skin route has not been studied in detail. The aim of this study was to define the
pharmacokinetics of testosterone delivered via the scrotal skin route. The study was a single-
center, three-phase cross-over pharmacokinetic study of three single doses (12.5, 25, 50 mg) of
testosterone cream administered in random sequence on different days with at least 2 days
between doses to healthy eugonadal volunteers with endogenous testosterone suppressed by
administration of nandrolone decanoate. Serum testosterone, DHT and estradiol concentrations
were measured by liquid chromatography, mass spectrometry in extracts of serum taken before
and for 16 h after administration of each of the three doses of testosterone cream to the scrotal
skin. Testosterone administration onto the scrotal skin produced a swift (peak 1.9-2.8 h), dose-
dependent (p < 0.0001) increase in serum testosterone with the 25 mg dose maintaining
physiological levels for 16 h. Serum DHT displayed a time- (p < 0.0001), but not dose-dependent,
increase in concentration reaching a peak concentration of 1.2 ng/mL (4.1 nm) at 4.9 h which was
delayed by 2 h after peak serum testosterone. There were no significant changes in serum
estradiol over time after testosterone administration. We conclude that testosterone administration to scrotal skin is well tolerated and produces dose-dependent peak serum testosterone concentration with a much lower dose relative to the non-scrotal transdermal route. Copyright © 2017 American Society of Andrology and European Academy of Andrology.

Status
ARTICLE IN PRESS

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Date Created
20170411

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2017

140.
A perspective on middle-aged and older men with functional hypogonadism: Focus on holistic management.
Grossmann M., Matsumoto A.M.
Embase
[Review]
AN: 614843999
Context: Middle-aged and older men (50 years), especially those who are obese and suffer from comorbidities, not uncommonly present with clinical features consistent with androgen deficiency and modestly reduced testosterone levels. Commonly, such men do not demonstrate anatomical hypothalamic-pituitary-testicular axis pathology but have functional hypogonadism that is potentially reversible. Evidence Acquisition: Literature review from 1970 to October 2016.
Evidence Synthesis: Although definitive randomized controlled trials are lacking, evidence suggests that in such men, lifestyle measures to achieve weight loss and optimization of
comorbidities, including discontinuation of offending medications, lead to clinical improvement and a modest increase in testosterone. Also, androgen deficiency-like symptoms and end-organ deficits respond to targeted treatments (such as phosphodiesterase-5 inhibitors for erectile dysfunction) without evidence that hypogonadal men are refractory. Unfortunately, lifestyle interventions remain difficult and may be insufficient even if successful. Testosterone therapy should be considered primarily for men who have significant clinical features of androgen deficiency and unequivocally low testosterone levels. Testosterone should be initiated either concomitantly with a trial of lifestyle measures, or after such a trial fails, after a tailored diagnostic work-up, exclusion of contraindications, and appropriate counseling. Conclusions: There is modest evidence that functional hypogonadism responds to lifestyle measures and optimization of comorbidities. If achievable, these interventions may have demonstrable health benefits beyond the potential for increasing testosterone levels. Therefore, treatment of underlying causes of functional hypogonadism and of symptoms should be used either as an initial or adjunctive approach to testosterone therapy. Copyright © 2017 by the Endocrine Society.
Klinefelter syndrome (KS) is the most common male sex chromosome disorder, affecting 1/660 men. It is caused by the presence of extra X chromosomes. The KS phenotype is traditionally described as a tall, slim, narrow-shouldered, broad-hipped man with hypergonadotropic hypogonadism and small testes. An association between KS and type 2 diabetes has long been recognized, but the pathogenesis is still unknown. If both hypogonadism and visceral obesity play a role in the development of insulin resistance in men, KS offers an interesting window into this relationship. Indeed, in addition to hypergonadotropic hypogonadism, with variable degrees of androgen deficiency, most 47,XXY KS patients present an unfavorable change in body composition, with increased truncal fat. In KS, both hypotestosteronemia and visceral obesity not only play an important and independent role in determining impaired insulin sensitivity, but may also be reciprocally influenced in a self-perpetuating vicious circle. Other possible mechanisms that may lead to insulin resistance in KS involve the extra copies of X chromosomes. This chapter discusses the main evidence linking KS and impaired insulin sensitivity, leading to insulin resistance and type 2 diabetes. Copyright © 2017 S. Karger AG, Basel.
"Cherchez La Femme": Modulation of Estrogen Receptor Function With Selective Modulators: Clinical Implications in the Field of Urology.
Helo S., Wynia B., McCullough A.

Embase
Sexual Medicine Reviews. (no pagination), 2017. Date of Publication: December 07, 2016.[Article In Press]
AN: 615092466

Introduction: Selective estrogen receptor modulators (SERMs) have been used off-label in men for more than 50 years. SERMs exert their action on the estrogen receptor agonistically or antagonistically. A fundamental knowledge of the complex molecular action and physiology of SERMs is important in understanding their use and future directions of study in men. Aim: To review the basic science and mechanism of the action of estrogens, the estrogen receptor, and SERMs, and the existing clinical publications on the use of SERMs in men for infertility and hypogonadism with their strengths and weaknesses and to identify the need for future studies.

Methods: After a review of publications on the basic science of estrogen receptors, a chronologic review of published evidence-based studies on the use of SERMs in men for infertility and hypogonadism was undertaken. Main Outcome Measures: Clinical publications were assessed for type of study, inclusion criteria, outcome measurements, and results. Strengths and weaknesses of the publications were assessed and discussed. Results: Few prospective rigorously controlled trials have been undertaken on the use of SERMs in men. Most existing trials are largely retrospective anecdotal studies with inconsistent inclusion and end-point measurements. The SERMs are complex and at times can produce paradoxical results. Their action likely depends on the genetics of the individual, his tissue-specific composition of estrogen receptors, the molecular structure and pharmacodynamics of the SERMs, and their metabolism.

Conclusion: Rigorously controlled trials of the use of SERMs in men are needed to better identify their clinical benefit and long-term safety in infertile and hypogonadal men. Recent placebo-controlled pharmaceutical industry SERM trials have demonstrated short-term safety and efficacy in men with secondary hypogonadism and eventually might provide an alternative to exogenous testosterone replacement therapy in men with secondary hypogonadism. Helo S, Wynia B, McCullough A. "Cherchez La Femme": Modulation of Estrogen Receptor Function With Selective Modulators: Clinical Implications in the Field of Urology. Sex Med Rev 2017;X:XXX-XXX.

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Status
ARTICLE IN PRESS
Institution
Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment.


Embase


[Article]

AN: 614732617

Importance: Most cognitive functions decline with age. Prior studies suggest that testosterone treatment may improve these functions. Objective: To determine if testosterone treatment compared with placebo is associated with improved verbal memory and other cognitive functions in older men with low testosterone and age-associated memory impairment (AAMI). Design, Setting, and Participants: The Testosterone Trials (TTrials) were 7 trials to assess the efficacy of testosterone treatment in older men with low testosterone levels. The Cognitive Function Trial evaluated cognitive function in all TTrials participants. In 12 US academic medical centers, 788 men who were 65 years or older with a serum testosterone level less than 275 ng/mL and impaired sexual function, physical function, or vitality were allocated to testosterone treatment (n = 394) or placebo (n = 394). A subgroup of 493 men met criteria for AAMI based on baseline subjective memory complaints and objective memory performance. Enrollment in the TTrials began June 24, 2010; the final participant completed treatment and assessment in June 2014.
Interventions: Testosterone gel (adjusted to maintain the testosterone level within the normal range for young men) or placebo gel for 1 year. Main Outcomes and Measures: The primary outcome was the mean change from baseline to 6 months and 12 months for delayed paragraph recall (score range, 0 to 50) among men with AAMI. Secondary outcomes were mean changes in visual memory (Benton Visual Retention Test; score range, 0 to -26), executive function (Trail-Making Test B minus A; range, -290 to 290), and spatial ability (Card Rotation Test; score range, -80 to 80) among men with AAMI. Tests were administered at baseline, 6 months, and 12 months. Results: Among the 493 men with AAMI (mean age, 72.3 years [SD, 5.8]; mean baseline testosterone, 234 ng/dL [SD, 65.1]), 247 were assigned to receive testosterone and 246 to receive placebo. Of these groups, 247 men in the testosterone group and 245 men in the placebo completed the memory study. There was no significant mean change from baseline to 6 and 12 months in delayed paragraph recall score among men with AAMI in the testosterone and placebo groups (adjusted estimated difference, -0.07 [95%CI, -0.92 to 0.79]; P = .88). Mean scores for delayed paragraph recall were 14.0 at baseline, 16.0 at 6 months, and 16.2 at 12 months in the testosterone group and 14.4 at baseline, 16.0 at 6 months, and 16.5 at 12 months in the placebo group. Testosterone was also not associated with significant differences in visual memory (-0.28 [95%CI, -0.76 to 0.19]; P = .24), executive function (-5.51 [95%CI, -12.91 to 1.88]; P = .14), or spatial ability (-0.12 [95%CI, -1.89 to 1.65]; P = .89). Conclusions and Relevance: Among older men with low testosterone and age-associated memory impairment, treatment with testosterone for 1 year compared with placebo was not associated with improved memory or other cognitive functions. Copyright © 2017 American Medical Association. All rights reserved.


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Testosterone treatment and coronary artery plaque volume in older men with low testosterone.

Importance: Recent studies have yielded conflicting results as to whether testosterone treatment increases cardiovascular risk. Objective: To test the hypothesis that testosterone treatment of older men with low testosterone slows progression of noncalcified coronary artery plaque volume.

Design, Setting, and Participants: Double-blinded, placebo-controlled trial at 9 academic medical centers in the United States. The participants were 170 of 788 men aged 65 years or older with an average of 2 serum testosterone levels lower than 275 ng/dL (82 men assigned to placebo, 88 to testosterone) and symptoms suggestive of hypogonadism who were enrolled in the Testosterone Trials between June 24, 2010, and June 9, 2014. Intervention: Testosterone gel, with the dose adjusted to maintain the testosterone level in the normal range for young men, or placebo gel for 12 months. Main Outcomes and Measures: The primary outcome was noncalcified coronary artery plaque volume, as determined by coronary computed tomographic angiography. Secondary outcomes included total coronary artery plaque volume and coronary artery calcium score (range of 0 to >400 Agatston units, with higher values indicating more severe atherosclerosis). Results: Of 170 men who were enrolled, 138 (73 receiving testosterone treatment and 65 receiving placebo) completed the study and were available for the primary analysis. Among the 138 men, the mean (SD) age was 71.2 (5.7) years, and 81% were white. At baseline, 70 men (50.7%) had a coronary artery calcification score higher than 300 Agatston units, reflecting severe atherosclerosis. For the primary outcome, testosterone treatment compared with placebo was associated with a significantly greater increase in noncalcified plaque volume from baseline to 12 months (from median values of 204 mm$^3$ to 232 mm$^3$ vs 317 mm$^3$ to 325 mm$^3$, respectively; estimated difference, 41 mm$^3$; 95%CI, 14 to 67 mm$^3$; P = .003). For the secondary outcomes, the median total plaque volume increased from baseline to 12 months from 272 mm$^3$ to 318 mm$^3$ in the testosterone group vs from 499 mm$^3$ to 541 mm$^3$ in the placebo
group (estimated difference, 47 mm3; 95%CI, 13 to 80 mm3; P = .006), and the median coronary artery calcification score changed from 255 to 244 Agatston units in the testosterone group vs 494 to 503 Agatston units in the placebo group (estimated difference, -27 Agatston units; 95%CI, -80 to 26 Agatston units). No major adverse cardiovascular events occurred in either group.

Conclusions and Relevance: Among older men with symptomatic hypogonadism, treatment with testosterone gel for 1 year compared with placebo was associated with a significantly greater increase in coronary artery noncalcified plaque volume, as measured by coronary computed tomographic angiography. Larger studies are needed to understand the clinical implications of this finding.

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PMID
145.
Testosterone and male aging: Faltering hope for rejuvenation.
Handelsman D.J.
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EMBASE
An open-label clinical trial to investigate the efficacy and safety of corifollitropin alfa combined with hCG in adult men with hypogonadotropic hypogonadism.

Embase

[Article]
AN: 614684133

Background: Hypogonadotropic hypogonadism (HH) in men results in insufficient testicular function and deficiencies in testosterone and spermatogenesis. Combinations of human chorionic gonadotropin (hCG) and recombinant follicle-stimulating hormone (recFSH) have been successful in the treatment of HH. Corifollitropin alfa is a long-acting FSH-analog with demonstrated action in women seeking infertility care. The aim of this study was to investigate the efficacy and safety of corifollitropin alfa combined with hCG to increase testicular volume and induce spermatogenesis in men with HH. Methods: This was a Phase III, multi-center, open-label, single-arm trial of corifollitropin alfa in azoospermic men aged 18 to 50 years with HH. After 16 weeks of pretreatment of 23 subjects with hCG alone, 18 subjects with normalized testosterone (T) levels who remained azoospermic entered the 52-week combined treatment phase with hCG twice-weekly and 150 mug corifollitropin alfa every other week. The increase in testicular volume (primary efficacy endpoint) and induction of spermatogenesis resulting in a sperm count >=1 x 106/mL (key secondary efficacy endpoint) during 52 weeks of combined treatment were
assessed. Safety was evaluated by the presence of anti-corifollitropin alfa antibodies and the occurrence of adverse events (AEs). Results: Mean (+/- SD) testicular volume increased from 8.6 (+/-6.09) mL to 17.8 (+/-8.93) mL (geometric mean fold increase, 2.30 [95% CI: 2.03, 2.62]); 14 (77.8%) subjects reached a sperm count >=1 x 10⁶/mL. No subject developed confirmed anti-corifollitropin alfa antibodies during the trial. Treatment was generally well tolerated. Conclusions: Corifollitropin alfa 150 mug administrated every other week combined with twice-weekly hCG for 52 weeks increased testicular volume significantly, and induced spermatogenesis in >75% of men with HH who had remained azoospermic after hCG treatment alone. Trial registration: ClinicalTrials.gov: NCT01709331. Copyright © 2017 The Author(s).
The incidence of erectile dysfunction (ED) is on the increase and it is estimated that it will affect about 322 million men globally by the year 2025 if adequate measures are not taken to curb it. Natural polyphenols in plant based diets have gained public interest in recent times due to their roles in the prevention of various disease that implicate free radicals/reactive oxygen species and recently on ED. However, the role of polyphenols in the management of ED has not been explored due perhaps to limited data available. Hence this study which reviewed the role of dietary polyphenols in the management of ED and their mechanisms of action. Literature search was carried out in several electronic data bases such as Pubmed, Google Scholar, Medline, Agora and Hinari from 1972 to 2016 to identify the current status of knowledge on the role of polyphenols in the management of erectile dysfunction. Progress made so far in this direction suggests inhibition of arginase, acetylcholinesterase, angiotensin converting enzyme, rho-kinase II; activation of endothelial and neuronal NO synthase; decreased synthesis of luteinizing hormone and testosterone reduction; activation of silent information regulator 2-related enzymes (sirtuin1) as well as free radical/reactive oxygen species inhibition as the mechanisms through which the polyphenols identified in this review exert beneficial roles in the management of ED.

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Objective: We investigated the effects of testosterone replacement therapy (TRT) on bone mineral density (BMD) among hypogonadal men with osteopenia/osteoporosis. Methods: From our previous EARTH study population, 74 patients with a clinical diagnosis of osteopenia or osteoporosis and hypogonadism were included in this study, as the TRT (n=35) and control (n=34) groups. The TRT group was administered 250mg of testosterone enanthate injection every 4 weeks for 12 months. The BMD, waist circumference, body mass index, body fat percentage, and muscle volume were measured at baseline and at 12 months. Blood biochemical data, including total cholesterol, triglycerides, HDL-cholesterol, hemoglobin A1c, and adiponectin values were also evaluated. Results: At the 12-month visit, BMD significantly increased in both groups. However, comparisons on changes of parameter values from baseline to the 12-month visit between the TRT and control groups were significantly different in BMD (5.0+/−3.0 vs. 5.0+/−3.2; p=.0434) and in adiponectin value (-0.90+/−3.33 vs. 0.10+/−2.04; p=.0192). There were no significant changes in other parameters. Conclusions: TRT for 12 months could improve BMD with a decrease in adiponectin levels among hypogonadal men with osteopenia/osteoporosis.
Objective To investigate associations between testosterone levels and major depressive disorder (MDD) in older men and women. Methods In a cross-sectional, 2-year prospective analyses within the Netherlands Study on Depression in Older persons cohort study, 469 participants comprised 350 patients with MDD and 119 nondepressed participants in the comparison group (mean age 70.5+/−7.3 years; 166 [35.4%] men). MDD was assessed by the Composite International Diagnostic Interview. Baseline plasma total testosterone and sex hormone binding globulin (SHBG) were assessed to calculate free testosterone. The Inventory of Depressive Symptomatology was assessed every 6 months. Results Whereas SHBG levels did not differ between the depressed/nondepressed groups (F(1,149)=0.075, p=0.78), men with MDD had lower mean total and free testosterone levels than the comparison group in the multivariate adjusted analyses (F(1,150)=7.249, p=0.008, Cohen's d=0.51; and F(1,149)=8.548, p=0.004 Cohen's d=0.55, respectively). This could be ascribed to lower testosterone in men with "pure" MDD and not in men with MDD and comorbid anxiety. Nine men (5.4%) had a total testosterone level<8nmol/L, of whom 8 suffered from MDD. In women, hormone levels showed no significant difference between the groups. In men (using all five measurement points during follow-up) baseline free testosterone was inversely associated with depression severity in the adjusted analyses (beta=-0.15, t(151)=−2.15, p=0.03). Conclusion Testosterone levels were lower in men with MDD compared with healthy men after adjustment for confounders, such as body mass index. No significant associations were found in women. Copyright © 2017 American Association for Geriatric Psychiatry
A variety of drugs may provoke acne, with drug-induced acne (DIA) often having some specific clinical and histopathologic features. DIA is characterized by a medical history of drug intake, sudden onset, and an unusual age of onset, with a monomorphous eruption of inflammatory papules or papulopustules. The location of the acne lesions is beyond the seborrheic zone. Corticosteroids, anabolic steroids, testosterone, halogens, isoniazid, lithium, and some new anticancer agents are drugs with undoubted causal relationship to acne. The diagnosis of DIA is made by a detailed history with a record of drug onset, dosage regimen and therapy duration, absence of additional triggering factors, and clinical relationship between the introduction of the
drug and the onset of an acne-like eruption. In all cases, the withdrawal of the drug should be followed by lessening of the acne lesions. Copyright © 2016 Elsevier Inc.

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151.
Eurycoma Longifolia as a potential adaptogen of male sexual health: a systematic review on clinical studies.
Thu H.E., Mohamed I.N., Hussain Z., Jayusman P.A., Shuid A.N.
Embase
[Article]
AN: 614621595
Eurycoma longifolia (EL) has been well recognized as a booster of male sexual health. Over the past few decades, numerous in vivo animal studies and human clinical trials have been conducted across the globe to explore the promising role of EL in managing various male sexual disorders, which include erectile dysfunction, male infertility, low libido, and downregulated testosterone levels. The aim of the present review is to analyze and summarize the literature on human clinical trials which revealed the clinical significance and therapeutic feasibility of EL in improving male sexual health. This systematic review is focused on the following databases: Medline, Wiley Online Library, BioMed Central, Hindawi, Web of Knowledge, PubMed Central and Google Scholar, using search terms such as "Eurycoma longifolia", "EL", "Tongkat Ali", "male sexual health", "sexual infertility", "erectile dysfunction", "male libido", and "testosterone levels". Notably, only human clinical studies published between 2000 and 2014 were selected and
thoroughly reviewed for relevant citations. Out of 150 articles, 11 met the inclusion criteria. The majority of articles included were randomized placebo-controlled trials, multiple cohort studies, or pilot trials. All these studies demonstrated considerable effects of EL on male sexual health disorders. Among them, 7 studies revealed remarkable association between the use of EL and the efficacy in the treatment of male sexual disorders, and remaining 4 studies failed to demonstrate sufficient effects on male sexual health. In summary, there is convincing evidence for the prominence of EL in improving the male sexual health. The review also substantiates the use of current methodology in the development of novel and more rationale natural herbal medicines for the management of male sexual disorders. Copyright © 2017 China Pharmaceutical University

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152.
Testosterone Plasma Concentration is Associated with Insulin Resistance in Male Hypertensive Patients.

Embase
Background: Low testosterone levels are a common finding among men with Type 2 Diabetes Mellitus (T2DM) and are inversely related to insulin resistance. Whether this relationship holds true in patients with hypertension, but normal glucose tolerance or prediabetes, is unclear.

Methods: We recruited 87 male outpatients with essential arterial hypertension, aged 35-70 years. Anthropometric data were collected, an Oral Glucose Tolerance Test (OGTT) performed, and the homeostasis model assessment of insulin resistance (HOMA-IR) score calculated. Follicle-Stimulating Hormone, Luteinizing Hormone, testosterone, Sex Hormone-Binding-Globulin and free-testosterone were measured. The concentrations of sex hormones were compared between normogluco tolerant, prediabetic and diabetic patients. Non-parametric tests were applied as appropriate to verify differences among groups, while multiple linear regression was used to predict the variability of testosterone and free-testosterone. Results: Total serum testosterone concentration was significantly lower in T2DM in comparison to normogluco tolerant subjects (p<0.01) and was inversely related to body mass index (r=- 0.25, p<0.01), waist circumference (r= 0.27, p<0.01), pre and post-OGTT plasma glucose (r=- 0.4, p<0.0001 and r=-0.29, p<0.01, respectively), pre and post-OGTT plasma insulin (r=- 0.42, p<0.0001 and r=- 0.42, p<0.0001) and HOMA-IR (r= 0.46, p<0.0001). Similar associations were observed for free testosterone; HOMA-IR was related to testosterone and free-testosterone even in patients with normal glucose tolerance (r= 0.47, p<0.01 and r= 0.34, p<0.05, respectively). At multivariate analysis HOMA-IR was the only variable associated to testosterone (p<0.001) and free-testosterone (p<0.05) plasma concentration. Conclusions: In males with hypertension, the link between insulin sensitivity and hypothalamic-pituitary-gonadal axis is maintained along the entire spectrum of glucose tolerance.

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Status EMBASE
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Health-related quality of life and psychological well-being in adults with differences/disorders of sex development.

Bennecke E., Thyen U., Gruters A., Lux A., Kohler B.

Embase
Clinical Endocrinology. 86 (4) (pp 634-643), 2017. Date of Publication: 01 Apr 2017.

Objective: Rare congenital conditions with incongruence of chromosomal, gonadal and phenotypic sex have been classified as differences/disorders of sex development (DSD). Included in DSD are conditions with diverse genetic aetiology, varying levels of prenatal androgen effects, phenotypes and, subsequently, different medical treatments. Quality of life (QoL) and psychological well-being are indicators of successful psychosocial adaptation to the conditions. We sought to investigate the HRQoL and psychological well-being in this population. Design: This multicentre clinical evaluation study was part of a German network related to DSD funded by the German Ministry of Science and Education (BMBF 2003 to 2007). Methods: To assess health-related quality of life (HRQoL), we used the Short Form Health Survey (SF-36), and for psychological well-being, the Brief Symptom Inventory (BSI). Participants were classified into five groups: females with CAH, females with XY DSD conditions where there is a partial androgen effect (partial androgen insensitivity, mixed/partial gonadal dysgenesis, disorders of androgen biosynthesis), females with XY DSD without androgen effect (complete androgen insensitivity, complete gonadal dysgenesis), males with XY DSD, and individuals with DSD conditions and other gender. Results: Participants included 110 adults with DSD (age range 17-62). We found a trend of lowered mental HRQoL and significant higher physical HRQoL for participants as compared to the norm. The high physical HRQoL especially applied to females with androgen effect and XY karyotype. Participants reported significant higher psychological distress compared to the norm. Forty-seven participants (42.7%) reported distress in a clinically relevant range on
the BSI. Conclusions: Although we did not find significant impairments in overall HRQoL, participants reported significant impaired psychological well-being. Specialized interdisciplinary care should focus in particular on psychological issues to ensure good overall health and well-being. Copyright © 2016 John Wiley & Sons Ltd

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154.
Hackett G.

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Introduction: Graham Jackson introduced the concept that erectile dysfunction (ED) is a marker for undiagnosed cardiovascular (CV) disease and future events. In the Princeton 3 guidelines, he recognized the important impact of testosterone deficiency (TD) on all-cause and CV mortality. Recent evidence suggests that testosterone therapy to target levels and for sufficient duration decreases CV events. Unfortunately, this had a modest impact on CV disease management
because ED is not incorporated into current risk calculators. This report is based on the Graham Jackson Memorial Lecture presented at the International Society for Sexual Medicine (ISSM) in Beijing in 2016. Aim: To examine recent evidence as to whether ED should be upgraded to a risk factor, especially with the high predictive value in younger men, and to develop a case for TD to be considered an independent risk factor based on a large number of long-term studies during the past 5 years. Methods: A Medline search was undertaken to include articles on ED and TD and related terms from 1998 to 2016 during the preparation of ISSM guidelines on ED and TD. Main Outcome Measures: A rational justification for ED and low testosterone to be considered risk factors for CV disease and be included in risk calculators. Results: The evidence for inclusion of ED and TD might be stronger than for accepted risk factors and have the advantages of being easily assessed, quantitative, symptomatic, and clinically relevant, especially in younger men. Because important studies are often published in endocrine, sexual medicine, urology, and cardiology journals, a multidisciplinary approach is needed. Conclusion: There is strong evidence that ED and low testosterone might be of more practical relevance to programs that decrease CV risk than some current recognized risk factors. Hackett G. The Graham Jackson Memorial Lecture ISSM 2016—“The Man Who Knew Too Much”: Time to Recognize Erectile Dysfunction and Low Testosterone as Independent Risk Factors for Cardiovascular Disease. Sex Med Rev 2017;X:XX-XX. Copyright © 2017.

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Comparison of the single dose pharmacokinetics, pharmacodynamics, and safety of two novel oral formulations of dimethandrolone undecanoate (DMAU): A potential oral, male contraceptive.
Dimethandrolone (DMA, 7alpha,11b-dimethyl-19-nortestosterone) has both androgenic and progestational activities, ideal properties for a male hormonal contraceptive. In vivo, dimethandrolone undecanoate (DMAU) is hydrolyzed to DMA. We showed previously that single oral doses of DMAU powder in capsule taken with food are well tolerated and effective at suppressing both LH and testosterone (T), but absorption was low. We compared the pharmacokinetics and pharmacodynamics of two new formulations of DMAU, in castor oil and in self-emulsifying drug delivery systems (SEDDS), with the previously tested powder formulation. DMAU was dosed orally in healthy adult male volunteers at two academic medical centers. For each formulation tested in this double-blind, placebo-controlled study, 10 men received single, escalating, oral doses of DMAU (100, 200, and 400 mg) and two subjects received placebo. All doses were evaluated for both fasting and with a high fat meal. All three formulations were well tolerated without clinically significant changes in vital signs, blood counts, or serum chemistries. For all formulations, DMA and DMAU showed higher maximum (p < 0.007) and average concentrations (p < 0.002) at the 400 mg dose, compared with the 200 mg dose. The powder formulation resulted in a lower conversion of DMAU to DMA (p = 0.027) compared with both castor oil and SEDDS formulations. DMAU in SEDDS given fasting resulted in higher serum DMA and DMAU concentrations compared to the other two formulations. Serum LH and sex hormone concentrations were suppressed by all formulations of 200 and 400 mg DMAU when administered with food, but only the SEDDS formulation was effectively suppressed serum T when given fasting. We conclude that while all three formulations of oral DMAU are effective and well tolerated when administered with food, DMAU in oil and SEDDS increased conversion to DMA, and SEDDS may have some effectiveness when given fasting. These properties might be advantageous for the application of DMAU as a male contraceptive. 

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Testosterone prevents protein loss via the hepatic urea cycle in human.
Lam T., Poljak A., McLean M., Bahl N., Ho K.K.Y., Birzniece V.
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AN: 614784586

Context: The urea cycle is a rate-limiting step for amino acid nitrogen elimination. The rate of urea synthesis is a true indicator of whole-body protein catabolism. Testosterone reduces protein and nitrogen loss. The effect of testosterone on hepatic urea synthesis in humans has not been studied. Objective: To determine whether testosterone reduces hepatic urea production. Design: An open-label study. Patients and intervention: Eight hypogonadal men were studied at baseline, and after two weeks of transdermal testosterone replacement (Testogel, 100 mg/day). Main outcomes measures: The rate of hepatic urea synthesis was measured by the urea turnover technique using stable isotope methodology, with 15N2-urea as tracer. Whole-body leucine turnover was measured, from which leucine rate of appearance (LRa), an index of protein breakdown and leucine oxidation (Lox), a measure of irreversible protein loss, were calculated. Results: Testosterone administration significantly reduced the rate of hepatic urea production (from 544.4 +/- 71.8 to 431.7 +/- 68.3 mumol/min; P < 0.01), which was paralleled by a significant reduction in serum urea concentration. Testosterone treatment significantly reduced net protein loss, as measured by percent Lox/LRa, by 19.3 +/- 5.8% (P < 0.05). There was a positive association between Lox and hepatic urea production at baseline (r2 = 0.60, P < 0.05) and after testosterone administration (r2 = 0.59, P < 0.05). Conclusion: Testosterone replacement reduces
protein loss and hepatic urea synthesis. We conclude that testosterone regulates whole-body protein metabolism by suppressing the urea cycle. Copyright © 2017 European Society of Endocrinology.

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157.
Symptomatic response to testosterone treatment in dieting obese men with low testosterone levels in a randomized, placebo-controlled clinical trial.
Ng Tang Fui M., Hoermann R., Prendergast L.A., Zajac J.D., Grossmann M.

Embase
[Article]
AN: 614134471
Background: Obese men commonly have reductions in circulating testosterone and report symptoms consistent with androgen deficiency. We hypothesized that testosterone treatment improves constitutional and sexual symptoms over and above the effects of weight loss alone.

Methods: We conducted a pre-specified analysis of a randomized double-blind, placebo-controlled trial at a tertiary referral center. About 100 obese men (body mass index (BMI) ≥30 kg m⁻²) with a repeated total testosterone level ≤12 nmol l⁻¹ and a median age of 53 years (interquartile range 47-60) receiving 10 weeks of a very-low-energy diet (VLED) followed by 46 weeks of weight maintenance were randomly assigned at baseline to 56 weeks of intramuscular testosterone undecanoate (n=49, cases) or matching placebo (n=51, controls). Pre-specified outcomes were the between-group differences in Aging Male Symptoms scale (AMS) and international index of erectile function (IIEF-5) questionnaires.

Results: Eighty-two men completed the study. At study end, cases showed significant symptomatic improvement in AMS score, compared with controls, and improvement was more marked in men with more severe baseline symptoms (mean adjusted difference (MAD) per unit of change in AMS score -0.34 (95% confidence interval (CI) -0.65, -0.02), P=0.04). This corresponds to improvements of 11% and 20% from baseline scores of 40 and 60, respectively, with higher scores denoting more severe symptoms. Men with erectile dysfunction (IIEF-5 ≤20) had improved erectile function with testosterone treatment. Cases and controls lost the same weight after VLED (testosterone -12.0 kg; placebo -13.5 kg, P=0.40) and maintained this at study end (testosterone -11.4 kg; placebo -10.9 kg, P=0.80). The improvement in AMS following VLED was not different between the groups (-0.05 (95% CI -0.28, 0.17), P=0.65).

Conclusions: In otherwise healthy obese men with mild to moderate symptoms and modest reductions in testosterone levels, testosterone treatment improved androgen deficiency symptoms over and above the improvement associated with weight loss alone, and more severely symptomatic men achieved a greater benefit. Copyright © 2017 Macmillan Publishers Limited, part of Springer Nature. All rights reserved.
Nakalanga Syndrome: Clinical Characteristics, Potential Causes, and Its Relationship with Recently Described Nodding Syndrome.

Foger K., Gora-Stahlberg G., Sejvar J., Ovuga E., Jilek-Aall L., Schmutzhard E., Kaiser C., Winkler A.S.

Embase


[Review]
AN: 614655790

Nakalanga syndrome is a condition that was described in Uganda and various other African countries decades ago. Its features include growth retardation, physical deformities, endocrine dysfunction, mental impairment, and epilepsy, amongst others. Its cause remains obscure.

Nodding syndrome is a neurological disorder with some features in common with Nakalanga syndrome, which has been described mainly in Uganda, South Sudan, and Tanzania. It has been considered an encephalopathy affecting children who, besides head nodding attacks, can also present with stunted growth, delayed puberty, and mental impairment, amongst other symptoms.

Despite active research over the last years on the pathogenesis of Nodding syndrome, to date, no convincing single cause of Nodding syndrome has been reported. In this review, by means of a thorough literature search, we compare features of both disorders. We conclude that Nakalanga and Nodding syndromes are closely related and may represent the same condition. Our findings may provide new directions in research on the cause underlying this neurological disorder.

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Status
Embase

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(Foger, Gora-Stahlberg, Winkler) Department of Neurology, Technical University of Munich, Munich, Germany  (Sejvar) Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, United States
Effects of taking tadalafil 5 mg once daily on erectile function and total testosterone levels in patients with metabolic syndrome.

Ozcan L., Polat E.C., Kocaaslan R., Onen E., Otunctemur A., Ozbek E.

[Article In Press]

AN: 614878125

We aimed to evaluate the efficacy of tadalafil 5 mg once-daily treatment on testosterone levels in patients with erectile dysfunction (ED) accompanied by the metabolic syndrome. A total of 40 men with metabolic syndrome were evaluated for ED in this study. All the patients received 5 mg tadalafil once a day for 3 months. Erectile function was assessed using the five-item version of the International Index of Erectile Function (IIEF) questionnaire. Serum testosterone, follicle-stimulating hormone and luteinising hormone levels were also evaluated, and blood samples were taken between 08.00 and 10.00 in the fasting state. All participants have three or more criteria of metabolic syndrome. At the end of 3 months, mean testosterone values and IIEF scores showed an improvement from baseline values (from 3.6 +/- 0.5 to 5.2 +/- 0.3, from 11.3 +/- 1.9 to 19 +/- 0.8 respectively). After the treatment, serum LH levels were decreased (from 5.6 +/- 0.6 to 4.6 +/- 0.5). There was significantly difference in terms of baseline testosterone and luteinising hormone values and IIEF scores (p < .05). Based on our findings, we recommend
tadalafil 5 mg once daily in those men with erectile dysfunction especially low testosterone levels accompanied by metabolic syndrome. Copyright © 2017 Blackwell Verlag GmbH.

Jasuja G.K., Bhasin S., Reisman J.I., Hanlon J.T., Miller D.R., Morreale A.P., Pogach L.M., Cunningham F.E., Park A., Berlowitz D.R., Rose A.J.
Embase
[Article]
AN: 613790122
Background: There has been concern about the growing off-label use of testosterone. Understanding the context within which testosterone is prescribed may contribute to interventions to improve prescribing. Objective: To evaluate patient characteristics associated with receipt of testosterone. Design: Cross-sectional. Setting: A national cohort of male patients, who had received at least one outpatient prescription within the Veterans Affairs (VA) system during Fiscal Year 2008- Fiscal Year 2012. Participants: The study sample consisted of 682,915 non-HIV male patients, of whom 132,764 had received testosterone and a random 10% sample, 550,151, had
not. Main Measures: Conditions and medications associated with testosterone prescription. Key Results: Only 6.3% of men who received testosterone from the VA during the study period had a disorder of the testis, pituitary or hypothalamus associated with male hypogonadism. Among patients without a diagnosed disorder of hypogonadism, the use of opioids and obesity were the strongest predictors of testosterone prescription. Patients receiving >100 mg/equivalents of oral morphine daily (adjusted odds ratio = 5.75, p < 0.001) and those with body mass index (BMI) >40 kg/m² (adjusted odds ratio = 3.01, p < 0.001) were more likely to receive testosterone than non-opioid users and men with BMI <25 kg/m². Certain demographics (age 40-54, White race), comorbid conditions (sleep apnea, depression, and diabetes), and medications (antidepressants, systemic corticosteroids) also predicted a higher likelihood of testosterone receipt, all with an adjusted odds ratio less than 2 (p < 0.001). Conclusions: In the VA, 93.7% of men receiving testosterone did not have a diagnosed condition of the testes, pituitary, or hypothalamus. The strongest predictors of testosterone receipt (e.g., obesity, receipt of opioids), which though are associated with unapproved, off-label use, may be valid reasons for therapy. Interventions should aim to increase the proportion of testosterone recipients who have a valid indication. Copyright © 2016, Society of General Internal Medicine.

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Bone mineral density and its determinants in men with opioid dependence.
Gotthardt F., Huber C., Thierfelder C., Grize L., Kraenzlin M., Scheidegger C., Meier C.

[Article]
AN: 607648342

Data on the influence of opioid substitution therapy (OST) on skeletal health in men is limited. This cross-sectional study aimed to determine the prevalence of low bone mass in male drug users and to evaluate the relationship between endogenous testosterone and bone mass. We recruited 144 men on long-term opioid maintenance therapy followed in the Center of Addiction Medicine in Basel, Switzerland. Data on medical and drug history, fracture risk and history of falls were collected. Bone mineral density (BMD) was evaluated by densitometry and serum was collected for measurements of gonadal hormones and bone markers. 35 healthy age- and BMI-matched men served as the control group. The study participants received OST with methadone (69 %), morphine (25 %) or buprenorphine (6 %). Overall, 74.3 % of men had low bone mass,
with comparable bone mass irrespective of OST type. In older men (>=40 years, n = 106), 29.2 % of individuals were osteoporotic (mean T-score -3.0 +/- 0.4 SD) and 48.1 % were diagnosed with osteopenia (mean T-score -1.7 +/- 0.4 SD). In younger men (n = 38), 65.8 % of men had low bone mass. In all age groups, BMD was significantly lower than in age-and BMI-matched controls. In multivariate analyses, serum free testosterone (fT) was significantly associated with low BMD at the lumbar spine (p = 0.02), but not at the hip. When analysed by quartiles of fT, lumbar spine BMD decreased progressively with decreasing testosterone levels. We conclude that low bone mass is highly prevalent in middle-aged men on long-term opioid dependency, a finding which may partly be determined by partial androgen deficiency. Copyright © 2016, The Japanese Society for Bone and Mineral Research and Springer Japan.

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162.
Sex steroids in relation to cardiac structure and function in men.
De Smet M.A.J., Lapauw B., De Backer T.

Embase
The prevalence of testosterone substitution as well as of androgen deprivation therapy in men is increasing. This review aims to summarise available knowledge of the effects of sex steroids on cardiac structure and function in men. MEDLINE was searched through PubMed. Original studies, systematic reviews and meta-analyses, and relevant citations were screened. A short-term hormonal intervention study in healthy young men with respect to echocardiographic parameters of structure and function was performed. Preclinical research provides sufficient evidence for the heart as a substrate for sex hormones. In animals, administration of oestradiol appears to have beneficial effects on cardiac structure and function, whereas administration of testosterone to noncastrated animals adversely affects cardiac function. However, the effects of sex steroids on cardiac function and structure appear more heterogeneous in human observational studies while comparative, prospective studies in humans are lacking. It is concluded that although effects of testosterone substitution as well as of androgen deprivation on cardiac structure and function can be expected based on pre-clinical research, there exists an important knowledge gap of the effects of hormonal intervention in men. As such, there is a need to address this question in future prospective intervention trials.
Efficacy and safety of testosterone gel 2% (TG) were evaluated in two phase 3, open-labelled, single-arm, multicentre studies (000023 and extension study 000077). Hypogonadal men having serum testosterone levels <300 ng/dl at two consecutive measurements were included. Study duration was 9 months (000023: 3 months; 000077: 6 months). Starting dose of TG (46 mg) was applied on upper arm/shoulder. The primary endpoint (000023) was responder rate (subjects with average 24-hour serum testosterone concentration 300-1050 ng/dl on Day 90). Study 000077 evaluated the safety of TG in patients rolling over from study 000023 over a period of 6 months. Of 180 subjects in 000023, 172 completed and 145 rolled over to 000077, with 127 completers. The responder rate was 85.5%. Fewer subjects in 000077 (12.7%) versus 000023 (31.8%) had maximum testosterone concentration (Cmax) >1500 ng/dl, with no significant safety concerns. Significant improvements in sexual function and quality of life were noted in both studies. Subjects experienced few skin reactions without notable increases in prostate-specific antigen and haematocrit levels. TG was efficacious with an acceptable safety profile. Cmax >1500 ng/dl did not exhibit distinct impact on safety parameters. However, further optimisation of titration schema to reduce Cmax is warranted while maintaining the average steady state total testosterone concentration. Copyright © 2017 Blackwell Verlag GmbH.
Effect of soy in men with type 2 diabetes mellitus and subclinical hypogonadism: A randomized controlled study.
Sathyapalan T., Rigby A.S., Bhasin S., Thatcher N.J., Kilpatrick E.S., Atkin S.L.
Embase
[Review]
AN: 614400238
Context: Isoflavones found in soy products have a chemical structure similar to estrogen, leading to concerns of an adverse estrogenic effect in men, particularly in those with type 2 diabetes mellitus (T2DM) who have low testosterone levels due to hypogonadism. Objective: The primary outcome was change in total testosterone levels. The secondary outcomes were the changes in glycemia and cardiovascular risk markers. Design: This was a randomized double-blind parallel study. Setting: This study occurred in a secondary care setting in United Kingdom. Participants: Two hundred men with T2DM and a total testosterone level <=12 nmol/L were included. Intervention: Fifteen grams of soy protein with 66 mg of isoflavones (SPI) or 15 g soy protein alone without isoflavones (SP) daily as snack bars for 3 months were administered. Results: There was no change in either total testosterone or in absolute free testosterone levels with either SPI or SP. There was an increase in thyrotropin (TSH) and reduction in free thyroxine (FT4; P < 0.01) after SPI supplementation. Glycemic control improved with a significant reduction in hemoglobin A1c (24.19 [7.29]mmol/mol, P<0.01) and homeostasis model of assessment - insulin resistance after SPI. Cardiovascular risk improved with a reduction in triglycerides, C-reactive protein, and diastolic blood pressure (DBP; P <0.05) with SPI vs SP supplementation. There was a 6% improvement in 10-year coronary heart disease risk after 3 months of SPI supplementation. Endothelial function improved with both SPI and SP supplementation (P < 0.01), with an increased reactive hyperemia index that was greater for the SPI group (P < 0.05). Conclusions: Testosterone levels were unchanged and there was a substantial improvement in glycaemia and...
cardiovascular risk markers with SPI compared with SP alone over 3 months. There was also a substantial increase in TSH and a reduction in fT4. Copyright © 2017 by the Endocrine Society.

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165.
Disruption of aromatase homeostasis as the cause of a multiplicity of ailments: A comprehensive review.
Patel S.
Embase
[Review]
AN: 614278230
Human health is beset with a legion of ailments, which is exacerbated by lifestyle errors. Out of the numerous enzymes in human body, aromatase, a cytochrome P450 enzyme is particularly very critical. Occurring at the crossroads of multiple signalling pathways, its homeostasis is vital for optimal health. Unfortunately, medications, hormone therapy, chemical additives in food, and
endocrine-disrupting personal care products are oscillating the aromatase concentration beyond the permissible level. As this enzyme converts androgens (C19) into estrogens (C18), its agitation has different outcomes in different genders and age groups. Some common pathologies associated with aromatase disruption include breast cancer, prostate cancer, polycystic ovary syndrome (PCOS), endometriosis, osteoporosis, ovarian cancer, gastric cancer, pituitary cancer, Alzheimer’s disease, schizophrenia, male hypogonadism, and transgender issues. Several drugs, cosmetics and pesticides act as the activators and suppressors of this enzyme. This carefully-compiled critical review is expected to increase public awareness regarding the threats resultant of the perturbations of this enzyme and to motivate researchers for further investigation of this field. Copyright © 2017 Elsevier Ltd

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166.
Biological functions as affected by summer season-related multiple environmental stressors (heat, nutritional and walking stress) in Malpura rams under semi-arid tropical environment.
Kumar D., Sejian V., Gaughan J.B., Naqvi S.M.K.
Embase
[Article In Press]
AN: 614736781
The study was conducted with the primary objective to establish the impact of simultaneously imposed multiple stressors (thermal, nutritional and walking) on various biological functions in Malpura rams. The study was conducted for a period of 45 days. Twenty adult Malpura rams
(average BW 44.9 Kg) were used in the present study. The rams were divided into two groups, CON (n = 10; Control) and MS (n = 10; multiple stressors). Both body weight (p < 0.05) and body condition scoring (p < 0.01) were lower in MS compared with CON rams. All the scrotal measurements reduced significantly (p < 0.01) in MS rams. All the testicular measurements also reduced significantly (p < 0.01) in MS as compared to CON rams. The seminal attributes, individual motility (p < 0.05), rapid motility (p < 0.05) and curvilinear velocity (p < 0.05) were significantly reduced in CON rams. However, slowness (p < 0.05), linearity (p < 0.05) and straightness (p < 0.05) parameters significantly increased in MS as compared to CON rams. In addition, plasma testosterone concentration was lower (p < 0.05) in MS rams. The study established the impact of multiple stressors on growth and reproductive performance of Malpura rams. Further, the results revealed that the only semen quality was affected by multiple stressors, but the semen production remained intact between the groups, indicating the extreme adaptive capability of Malpura rams to hot semi-arid tropical environment. Copyright © 2017 Informa UK Limited, trading as Taylor & Francis Group

Androgen deprivation causes selective deficits in the biomechanical leg muscle function of men during walking: a prospective case-control study.
Background: Although muscle mass declines with testosterone deficiency in men, previous studies of muscle function have not demonstrated consistent deficits, likely due to relatively insensitive methodology. Our objective was to determine the effects of testosterone deprivation on the biomechanical function of individual lower-limb muscles. Methods: We conducted a 12-month prospective, observational case-control study of 34 men newly commencing androgen deprivation treatment (ADT) for prostate cancer and 29 age-matched prostate cancer controls. Participants were assessed at 0, 6, and 12 months while walking in a biomechanics laboratory. We combined video-based motion capture and ground reaction force data with computerized musculoskeletal modelling to assess the following primary outcomes: (i) peak joint torques at the hip, knee and ankle, and corresponding individual muscle forces; (ii) individual muscle contributions to acceleration of the body's centre of mass; and (iii) walking speed, stride length, and step width. A linear mixed model was used to compare mean differences between groups. Results: Compared with controls over 12 months, men receiving ADT had a mean reduction in total testosterone level from 14.1 to 0.4 nmol/L, and demonstrated more marked decreases in peak hip flexor torque by 14% [mean difference -0.11 N/kg (-0.19, -0.03), P = 0.01] and peak knee extensor torque by 16% [-0.11 N/kg (-0.20, -0.02), P = 0.02] of the initial mean value. Correspondingly, iliopsoas force decreased by 14% (P = 0.006), and quadriceps force decreased by 11%, although this narrowly missed statistical significance (P = 0.07). Soleus decreased contribution to forward acceleration of the body's centre of mass by 17% [mean difference -0.17 m/s² (-0.29, -0.05), P < 0.01]. No significant changes between groups were observed in other joint torques or individual muscle contributions to acceleration of the body. Step width increased by 18% [mean adjusted difference 1.4 cm (0.6, 27.4), P = 0.042] in the ADT group compared with controls, with no change in stride length or walking speed. Conclusions: Testosterone deprivation selectively decreases lower-limb muscle function, predominantly affecting muscles that support body weight, accelerate the body forwards during walking, and mediate balance. Future exercise and pro-myogenic interventional studies to mitigate ADT-associated sarcopenia should target these deficits.
Erectile dysfunction in fit and healthy young men: Psychological or pathological?

Rastrelli G., Maggi M.

Embase

Translational Andrology and Urology. 6 (1) (pp 79-90), 2017. Date of Publication: 2017.

[Review]

AN: 614521507

Epidemiological studies consistently show that prevalence of erectile dysfunction (ED) increases with ageing. Nonetheless, complaints of ED even in younger men are becoming more and more frequent. Healthcare professionals working in Sexual Medicine but even those operating in different clinical contexts might be adequately prepared to answer this increasing requirement. ED in younger men is likely to be overlooked and dismissed without performing any medical assessment, even the most basic ones, such as collection of medical history and physical exam. This is due to the widespread assumption that ED in younger individuals is a self-limiting condition, which does not deserve any clinical evaluation or therapy and can be managed only with patient reassurance. However, evidence shows that, in younger subjects, organic, psychological and relational conditions can contribute to the pathogenesis of ED and all these conditions might be evaluated and treated, whenever necessary. Among the organic conditions
contributing to the onset of ED, metabolic and cardiovascular (CV) risk factors are surprisingly of particular relevance in this age group. In fact, in younger men with ED, even more than in older ones, recognizing CV risk factors or conditions suggestive of cardio-metabolic derangements can help identifying men who, although at low absolute risk due to young age, carry a high relative risk for development of CV events. In this view, the assessment of a possible organic component of ED even in younger individuals acquires a pivotal importance, because it offers the unique opportunity to unearth the presence of CV risk factors, thus allowing effective and high quality preventive interventions. Copyright © Translational Andrology and Urology. All rights reserved.

169.
Adherence to treatment in men with hypogonadotrophic hypogonadism.
Dwyer A.A., Tiemensma J., Quinton R., Pitteloud N., Morin D.

Embase
Clinical Endocrinology. 86 (3) (pp 377-383), 2017. Date of Publication: 01 Mar 2017.

[Article]
AN: 614107039

Objective: Men with congenital hypogonadotrophic hypogonadism (CHH) typically require lifelong hormonal therapy, and discontinuing treatment can have negative health consequences. Little is known about adherence to treatment or the psychosocial impact of CHH. Design: A sequential, multiple methods approach was used. A quantitative online survey assessed adherence to treatment, depressive symptoms and illness perceptions. Subsequently, qualitative focus groups
explored patient-reported factors for adherence. Patients: Adult men with CHH on at least 1 year of treatment were recruited internationally. Measurements: Adherence (Morisky medication adherence scale), depressive symptoms (Zung self-rating depression scale) and patient perception of CHH (revised illness perception questionnaire) were assessed in an online survey, and comparisons were made to reference groups. Patient focus group discussions were conducted and thematic analysis was employed to identify patient-reported factors for adherence.

Results: In total, 101 men on long-term treatment were included (mean age 37 +/- 11 years). Forty three percent (43/101) exhibited low medication adherence and a significantly elevated prevalence of mild, moderate or severe depressive symptoms (27%, 17%, 20%, respectively, all P < 0.001 vs reference population). Patients reported negative illness perceptions and significant psychosocial consequences. Focus group discussions (n = 3, 26 total patients) identified patient-, health professional- and healthcare system-related barriers as targets for improving adherence.

Conclusions: Congenital hypogonadotrophic hypogonadism men are challenged to adhere to long-term treatment. Poor adherence may contribute to adverse effects on bone, sexual and psychological health. The psychosocial morbidity of CHH is significant and appears to be underappreciated by healthcare providers.
Frailty is a clinical condition related to changes in metabolism, to sarcopenia, and to decline in muscle mass and strength, bone mineral density, and physical function with aging. The pathophysiology of frailty is multifactorial and associated with comorbidities. Testosterone is implicated in regulating metabolic functions, maintenance of muscle and bone, and inhibition of adipogenesis. In older individuals, reduced testosterone is thought to contribute to an altered state of metabolism, loss of muscle and bone, and increased fat, leading to sarcopenia, sarcopenic obesity, and frailty. While no direct relationship between testosterone deficiency (commonly known as hypogonadism) and frailty has been established (due to the multifactorial nature of frailty), clinical evidence suggests that testosterone deficiency is associated with increased sarcopenia and obesity. Testosterone treatment in frail older men with limited mobility and with testosterone deficiency improved insulin resistance, glucose metabolism, and body composition. These changes contribute to better physical function and improved quality of life. Because frailty increases disability, comorbidities, and the risk of hospitalization, institutionalization, and mortality in older men, it is warranted to explore the potential usefulness of testosterone treatment in frail men with hypogonadism in order to attenuate the progression of sarcopenia and frailty. In this paper, we will discuss the impact of testosterone deficiency on frailty and the potential role of testosterone treatment in ameliorating and reducing the progression of frailty. Such an approach may reduce disability and the risk of hospitalization and increase functional independence and quality of life. Copyright © 2016 S. Karger AG, Basel.

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Testosterone vs. aromatase inhibitor in older men with low testosterone: effects on cardiometabolic parameters.

Dias J.P., Shardell M.D., Carlson O.D., Melvin D., Caturegli G., Ferrucci L., Chia C.W., Egan J.M., Basaria S.

Embase
Andrology. 5 (1) (pp 31-40), 2017. Date of Publication: 01 Jan 2017.

Testosterone (T) replacement is being increasingly offered to older men with age-related decline in testosterone levels. The effects of long-term testosterone replacement and aromatase inhibition (AI) on glucose homeostasis and cardiometabolic markers were determine in older non-diabetic men with low testosterone levels. Men >=65 years, mean age 71 +/- 3 years with serum total T < 350 ng/dL were randomized in a double-blind, placebo-controlled, parallel-group, proof-of-concept trial evaluating the effects of 5 g transdermal testosterone gel (TT) (n = 10), 1 mg anastrozole (n = 10) or placebo (n = 9) daily for 12 months. Homeostatic Model Assessment of insulin resistance (HOMAIR) was the primary outcome. Secondary outcomes included OGIS in response to OGGT, fasting lipids, C-reactive protein (CRP), adipokines, and abdominal and mid-thigh fat by computed tomography. All outcomes were assessed at baseline and 12 months. After 12 months, absolute changes in HOMAIR in both treatment arms (TT group: -0.05 +/- 0.21); (AI group: 0.15 +/- 0.10) were similar to placebo (-0.11 +/- 0.26), as were CRP and fasting lipid
levels. Adiponectin levels significantly decreased in the TT group (-1.8 +/- 0.9 mg/L, p = 0.02) and abdominal subcutaneous fat (-60.34 +/- 3.19 cm2, p = 0.003) and leptin levels (-1.5 +/- 1.2 ng/mL, p = 0.04) were significantly lower with AI. Mid-thigh subcutaneous fat was reduced in both treatment arms (TT group: -4.88 +/- 1.24 cm2, p = 0.008); (AI group: -6.05 +/- 0.87 cm2, p = 0.0002). In summary, in this proof-of-concept trial, changes in HOMAIR AI were similar in all three groups while the effects of intervention on subcutaneous fat distribution and adipokines were variable. Larger efficacy and safety trials are needed before AI pharmacotherapy can be considered as a treatment option for low T levels in older men. Copyright © 2016 American Society of Andrology and European Academy of Andrology

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172.
Testicular growth and spermatogenesis: new goals for pubertal hormone replacement in boys with hypogonadotropic hypogonadism? -a multicentre prospective study of hCG/rFSH treatment outcomes during adolescence-.
Context/objective: Testosterone treatment for pubertal induction in boys with hypogonadotropic hypogonadism (HH) provides virilization, but does not induce testicular growth or fertility. Larger studies evaluating the outcomes of gonadotropin replacement during adolescence have not been reported to date; whether previous testosterone substitution affects testicular responses is unresolved. We aimed to assess the effects of human chorionic gonadotropin (hCG) and recombinant FSH (rFSH) in boys and adolescents with HH with respect to a) testicular growth, b) spermatogenesis, c) quality of life (QoL) and to identify factors influencing therapeutic success.

Design/setting: A prospective case study was conducted in 26 paediatric endocrine centres.

Patients/interventions: HCG and rFSH were administered until cessation of testicular growth and plateauing of spermatogenesis to (1) prepubertal HH boys with absent or early arrested puberty (group A) and to (2) HH adolescents who had previously received full testosterone replacement (group B). Outcome measures: Bi-testicular volumes (BTVs), sperm concentrations and QoL.

Results: Sixty (34 A/26 B) HH patients aged 14-22 years were enrolled. BTVs rose from 5 +/- 5 to 34 +/- 3 ml in group A vs 5 +/- 3 to 32 +/- 3 ml in group B, with normal final BTVs (>=24 ml) attained in 74%/70% after 25/23 months in A/B, respectively. Sperm in the ejaculate were found in 21/23(91%)/18/19(95%), with plateauing concentrations after 31/30 months of hCG and 25/25 months of combined treatment in A/B. Sperm concentrations were normal (>=15 mill/ml) in 61%/32%, with mean concentrations of 40 +/- 73 vs 19 +/- 38 mill/ml in A/B (n.s.). Outcomes were better in patients without bilateral cryptorchidism, with non-congenital HH causes, higher baseline BTVs, and higher baseline inhibin B and AMH levels. QoL increased in both groups.

Conclusions: HCG/rFSH replacement during adolescence successfully induces testicular growth and spermatogenesis, irrespective of previous testosterone replacement, and enhances QoL.
Testicular responses to hCG stimulation at varying doses in men with spinal cord injury.
Bauman W.A., la Fountaine M.F., Cirignliaro C.M., Kirshblum S.C., Spungen A.M.
Embase
[Article In Press]
AN: 614507585
Study design: Prospective. Objectives: To test whether provocative stimulation of the testes identifies men with chronic spinal cord injury (SCI), a population in which serum testosterone concentrations are often depressed, possibly due to gonadal dysfunction. To accomplish this objective, conventional and lower than the conventional doses of human chorionic gonadotropin (hCG) were administered. Methods: Thirty men with chronic SCI (duration of injury >1 year; 18 and 65 years old; 16 eugonadal (≥12.1nmoll−1) and 14 hypogonadal (12.1nmoll−1)) or able-bodied (AB) men (11 eugonadal and 27 hypogonadal) were recruited for the study. Stimulation tests were performed to quantify testicular responses to the intramuscular administration of hCG at three dose concentrations (that is, 400, 2000 and 4000IU). The hCG was administered on two consecutive days, and blood was collected for serum testosterone in the early morning prior to each of the two injections; subjects returned on day 3 for a final blood sample collection. Results: The average gonadal response in the SCI and AB groups to each dose of hCG was not significantly different in the hypogonadal or eugonadal subjects, with the mean serum testosterone concentrations in all groups demonstrating an adequate response. Conclusions: This work confirmed the absence of primary testicular dysfunction without additional benefit demonstrated of provocative stimulation of the testes with lower than conventional doses of hCG. Our findings support prior work that suggested a secondary testicular dysfunction that occurs in a majority of those with SCI and depressed serum testosterone concentrations. Spinal Cord advance online publication, 21 February 2017; doi:10.1038/sc.2017.8. Copyright © 2017 International Spinal Cord Society
Status
174.
Treatment of Nonfunctional Pituitary Adenoma Postoperative Remnants: Adjuvant or Delayed Gamma Knife Radiosurgery?
Embase
World Neurosurgery. 100 (pp 361-368), 2017. Date of Publication: 01 Apr 2017.
[Article]
AN: 614405919
Objective It is still not clear whether Gamma Knife radiosurgery (GKRS) for nonfunctional pituitary adenomas should be used as a standard adjuvant postoperative therapy or applied when there is documented progression of the remnant on follow-up magnetic resonance imaging. Methods We performed a retrospective study of patients with nonfunctional pituitary adenomas who underwent primary surgery and GKRS between 2002 and 2015. Patients were divided into 2 groups on the basis of the GKRS indication: adjuvant treatment (GKRS <=6 months postoperatively) or delayed treatment (GKRS if documented progression occurred on the follow-up magnetic resonance imaging). Results Fifty patients were included and grouped based on adjuvant (n = 13) or delayed (n = 37) GKRS following primary surgery. The adjuvant and delayed groups had 10-year actuarial tumor control rates of 92% and 96% (P = 0.408), respectively. The 10-year actuarial endocrinologic control rate was 82% for the adjuvant group and 49% for the delayed group (P = 0.597). None of the patients developed any new neurologic deficit post-GKRS. GKRS-induced
complications (intratumoral bleeding and tumoral tissue inflammation) occurred in 6% of the patients, of whom 4% were in the delayed group and 2% in the adjuvant group. Conclusion Adjuvant treatment with GKRS yields the same high long-term tumor control as delayed GKRS. Neither adjuvant nor delayed GKRS induced additional neurologic complications. There is a trend that adjuvant GKRS induces less additional endocrinologic deficits compared with delayed GKRS. Copyright © 2017 Elsevier Inc.

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175.
Novel cases of Tunisian patients with mutations in the gene encoding 17beta-hydroxysteroid dehydrogenase type 3 and a founder effect.
Embase
[Article]
17beta-Hydroxysteroid dehydrogenase type 3 (17beta-HSD3) is expressed almost exclusively in the testis and converts DELTA4-androstene-3,17-dione to testosterone. Mutations in the HSD17B3 gene causing 17beta-HSD3 deficiency are responsible for a rare recessive form of 46, XY Disorders of Sex Development (46, XY DSD). We report novel cases of Tunisian patients with 17beta-HSD3 deficiency due to previously reported mutations, i.e. p.C206X and p.G133R, as well as a case with the novel compound heterozygous mutations p.C206X and p.Q176P. Moreover, the previously reported polymorphism p.G289S was identified in a heterozygous state in combination with a novel non-coding variant c.54G > T, also in a heterozygous state, in a male patient presenting with micropenis and low testosterone levels. The identification of four different mutations in a cohort of eight patients confirms the generally observed genetic heterogeneity of 17beta-HSD3 deficiency. Nevertheless, analysis of DNA from 272 randomly selected healthy controls from the same geographic area (region of Sfax) revealed a high carrier frequency for the p.C206X mutation of approximately 1 in 40. Genotype reconstruction of the affected pedigree members revealed that all p.C206X mutation carriers harbored the same haplotype, indicating inheritance of the mutation from a common ancestor. Thus, the identification of a founder effect and the elevated carrier frequency of the p.C206X mutation emphasize the importance to consider this mutation in the diagnosis and genetic counseling of affected 17beta-HSD3 deficiency pedigrees in Tunisia. Copyright © 2016 Elsevier Ltd

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2017
The treatment of hypogonadism in men is of great interest to both patients and providers. There are a number of testosterone formulations currently available and several additional formulations under development. In addition, there are some lesser-used alternative therapies for the management of male hypogonadism, which may have advantages for certain patient groups. The future of hypogonadism therapy may lie in the development of selective androgen receptor modulators that allow the benefits of androgens whilst minimizing unwanted side effects.

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2017
Background: HIV-infected adults have increased fracture risk. Objectives: To generate pilot data comparing bone density, structure, and strength between HIV-infected adults with and without a prior fracture. Methods: Adults with and without a prior fracture after their HIV diagnosis were matched 1:1 based on age, sex, race, and smoking history. Participants underwent dual-energy X-ray absorptiometry (DXA), trabecular bone score (TBS), hip structural analyses (HSA), vertebral fracture assessment (VFA), high-resolution peripheral quantitative tomography (HR-pQCT) and measurement of bone turnover markers. Results were compared between cases and controls, with differences expressed as percentages of control group values. Results: 23 pairs were included. On DXA, cases had lower areal bone mineral density (aBMD) at the total hip (median difference in T-score -0.25, p = 0.04), but not the lumbar spine (median difference in T-score 0.10, p = 0.68). Cases had greater abnormalities in HSA and most HR-pQCT and HSA measures, by up to 15%. VFA revealed two subclinical fractures among cases but none among controls. TBS, CTX, and P1NP levels were similar between groups, with differences of 1.9% (p = 0.90), 9.7% (p = 0.55), and 10.0% (p = 0.24), respectively. For each parameter, we report the median and interquartile range for the absolute and relative difference between cases and controls, the correlation between cases and controls, and our recruitment rates, to inform the design of future studies. Conclusions: These pilot data suggest potential differences in bone structure, estimated bone strength, and asymptomatic vertebral fractures among HIV-infected adults with and without fracture, warranting further study as markers of fracture risk in HIV.
Objective Late-onset hypogonadism, or androgen deficiency in the aging male, is a significant cause of morbidity in older men. Many men in the low normal or equivocal range for low testosterone level exhibit signs and symptoms of hypogonadism. Serum testosterone is an imperfect marker for hypogonadism as symptoms vary greatly within the low to low normal range in addition to variations among testosterone assays. Perineal ultrasound can be effectively used to examine the bulbocavernosus muscle (BCM), an androgenized tissue that may be impacted by androgen receptor activity. Methods This study was a retrospective analysis of men who underwent perineal ultrasound for hypogonadism. The ultrasound data were used to calculate the area of the BCM and correlate it with indices of hypogonadism in symptomatic men including free and total testosterone and dual-energy X-ray absorptiometry (DEXA). Results The results demonstrate that there is a significant correlation between total and free testosterone and BCM area in hypogonadal patients. Comparison between BCM area and total testosterone showed $R^2 = 0.061$ and $p = 0.0187$ and comparison between BCM area and free testosterone showed $R^2 = 0.0957$ and $p = 0.0034$. In addition, low BCM was also correlated with DEXA results showing osteoporosis and osteopenia ($R^2 = 0.2239$, $p = 0.0027$). Conclusion There has been recent
controversy over the safety of testosterone replacement therapy. This might be particularly important in men with hypogonadal symptoms but a low normal testosterone level. Our study investigated the use of perineal ultrasound to measure BCM as a surrogate marker for poor androgenized men presenting with hypogonadism. Copyright © 2017 Editorial Office of Asian Journal of Urology

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179.
Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: An overview of Cochrane Reviews.

Embase

[Article]
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This is a protocol for a Cochrane Review (Overview). The objectives are as follows: To assess adverse events associated with medium- and long-term use of opioids for CNCP. Copyright © 2017 The Cochrane Collaboration.

Status
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Institution
Zinc Deficiency after Gastric Bypass for Morbid Obesity: a Systematic Review.
Mahawar K.K., Bhasker A.G., Bindal V., Graham Y., Dudeja U., Lakdawala M., Small P.K.

Obesity Surgery. 27 (2) (pp 522-529), 2017. Date of Publication: 01 Feb 2017.
[Review]
AN: 613425245

Up to 50% of patients have zinc deficiency before bariatric surgery. Roux-en-Y gastric bypass (RYGB) is the commonest bariatric procedure worldwide. It can further exacerbate zinc deficiency by reducing intake as well as absorption. The British Obesity and Metabolic Surgery Society, therefore, recommends that zinc level should be monitored routinely following gastric bypass. However, the American guidance does not recommend such monitoring for all RYGB patients and reserves it for patients with 'specific findings'. This review concludes that clinically relevant Zn deficiency is rare after RYGB. Routine monitoring of zinc levels is hence unnecessary for asymptomatic patients after RYGB and should be reserved for patients with skin lesions, hair loss, pica, dysgeusia, hypogonadism or erectile dysfunction in male patients, and unexplained iron deficiency anaemia. Copyright © 2016, Springer Science+Business Media New York.
Prevalence of hypogonadism in male Type 2 diabetes mellitus patients with and without coronary artery disease.

Madhu S., Aslam M., Aiman A., Siddiqui A., Dwivedi S.

Embase

[A]rticle
AN: 613957521

Aim: The present study is carried out to investigate hypogonadism using serum testosterone levels in male Type 2 diabetes mellitus (T2DM) subjects with and without coronary artery disease (CAD). Subjects and Methods: A total of 150 age and body mass index-matched male subjects in
the age group of 30-70 years were recruited in three groups; Group A-subjects with normal glucose tolerance, Group B-T2DM subjects without CAD, and Group C-T2DM subjects with CAD (n = 50 each group). Subjects with CAD were diagnosed on the basis of electrocardiogram, treadmill testing, stress echocardiography, or coronary angiography. Total testosterone (TT), free testosterone (FT), bioavailable testosterone, calculated FT and glycemic parameters were measured and compared between all the three study groups. One-way ANOVA followed by post hoc Tukey's test and Pearson's coefficient of correlation tests were used for analysis. Results: Hypogonadism (TT <3 ng/ml) was observed in 40% (20/50) of subjects in Group C and 32% (16/50) of subjects in Group B as compared to only 14% (7/50) of subjects in Group A (Groups A vs. B; P = 0.055, Groups A vs. C; P = 0.006 and Groups B vs. C; P = 0.53). Group C subjects had significantly lower levels of TT (3.55 +/- 1.46 ng/ml vs. 4.73 +/- 2.17 ng/ml, P = 0.005), calculated FT (0.062 +/- 0.0255 pg/ml vs. 0.0951 +/- 0.0508 pg/ml, P<= 0.001), and bioavailable testosterone (1.48 +/- 0.65 ng/ml vs. 2.18 +/- 1.20 ng/ml, P <= 0.001) compared to control Group A subjects. There was no significant difference in any of the testosterone parameters between Groups A and B. Furthermore, an overall positive correlation was found between hypogonadism and CAD (r = 0.177, P = 0.030, n = 150). Conclusion: We observed hypogonadism as indicated by low testosterone levels in a significant proportion of male T2DM subjects with CAD. Copyright © 2017 Indian Journal of Endocrinology and Metabolism.

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20170120
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182.
Testosterone Replacement-Freedom From Symptoms or Hormonal Shackles?.
Introduction The question of whether to initiate men on testosterone replacement therapy (TRT) and for how long remains a relevant question to be answered. Aim To determine when to start patients on TRT, determine the benefits of TRT, and whether starting patients on TRT condemns them to a lifetime of hormonal replacement. Methods A literature review of relevant publications in PubMed was used. Main Outcome Measures Main outcome measures were evidence for initiating TRT, benefits of TRT, pathophysiology of TRT, and evidence for duration of TRT. Results Although the exact threshold of serum testosterone levels that define hypogonadism is still strongly debated, the presence of symptoms associated with low levels of testosterone can be considered to help make the diagnosis. Although the proper duration of TRT has yet to be established, maintenance of symptom improvement after discontinuing TRT has been observed, which is a promising result. Studies also have shown a return to hormonal baseline after discontinuation of TRT. Conclusion It has been established that patients with testosterone deficiency benefit from TRT. Preliminary evidence seems to show that men who are initiated on TRT are not condemned to a lifetime of hormonal therapy, although many men might choose to continue treatment because of improvement in their symptoms. Copyright © 2016 International Society for Sexual Medicine

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Introduction
Deterioration in sexual functioning is one of the major and serious complications of diabetes. This common metabolic disorder not only affects sexuality through microvascular and nerve damage but also has psychological aspects. In men, the primary complications are erectile dysfunction, ejaculatory dysfunction, and loss of libido. Women similarly experience sexual problems, including decreased libido and painful intercourse. Aim To summarize the effects of diabetes on sexuality, evaluate the impact of diabetes on sexual function, and assess the conventional and novel treatment approaches based on recent studies. Methods A literature review of peer-reviewed journal articles and guidelines was performed. Main Outcome Measures To assess the effects of diabetes on sexuality and to focus on treatment approaches. Results Male and female sexual dysfunctions are a significant complication of diabetes. Tight glycemic control seems to be beneficial in delaying the onset of sexual problems and ameliorating them when they are present. Erectile dysfunction occurs as one of the first problems. The current mainstay of treatment for erectile dysfunction is therapy with phosphodiesterase type 5 inhibitors and then a stepwise approach of management. Men also can experience ejaculation problems and loss of libido. Diabetes also can decrease testosterone levels, which further decreases libido. Hypogonadal men with diabetes might benefit from testosterone replacement therapy. Diabetic women also can have sexual problems. These problems mainly include loss of libido, decrease in arousal and lubrication resulting in painful intercourse, and loss of orgasm. All these challenges require a multidisciplinary approach. Conclusion Diabetes has detrimental effects on the sexual function of patients. Diabetologists who primarily care for the patient should not only focus on the glycemic control of their patients but also address their sexual complaints, because these problems can significantly impair their quality of life. Urologists, gynecologists, endocrinologists, and psychiatrists should work in a multidisciplinary manner for the treatment of decreased sexual functioning as a result of diabetes. Copyright © 2016 International Society for Sexual Medicine Status EMBASE Institution
A general theory of sexual differentiation.
Arnold A.P.
Embase
Journal of Neuroscience Research. 95 (1-2) (pp 291-300), 2017. Date of Publication: 01 Jan 2017.
[Review]
AN: 613128545
A general theory of mammalian sexual differentiation is proposed. All biological sex differences are the result of the inequality in effects of the sex chromosomes, which are the only factors that differ in XX vs. XY zygotes. This inequality leads to male-specific effects of the Y chromosome, including expression of the testis-determining gene Sry that causes differentiation of testes. Thus, Sry sets up lifelong sex differences in effects of gonadal hormones. Y genes also act outside of the gonads to cause male-specific effects. Differences in the number of X chromosomes between XX and XY cells cause sex differences in expression (1) of Xist, (2) of X genes that escape inactivation, and (3) of parentally imprinted X genes. Sex differences in phenotype are ultimately the result of multiple, independent sex-biasing factors, hormonal and sex chromosomal. These factors act in parallel and in combination to induce sex differences. They also can offset each other to reduce sex differences. Other mechanisms, operating at the level of populations, cause groups of males to differ on average from groups of females. The theory frames questions for further study, and directs attention to inherent sex-biasing factors that operate in many tissues to cause sex differences, and to cause sex-biased protection from disease. © 2016 Wiley Periodicals, Inc. Copyright © 2016 Wiley Periodicals, Inc.
Endoscopic Versus Microscopic Transsphenoidal Approach for Pituitary Adenomas: Comparison of Outcomes During the Transition of Methods of a Single Surgeon.

Eseonu C.I., ReFaey K., Rincon-Torroella J., Garcia O., Wand G.S., Salvatori R., Quinones-Hinojosa A.

World Neurosurgery. 97 (pp 317-325), 2017. Date of Publication: 01 Jan 2017.

Objective The transition from microscopic to fully endoscopic transsphenoidal surgery requires a surgeon to assess how the change in technique will affect the extent of tumor resection (EOR), outcomes, and complications. We compared a single surgeon's experience transitioning from one technique to the other and examined the operative outcomes and EOR between microscopic versus endoscopic transsphenoidal surgery. Methods Retrospective data analysis of adult patients who were treated surgically for a pituitary adenoma between August 2005 and May 2015 by a single neurosurgeon, who was originally trained and practiced in the microscopic transsphenoidal approach. Patient demographics, perioperative conditions, tumor characteristics, operative times, volumetric EOR, postoperative outcome, and the endoscopic learning curve were evaluated. Results One hundred and nine patients underwent microscopic transsphenoidal surgery and 275 patients underwent a fully endoscopic approach. The patient characteristics
were similar in the 2 groups. Operative room time was significantly shorter in the endoscopic group than in the microscopic group (180.2 vs. 215.6 minutes; P < 0.001). The endoscopic and microscopic groups had similar volumetric EOR (85.1% vs. 82.8%; P = 0.371) as well as residual tumor volume (1.06 cm³ vs. 1.15 cm³; P = 0.765). The mean length of hospital stay was 2.4 days in the endoscopic group and 3.2 days in the microscopic group (P = 0.03). Conclusions During the transition from the microscopic to the endoscopic approach, similar surgical outcomes and EOR were achieved in the 2 cohorts. In our experience, the endoscopic approach offers the advantage of shorter operative times and lengths of hospital stays after the surgeon has developed more experience with the technique. Copyright © 2016 Elsevier Inc.

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186.
The Effects of Vitamin D-K-Calcium Co-Supplementation on Endocrine, Inflammation, and Oxidative Stress Biomarkers in Vitamin D-Deficient Women with Polycystic Ovary Syndrome: a Randomized, Double-Blind, Placebo-Controlled Trial
Razavi M, Jamilian M, Karamali M, Bahmani F, Aghadavod E, Asemi Z
EBM Reviews - Cochrane Central Register of Controlled Trials
Hormone and metabolic research. 48(7):446-451, 2016.
[Journal: Article]
AN: CN-01177722
The current study was conducted to assess the effects of Vitamin D-K-calcium co-supplementation on endocrine, inflammation, and oxidative stress biomarkers in Vitamin D-deficient women with polycystic ovary syndrome (PCOS). This randomized double-blind, placebo-controlled trial was performed on 60 Vitamin D-deficient women diagnosed with PCOS aged 18-40 years old. Participants were randomly allocated into 2 groups to intake either 200 IU Vitamin D, 90 mug vitamin K plus, 500 mg calcium supplements (n=30), or placebo (n=30) twice a day for 8 weeks. Endocrine, inflammation, and oxidative stress biomarkers were quantified at the beginning and the end of the study. After 8 weeks of intervention, compared with the placebo, Vitamin D-K-calcium co-supplementation resulted in a significant reduction in serum-free testosterone (-2.1+/−1.6 vs.+0.1+/−1.0 pg/ml, p<0.001) and dehydroepiandrosterone sulfate (DHEAS) levels (-0.8+/−1.0 vs.−0.1+/−0.5 mug/ml, p=0.006). In addition, a significant increase in plasma total antioxidant capacity (TAC) (+75.7+/−126.1 vs.−80.4+/−242.8 mmol/l, p=0.005) and a significant difference in plasma malondialdehyde (MDA) concentrations (+0.03+/−0.6 vs.+1.4+/−2.4 mumol/l, p=0.005) was observed following the supplementation with Vitamin D-K-calcium compared with the placebo. A trend toward a greater decrease in luteinizing hormone was observed in Vitamin D-K-calcium co-supplement group compared to placebo group (-7.0 vs.−1.2 IU/l, p=0.09). We did not find any significant effect of Vitamin D-K-calcium co-supplementation on prolactin, follicle-stimulating hormone, 17-OH progesterone, inflammatory markers, and glutathione levels. Overall, Vitamin D-K-calcium co-supplementation for 8 weeks among Vitamin D-deficient women with PCOS had beneficial effects on serum DHEAS, free testosterone, plasma TAC, and MDA levels.

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Publisher
Georg Thieme Verlag

Clinical features and morbidities of Hb H disease in Taiwan
Lu MY, Kuo MC, Wang SC, Chen SH, Ko BS, Chang C-S, Tang J-L
EBM Reviews - Cochrane Central Register of Controlled Trials
Introduction Patients with non-transfusion-dependent thalassemia experience a wide array of clinical complications despite their independence from frequent, regular red blood cell transfusions. They have the higher incidence of osteoporosis, extramedullary hematopoiesis (EMH), hypogonadism, cholelithiasis, thromboembolic disease, pulmonary hypertension, silent cerebral ischemia, and leg ulcers. Thalassemia is highly prevalent in Taiwan and Hb H disease is predominant. But limited data are available about clinical features and morbidities. Here, we studied clinical features and morbidities in Taiwanese patients with Hb H disease.

Methods & Results We collected 90 patients with Hb H disease in three hospitals since 2014 Nov till 2016 July. Male to female were 43/59. The mean age was 33.1 years (from 0.5 to 92.3 years). Two cases died of pulmonary hypertension and old age at 31 years old and 87 years old. Alfa-globin gene genotype studies were done in 44 cases. The (α-α(SEA)) type of alpha(0)-thalassemia mutation was detected in all patients. Twenty-four (57.1%) cases were deletional (α(3.7)/α(4.2)/unknown 19/4/1) and 20 (42.9%) were nondeletional (CS/RS 18/2) type. The mean of Hemoglobin (Hb) and serum ferritin level were 8.7 g/dL and 730 ng/mL. We also revealed the positive correlation between age and serum ferritin level. The liver iron concentration (LIC) were 6.694 mg Fe/g dw (n=35). The Hb, ferritin and LIC level were not different between deletional and non-deletional groups. They received the transfusion management: 1 with regular transfusion 6 weeks interval, 5 with irregular transfusion 6 weeks interval, 27 with occasional transfusion and 57 without transfusion. Fifteen cases received splenectomy. There were significantly higher prevalence for transfusion frequency and splenectomy in non-deletional group. The prevalence of morbidities were 16/79 for cholelithiasis, 12/90 for thromboembolic event, 4/90 for heart failure symptoms (2 for pulmonary hypertension), 5/90 for arrhythmia, 3/90 for bone fracture, 5/20 for osteoporosis and 0 for renal stone. There were non-significantly higher prevalence for morbidities in non-deletional group.

Discussion & Conclusion The study provides the clinical features and the prevalence of morbidities in Hb H disease in Taiwan. Surprisingly, the prevalence of thromboembolic event and pulmonary hypertension are overlooked in our routine Hb H disease care. We need to schedule close and careful clinical follow up of Hb H patients as they get older, they get some morbidities or they are nondeletional genotype.

Institution
M.Y. Lu
Publisher
American Society of Hematology
Safet}y, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of AG-519, an allost}eric activator of pyruvate kinase-R, in healthy subjects

EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Conference Abstract]
AN: CN-01335141  NEW

BACKGROUND Pyruvate kinase (PK) deficiency is a congenital hemolytic anemia caused by deficiency of the glycolytic enzyme red cell PK (PK-R) due to mutations in the PKLR gene. PK catalyzes the last enzymatic step in the glycolytic pathway and is the main source of adenosine triphosphate (ATP) production in red blood cells. PKLR mutations lead to defective proteins that are hypothesized to reduce ATP levels in red cells, leading to hemolysis. Small molecule allost}eric activation of PK-R resulting in increases in ATP and decreases in 2,3-diphosphoglycerate (2,3-DPG) in healthy volunteers has been observed with an earlier molecule, AG-348, the first small molecule PK-R activator to enter clinical trials (Yang et al. EHA 2015, S138). AG-519 is the second small molecule PK-R activator to enter clinical trials. AG-519 is a potent, highly selective and orally bioavailable PK-R activator devoid of the aromatase inhibitory effects that were observed with AG-348. AIMS AG-519 is currently being tested in a randomized, double-blind, phase 1 study in healthy volunteers (NCT02630927), with the objective of identifying a safe and pharmacodynamically active dose and schedule to support potential ongoing development in patients with PK deficiency. Here we report the first 4 cohorts of the multiple ascending dose (MAD) phase of this study. The single ascending dose (SAD) phase of the study and the first two cohorts of the MAD phase of the study have been reported previously (Barbier et al. EHA 2016, P752). METHODS Healthymen and women (non-childbearing potential) aged 18-60 years who provided informed consent were eligible. The MAD phase of the study consisted of 5 dose cohorts. The dose levels administered were determined during interim data reviews of each completed MAD cohort, as well as data from completed SAD cohorts. At each dose level, 8 subjects were enrolled and randomized to receive AG-519 (n=6) or placebo (n=2)
twice daily (BID; approximately every 12 hours) for 14 days. Safety assessments included adverse events (AEs), vital signs, electrocardiogram and clinical laboratory parameters. Serial blood samples were drawn to measure plasma concentrations of AG-519 and whole blood concentrations of 2,3-DPG and ATP for pharmacokinetic and pharmacodynamic (PD) assessments. RESULTS Data are available for 32 subjects enrolled across 4 dose cohorts in the MAD phase of the study: 8 subjects each in cohort 1 (125 mg BID), cohort 2 (375 mg BID), cohort 3 (25 mg BID), and cohort 4 (300 mg BID). Blinded safety reviews indicated that multiple doses up to 375 mg have been well tolerated with no serious AEs or dose-limiting toxicities reported to date. One case of probable drug-induced Grade 2 thrombocytopenia was previously reported in 1 subject in the 375 mg cohort; the event was rapidly reversible with no clinical sequelae. The protocol was amended to require daily monitoring of platelets in subsequent cohorts and no other subjects have developed thrombocytopenia during treatment. The preliminary analysis of free testosterone and estradiol confirmed the absence of aromatase inhibitory activity. AG-519 steady-state was reached the third day after the first dose based on trough concentration values. The clearance of AG-519 after multiple doses was similar to that observed after single doses in the SAD cohorts. Dose-dependent increases in ATP in blood (Figure 1) and decreases in 2,3-DPG in blood correlated with dose-dependent increases in exposure of AG 519, with a peak effect at or below 375 mg BID. ATP response at 25 mg appears to be greater than 50% of maximal response. Results from the fifth MAD cohort, which evaluated the PD results with 10 mg BID, will be presented. ATP = adenosine triphosphate; BID = twice daily CONCLUSION AG-519 is well tolerated in healthy subjects at doses ranging from 25 mg to 375 mg BID for 14 days. The robust dose-dependent changes in ATP and 2,3-DPG concentrations in blood from healthy volunteers are consistent with increased activity of PK-R, the expected PD effect of AG-519. These data support the hypothesis that AG-519 may be able to enhance glycolytic activity in red cells of patients with PK deficiency to address the underlying cause of the disease.

Exercise improves the effects of testosterone replacement therapy and the durability of response after cessation of treatment: a pilot randomized controlled trial
The effects of the combination of exercise and TRT on symptoms of late-onset hypogonadism (LOH) and the durability of response after cessation of TRT were investigated. A total of fifty patients with erectile dysfunction (ED) who had a sedentary lifestyle and low serum total testosterone (T) levels were enrolled and followed for 20 weeks. Patients were randomly divided into two groups; all of them received T gel for 12 weeks and it was discontinued for 8 weeks. Patients assigned to Group II were offered a supervised exercise program for 20 weeks. Measurement of serological testing was performed and self-assessment questionnaires and Global Assessment Question (GAQ) were asked. Baseline characteristics and the initial symptom scores showed no significant difference between the two groups. Serum total T levels and the symptom scores were increased at 12 weeks in both groups, and Group II showed better results with statistical significance. There was a decrease in T levels and worsening of symptom scores at week 20 compared to week 12 in both groups, and Group II showed better results with statistical significance. On the GAQ, Group II showed higher ratio of “yes” at week 12 and the same tendency was sustained at week 20 with significant difference between two groups. The combination of exercise and TRT showed significant improvements in serum T levels and LOH symptoms compared to TRT alone. In addition, these improvements were maintained in the combination group with continuous exercise, even after cessation of TRT. Copyright (C) 2016 AJA, SIMM & SJTU. All rights reserved.

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Publisher
Medknow Publications (B9, Kanara Business Centre, off Link Road, Ghatkopar (E), Mumbai 400 075, India)
Objective: Weight reduction is the most important treatment target when polycystic ovary syndrome (PCOS) is linked to obesity. In addition, weight independent targets that are intrinsically related to the syndrome should also be involved in treatment algorithm in obese PCOS. Glucagon-like peptide 1 (GLP-1) receptor agonist liraglutide (LIRA) is linked with dose dependent weight lowering potential in different obesity related populations. Dose of 3 mg was recently approved as an anti-obesity drug. Metformin is weight neutral, yet it could enhance weight lowering potential of liraglutide via synergistic stimulatory modulation of GLP-1 axis. Furthermore, it also has impact on steroidogenesis at the ovarian level. The aim of this study was to evaluate whether low dose liraglutide in combination with metformin affects body weight as effectively than high dose liraglutide alone in obese PCOS. Design/Participants/Main Outcome Measure: 30 obese women with PCOS (aged 33.1 +/- 6.1 years, BMI 38.3 +/- 5.4 kg/m^2, mean +/- SD) were randomized to combined treatment (COMBO) with MET 1000 mg BID and liraglutide 1.2 mg QD (N=15) or liraglutide 3 mg (LIRA3) QD alone (N=15) for 12 weeks. The primary outcome was change in anthropometric measures of obesity. Secondary outcomes included metabolic and hormonal changes. Results: 30 women completed the study. Subjects treated with COMBO lost on average 3.6 +/- 2.5 kg (p=0.002) compared with a 6.3 +/- 3.7 kg weight loss in LIRA3 group (p=0.001). BMI decreased for 1.3 +/- 0.9 kg/m^2 in COMBO arm (p=0.002) compared to 2.2 +/- 1.3 kg/m^2 in LIRA3 arm (p=0.001). The between treatment differences of the weight changes have not been statistically significant yet (p=0.062). Reduction of waist circumference in LIRA3 group was significantly greater than in women treated with COMBO (-4.2 +/- 3.4 vs -2.2 +/- 6.2 cm, p=0.014). From baseline to study end LIRA3 and COMBO resulted in a significant reduction of post OGTT glucose levels (p=0.002 and p=0.016, respectively). Women treated with COMBO had significant reduction of total testosterone (from 1.8 +/- 0.9 to 1.5 +/- 0.8 nmol/l, p=0.023). Androstendione decrease tended to be greater in COMBO compared to LIRA3 (-2.0 +/- 2.6 vs 0.6 +/- 2.7 nmol/l, p=0.094). The side effects in COMBO were of milder intensity, yet they were transit in both arms. They were reported by 8/15 in LIRA3 and 6/15 women in COMBO group. Conclusion: Short-term interventions with low dose liraglutide in combination with metformin and high dose liraglutide alone both led to significant
weight reduction in obese women with PCOS. The between treatment difference was not statistically significant. However, a dualtargeting treatment approach further improved androgen profile and enabled lower dose regimen of liraglutide at the expanse of better tolerability.

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191. Short-term sex steroid withdrawal increases adiposity in healthy men without impairing insulin sensitivity or glucose tolerance. Short-term sex steroid withdrawal increases adiposity in healthy men without impairing insulin sensitivity or glucose tolerance

Rubinow KB, Chao JH, Kratz M, Amory JK, Matsumoto AM, Page ST

EBM Reviews - Cochrane Central Register of Controlled Trials


[Journal: Conference Abstract]

Introduction: Testosterone deprivation increases risk of insulin resistance in men, but whether this risk is independent of changes in body composition is unknown. Further, the metabolic roles of testosterone and its metabolite estradiol have not been clearly defined in men, nor have the respective metabolic effects of partial and complete testosterone deprivation. Hypothesis: We hypothesized that short-term sex steroid deprivation would lead to diminished insulin sensitivity in healthy men prior to the development of changes in body composition. Further, we predicted that changes in insulin sensitivity would result from androgen rather than estrogen withdrawal.

Experimental Design: Fifty-two healthy men (19-55 years of age) were enrolled in the study. All subjects received the GnRH antagonist acyline and were randomized to receive one of the following: placebo gel (Castrate), 1.25g testosterone gel (Low T/E), 5g testosterone gel (Normal T/E), or 5g testosterone gel with letrozole (Normal T/Low E) daily for 4 weeks. At baseline and end-of-treatment, body composition was measured by dual-energy x-ray absorptiometry, and glucose tolerance was assessed through a 75-gram oral glucose tolerance test. Insulin sensitivity was quantified by the Matsuda index, and insulin resistance was calculated by the homeostasis
model assessment of insulin resistance (HOMA-IR). Major Results: Predicted circulating sex steroid concentrations were achieved in all treatment groups. Significant differences in fat mass were observed among groups (baseline vs. week 4, p=0.003) and attributable to both testosterone and estrogen exposure (beta=-0.34, p=0.055 and beta=-0.35, p=0.046, respectively). Differences in lean mass were also evident across groups (p=0.03) and influenced solely by androgen exposure (beta=0.74, p=0.002). Treatment group did not confer a significant effect on insulin sensitivity (p=0.16 for Matsuda index), glucose tolerance (p=0.87 for AUCglucose), or insulin resistance (p=0.14 for HOMA-IR). Conclusions: Adverse changes in body composition occur within 4 weeks of sex steroid deprivation in healthy men. Increases in adiposity and decreases in lean mass are evident with both partial and complete sex steroid withdrawal but occur in the absence of associated impairment in insulin sensitivity or glucose tolerance. These findings underscore the potential dissociation between increased adiposity and insulin resistance and support the role of estradiol as an important determinant of adiposity in men.

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Publisher
Endocrine Society

Can early clinical parameters predict post-traumatic pituitary dysfunction in severe traumatic brain injury?
EBM Reviews - Cochrane Central Register of Controlled Trials

Background: Post-traumatic hypopituitarism is a major complication after severe head trauma. The aim of our study was to evaluate the possible role of early clinical parameters in the development of endocrine deficits. Methods: Data on endocrine function, on-admission clinical-, laboratory-, and ICU-monitored parameters were available in 63 patients of the surviving 86 severe head injury patients (post-resuscitation GCS under 8) treated at one neurosurgical center during a 10-year period. Results: Hypopituitarism was diagnosed in 68.3 % of the patients. The most frequently affected pituitary axis was the growth hormone (GH): GH deficiency or
insufficiency was present in 50.8%. Central hypogonadism affected 23.8% of male patients; hypothyroidism and secondary adrenal failure were found in 22.2 and 9.5% of the investigated population, respectively. Early onset (within 1 year of brain injury) hypopituitarism was found in 24 patients. No connection was found between the development of hypopituitarism and any of the clinical parameters assessed on-admission or at ICU. Significant correlations were found between early endocrine dysfunctions and surgical intervention (OR: 4.64) and the diagnosis of subdural hematoma (OR: 12). In our population, after road traffic accidents, the development of late-onset hypopituitarism was less prevalent (OR: 0.22). Conclusions: Since our results do not indicate any reliable predictive parameter for the development of endocrine dysfunction in a cohort of patients with severe traumatic brain injury, regular endocrine screening of this specific patient population seems obligatory. Copyright (C) 2016, Springer-Verlag Wien.

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193.
Efficacy and safety of triptorelin 6-month formulation in patients with central precocious puberty

EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Article]
AN: CN-01246671
Background: Triptorelin is an established treatment for central precocious puberty (CPP) as 1- and 3-month formulations. The current triptorelin 22.5 mg 6-month formulation is approved for prostate cancer therapy. This is the first study in patients with CPP. Methods: The efficacy and safety of the triptorelin 6-month formulation in CPP were investigated. The primary objective was to evaluate the efficacy in achieving luteinizing hormone (LH) suppression to pre-pubertal levels at month 6. This was an international, non-comparative phase III study over 48 weeks. Eighteen medical centers in the US, Chile and Mexico participated. Forty-four treatment naive patients (39 girls and five boys) aged at treatment start 2.8 years for girls and 2.9 years for boys with an
advancement of bone age over chronological age > 1 year were to be included. Triptorelin was administered im twice at an interval of 24 weeks. LH, follicle stimulating hormone (FSH) (basal and stimulated), estradiol (girls), testosterone (boys), auxological parameters, clinical signs of puberty and safety were assessed. Results: Forty-one patients (93.2%) showed pre-pubertal LH levels (stimulated LH < 5 IU/L) at month 6 and maintained LH suppression through month 12. The percentage of patients with LH suppression exceeded 93% at each time point and reached 97.7% at month 12. No unexpected drug-related adverse events were reported. Conclusions: The triptorelin 6-month formulation was safe and effective in suppressing the pituitary-gonadal axis in children with CPP. The extended injection interval may improve compliance and increase comfort in the management of CPP. Copyright (C) 2016 Walter de Gruyter GmbH, Berlin/Boston.

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Publisher
Walter de Gruyter GmbH (E-mail: info@degruyter.com)

194.
Low Testosterone in Men with Cardiovascular Disease or Risk Factors: to Treat or Not To Treat?
Cassimatis DC, Crim MT, Wenger NK
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Review]
AN: CN-01247787
Current evidence supports the use of testosterone replacement in men with the clinical-biochemical syndrome of hypogonadism, defined as low testosterone serum levels and symptoms such as fatigue, exercise intolerance, erectile dysfunction, low libido, or depression. Although the evidence consistently shows that hypogonadism is associated with elevated cardiovascular risk, evidence is mixed regarding whether testosterone (T) replacement provides cardiovascular (CV) benefit or harm. For a man with symptomatic hypogonadism in the setting of CV disease, clinical heart failure, and/or traditional CV risk factors (hypertension, diabetes, and hyperlipidemia), a balanced approach would be to counsel him that overall, the evidence should not dissuade him from utilizing T replacement for non-cardiac symptom relief but that more data are needed before a definitive recommendation can be made about T replacement for CV benefit.
The preponderance of available evidence, reviewed in this article, suggests that T replacement, at appropriate doses and with monitored response, is likely to be safe for men with CV disease or CV risk factors and may even reduce major adverse cardiovascular events (MACE). The 2015 American Association of Clinical Endocrinologists and American College of Endocrinology position statement supports this stance and calls for improved prospective data. There is a clear need for a large, prospective randomized trial evaluating the impact of T replacement on MACE, for men both with and without CV disease or CV risk factors. Clinicians should be aware that all men who elect to take T replacement therapy require regular follow-up with the prescribing physician to include both clinical assessment and surveillance laboratory assessment of total T level, complete blood count, and prostate specific antigen. Copyright (C) 2016, Springer Science+Business Media New York.

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Publisher
Springer Healthcare

195.
Testosterone use and HIV serostatus among men who have sex with men in the MACS
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Conference Abstract]
AN: CN-01250488
Background: Testosterone therapy (TTh) use has increased markedly in the U.S over the past decade, with current prevalence of about 3% among men >40 years. Given the possible cardiovascular risks associated with TTh use and high burden of cardiovascular disease (CVD) in HIV-infected (HIV+) men, data on the levels and reasons for TTh use in this population are needed. We describe the incidence, prevalence, and characteristics of TTh use among HIV+ and HIV-uninfected (HIV-) men who have sex with men (MSM) in the Multicenter AIDS Cohort Study
Methods: Data on self-reported testosterone use was collected semiannually since 2012. Our analytic sample included 2319 (1223 HIV+/1096 HIV-) men in Baltimore, Chicago, Pittsburgh, and Los Angeles who completed one or more study visits from 2012-2014. We calculated incident and prevalent TTh use and compared reasons for TTh use by HIV serostatus using Chi-square tests. We used multivariable Poisson regression models with robust variance to estimate prevalence ratios (PR) for TTh use by HIV serostatus and demographic factors. Results: Compared to the HIV- men, HIV+ men were older (median and intraquartile range 59 years (53-66) v 54 years (46-60)) and more likely to be non-white (47% v 27%). TTh prevalence at the most recent visit among HIV+ compared to HIV- men was nearly 4-fold higher in men aged 60 and older (26% v 7%, p<0.001), and almost 3-fold higher among men younger than 60 (18% v 7%, p<0.001 among 50-59 years; 6% v 2%, p=0.03 among <50 years). The TTh initiation rate from 2012-2014 was 21.4/1000 person years. Among the 266 men (197 HIV+/69 HIV-) on TTh, the major self-reported reason for use was low testosterone (88%). HIV+ men were more likely than HIV- men to use TTh to improve strength or energy (36% v 22%, p=0.04), build muscle (26% v 7%, p=0.001), or combat wasting (15% v 1%, p<0.01). In multivariable analysis, the prevalence of TTh was 3.8 times greater in HIV+ compared to HIV- men (p<0.001), and was significantly less prevalent among non-white men (Table 1). We observed strong geographic differences, with the prevalence of TTh use 2.7 and 1.7 times higher among LA and Baltimore men, respectively, compared to Pittsburgh men. Conclusions: MSM in the MACS reported very high rates of TTh use, particularly among older HIV+ men. Given the high TTh use and CVD burden among HIV+ men, the benefits and risks of TTh use should be carefully examined in future studies and closely monitored in clinical practice. (Table Presented).
Objective: Testosterone deficiency (TD) is considered by some as a health epidemic and linked to serious health comorbidities. The standard therapy for TD is testosterone supplementation therapy (TST), but alternative therapies such as clomiphene citrate (CC) and human chorionic gonadotropins (HCG) have been successfully used for decades. To compare the objective markers of therapy and patient satisfaction across several groups.

Methods: A prospective study included 324 patients diagnosed with TD. Patients were randomly enrolled into four groups: group A (n = 80) took TST as testosterone undecanoate (Nebido) 1000 mg injection; group B (n = 90) took clomiphene citrate 50 mg tablets daily; group C (n = 78) HCG 5000 international units twice weekly; group D (n = 76) combination therapy of CC and HCG. All patients had thorough physical examination, body mass index (BMI) calculated, and laboratory tests including testosterone, glycosylated hemoglobin (HbA1c) before therapy, at 1 month and at 3 months from starting therapy. Patient demographics, comorbidities and ADAM questionnaire (qADAM) scores were recorded. Results: Mean age of the study population was 43 years. Before therapy, the mean BMI was 31.2, mean HbA1c was 6.59%, mean testosterone was 2.28 nmol/L and qADAM score was 20. Testosterone increased in all groups. Testosterone increase from 0-1 months was biggest in the Nebido group and smallest in the HCG group. Testosterone increase from 0-3 months was biggest in the HCG+Clomid combination group and smallest in HCG group. There was no statistically significant difference between groups. HbA1c reduced in all groups from 0-3 months. BMI reduced in all groups from 0-3 months. qADAM score increased in all groups from 0-1 months. The biggest increase was in the Nebido group and smallest in the HCG group. qADAM increased in all groups from 0-3 months, the biggest increase being in group D and smallest in group C. Conclusion: Therapy with clomiphene, HCG or a combination are feasible options in hypogonadal men as alternatives to testosterone supplementation therapy. They are as effective as TST in restoring serum T and improving patient quality of life.

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Publisher
Elsevier
The effect of testosterone therapy on muscle mass, bone mass and haemoglobin in hypogonadal men with cirrhosis

Sinclair M, Gow P, Grossmann M, Hoermann R, Scodellaro T, Angus P

EBM Reviews - Cochrane Central Register of Controlled Trials


[Journal: Conference Abstract]

AN: CN-01267111 NEW

Background and Aims: Low testosterone and sarcopenia are common in men with cirrhosis and both are associated with adverse outcome. The effect of testosterone therapy on body composition has not previously been investigated in this population. Methods: We conducted a 12 month double-blinded, randomised, placebo-controlled trial of intramuscular testosterone decanoate in 101 men with established cirrhosis and low serum testosterone (total testosterone <12 nmol/L or free testosterone <230 pmol/L). Total body composition was quantified using dual-energy X-ray absorptiometry. Results: Appendicular lean muscle mass was significantly higher in the active group compared to placebo at 12 months (mean adjusted difference (MAD) 1.69 kg, CI 0.40-2.97 kg, p = 0.021). Total lean mass was similarly higher in the active group (MAD 4.74 kg, CI 1.75- 7.74 kg, p = 0.008). Fat mass was lower in the actively treated group (MAD-4.34 kg, CI- 2.04 to -6.64 kg, p < 0.001). Bone mineral density was significantly higher at the femoral neck and total bone mass were both significantly higher in the active group (MAD in T score 0.287 points, CI 0.140-0.4340.140-0.434, p < 0.001; (MAD in bone mass 0.08 kg, CI 0.01-0.15 kg, p = 0.009). Haemoglobin was significantly higher in actively treated patients (MAD 10.2 g/L, CI 1.50-18.9 g/L, p = 0.041) and HbA1c was lower (MAD -0.35%, CI -0.05 to -0.54, p = 0.028). No serious adverse effects were reported. There were more deaths on placebo (25.5%) than active treatment (16%) but this was not significant (p = 0.352). Conclusions: Testosterone therapy in men with cirrhosis and low baseline testosterone levels safely improves muscle mass, bone mass and haemoglobin, and reduces fat mass and HbA1c. This is a promising new therapy for systemic complications of cirrhosis that targets a specific hormonal imbalance in men with cirrhosis. (Figure Presented).
Circulating microvesicles correlate with body composition, plasma lipids and markers for ectopic fat in testosterone deficient type 2 diabetic men

Botha J, Magnussen LV, Nielsen MH, Nielsen TB, Hojlund K, Andersen MS, Handberg A

EBM Reviews - Cochrane Central Register of Controlled Trials


[Journal: Conference Abstract]

AN: CN-01267761  NEW

Background and aims: Low testosterone in men has been associated with the metabolic syndrome (MetSy) and type 2 diabetes (T2D), and testosterone replacement therapy (TRT) shown to improve several components associated with higher T2D risk. The multifunctional receptor CD36 may be involved in dyslipidaemia, insulin resistance and ectopic fat storage in MetSy. We aimed to investigate how plasma levels of specific microvesicle (MV) phenotypes are associated with insulin sensitivity, body composition, plasma lipids and ectopic fat accumulation in the liver and hypothesized that the changes elicited by TRT are reflected in levels of circulating MVs. Materials and methods: Thirty-nine Caucasian males with T2D and low testosterone levels were assigned to either TRT or placebo (CTRL) groups, subjected to a 24-week treatment regime, and evaluated at baseline and after 24 weeks. MVs were analysed by flow cytometry and defined as lactadherin binding particles within the 0.1-1.0μm gate. MVs of platelet (PMV), monocyte (MMV) and endothelial cell (EMV) origin were identified by cell-specific markers and their expression of CD36 was investigated. Data were analysed by Wilcoxon's s-r test and Spearman's ranked correlation analysis (rho). Results: Triglycerides correlated with PMVs, CD36+PMVs, EMVs, CD36+EMVs, MMVs and CD36+MMVs (rho=0.37-0.58, p<0.05). Furthermore, indicators of ectopic liver fat, alanine aminotransferase (ALT) and gamma
glutamyltransferase (GGT) correlated with PMVs, EMVs, CD36+PMVs and CD36+MMVs (rho=0.33-0.49, p<0.05). Body composition measures were associated with CD36+MMV (rho=0.33-0.35, p<0.05), while insulin sensitivity was not correlated with any of the studied MV phenotypes. No differences in any MV levels were identified between TRT and CTRL at the end of the trial period. Conclusion: MetSy components were associated with MV phenotypes, in particular CD36+MVs, which may support the involvement of CD36 in MetSy pathogenesis. Although TRT improved body composition measures, levels of MV phenotypes were unaffected, thus refuting our hypothesis.

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Publisher
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199.
Testosterone replacement therapy
Shoskes DA, Hakim LS
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Editorial]
AN: CN-01286193 NEW
Publisher
AME Publishing Company (E-mail: info@amepc.org)

200.
Winners, losers, and posers: the effect of power poses on testosterone and risk-taking following competition
Smith KM, Apicella CL
EBM Reviews - Cochrane Central Register of Controlled Trials
A contribution to a special issue on Hormones and Human Competition. The effect of postural power displays (i.e. power poses) on hormone levels and decision-making has recently been challenged. While Carney et al. (2010) found that holding brief postural displays of power leads to increased testosterone, decreased cortisol and greater economic risk taking, this failed to replicate in a recent high-powered study (Ranehill et al. 2015). It has been put forward that subtle differences in social context may account for the differences in results. Power displays naturally occur within the context of competitions, as do changes in hormones, and researchers have yet to examine the effects of poses within this ecologically relevant context. Using a large sample of 247 male participants, natural winners and losers of a physical competition were randomly assigned to hold a low, neutral or high-power postural display. We found no main effect of pose type on testosterone, cortisol, risk or feelings of power. Winners assigned to a high-power pose had a relative, albeit small, rise in testosterone compared to winners who held neutral or low-power poses. For losers, we found little evidence that high-power poses lead to increased testosterone relative to those holding neutral or low-powered poses. If anything, the reverse was observed - losers had a reduction in testosterone after holding high-power poses. To the extent that changes in testosterone modulate social behaviors adaptively, it is possible that the relative reduction in testosterone observed in losers taking high-powered poses is designed to inhibit further winner-like behavior that could result in continued defeat and harm. Still, effects were small, multiple comparisons were made, and the results ran counter to our predictions. We thus treat these conclusions as preliminary. Copyright (C) 2016 Elsevier Inc.

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Dimethandrolone (DMA, 7alpha,11beta-dimethyl-19-nortestosterone) has both androgenic and progestational activities, ideal properties for a male hormonal contraceptive. In vivo, dimethandrolone undecanoate (DMAU) is hydrolyzed to DMA. We showed previously that single oral doses of DMAU powder in capsule taken with food are well tolerated and effective at suppressing both LH and testosterone (T), but absorption was low. We compared the pharmacokinetics and pharmacodynamics of two new formulations of DMAU, in castor oil and in self-emulsifying drug delivery systems (SEDDS), with the previously tested powder formulation. DMAU was dosed orally in healthy adult male volunteers at two academic medical centers. For each formulation tested in this double-blind, placebo-controlled study, 10 men received single, escalating, oral doses of DMAU (100, 200, and 400 mg) and two subjects received placebo. All doses were evaluated for both fasting and with a high fat meal. All three formulations were well tolerated without clinically significant changes in vital signs, blood counts, or serum chemistries. For all formulations, DMA and DMAU showed higher maximum (p < 0.007) and average concentrations (p < 0.002) at the 400 mg dose, compared with the 200 mg dose. The powder formulation resulted in a lower conversion of DMAU to DMA (p = 0.027) compared with both castor oil and SEDDS formulations. DMAU in SEDDS given fasting resulted in higher serum DMA and DMAU concentrations compared to the other two formulations. Serum LH and sex hormone concentrations were suppressed by all formulations of 200 and 400 mg DMAU when administered with food, but only the SEDDS formulation was effectively suppressed serum T when given fasting. We conclude that while all three formulations of oral DMAU are effective and well tolerated when administered with food, DMAU in oil and SEDDS increased conversion to DMA, and SEDDS may have some effectiveness when given fasting. These properties might be advantageous for the application of DMAU as a male contraceptive. Copyright (C) 2016 American Society of Andrology and European Academy of Andrology.

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Publisher
Blackwell Publishing Ltd (E-mail: customerservices@oxonblackwellpublishing.com)
The correlation of insulin resistance with B cell function, metabolic, and hormonal parameters in type 2 diabetic women treated with metformin

Khalaf BH, Abdulridha MK, Kadhim KA, Najim HD

EBM Reviews - Cochrane Central Register of Controlled Trials


AN: CN-01288610 NEW

Beta cell dysfunction and insulin resistance are believed to cause persistent hyperglycemia which characterizes type 2 diabetes. Previous study found potential relationship between elevated free testosterone level and an insulin resistance status in hyperprolactinemia women. Treatment with different doses of metformin result in a significant reduction in prolactin level. This study is designed to explore the potential role of metformin in improving beta cell function via its effect on ameliorating metabolic and hormonal parameters in type 2 diabetic women by direct or indirect relationship. A 20 middle age newly diagnosed type II diabetes mellitus female patients treated with 1500mg metformin daily for 6 months. Fasting blood glucose, fasting serum insulin, HOMA-IR, HOMA-B, serum prolactin, total and free testosterone were measured. Following three to six months with metformin therapy, significant improvement in glycemic parameters, insulin resistance, beta cell function was clear (P<0.05). Similarly for endogenous total and free testosterone, and serum prolactin levels were significantly reduced (P<0.05). Fasting serum insulin positively correlated only with serum prolactin after 6 months of metformin therapy (P<0.05). Fasting serum insulin and IR showed negative correlation with free testosterone at the baseline and after metformin therapy (P<0.05). The reduction in serum prolactin and endogenous total and free testosterone following metformin therapy may potentially reduce fasting serum insulin, insulin resistance, and thereby improves beta cell function. Copyright (C) 2016, International Journal of Pharmaceutical Sciences Review and Research, All rights reserved.

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Global Research Online (Plot No: 6, R. K. Lake view, Hebbagudi, Anekal Taluk, Bangalore, India)
Reproductive hormone analyses and effects of adjuvant zoledronic acid in early breast cancer - An AZURE (BIG 01/04) sub-study


EBM Reviews - Cochrane Central Register of Controlled Trials


AN: CN-01289377  NEW

Purpose: Adjuvant bisphosphonates have been shown to improve disease outcomes in early breast cancer in women who are postmenopausal at the start of treatment. We explored the influence of pretreatment serum levels of reproductive hormones in the hypothalamic-pituitary-gonadal (HPG) axis from a subset of patients included in the AZURE trial to investigate their impact on disease recurrence and whether reproductive hormone measurements are of value in selecting patients for treatment with adjuvant zoledronic acid.

Patients and methods; The AZURE trial is an academic, multi-centre, international phase III trial that randomised patients to standard adjuvant therapy (chemotherapy and/or endocrine therapy)+/-intravenous zoledronic acid, 4 mg for 5 years. Serum from 865 patients taken at randomisation was stored at -80 C prior to central batch analysis for inhibin A, oestradiol and follicle stimulating hormone (FSH). We assessed the clinical value of pretreatment hormone levels for predicting invasive disease free survival (IDFS), skeletal recurrence and distant recurrence and response to treatment with zoledronic acid.

Results: Oestradiol in the postmenopausal range (<50 pmol/l) was associated with a significantly shorter IDFS (HR 1.36 95%CI: 1.05-1.78 p=0.022), predominantly due to distant recurrence (HR 1.33 95%CI: 0.98-1.81 p=0.065), compared to oestradiol >50pmol/l. In contrast, FSH in the postmenopausal range (>26 IU/l) was associated with a longer time to bone as first recurrence (HR 0.66 95%CI: 0.41-1.04 p=0.072) compared to an FSH <26 IU/l. When all 3 hormone levels were within the assay specified postmenopausal range, a trend to improved IDFS was seen with addition of zoledronic acid in biochemically postmenopausal women only (postmenopausal HR=0.81; 95%CI: 0.54-1.22, non-postmenopausal HR=0.99; 95%CI: 0.69-1.39) with risk reductions that mirrored the results of the main AZURE study, although the interaction between menopausal status and treatment effect was not statistically significant (p=0.47). Conclusion: Oestradiol and FSH may influence the pattern of disease recurrence with postmenopausal levels possibly creating a less conducive environment for the formation of bone metastases, therefore disseminated tumour cells could seek alternative niches outside of bone. Biochemical evaluation of a panel of reproductive hormones may be helpful to assist selection of patients for adjuvant zoledronic acid when menopausal status is unknown. Copyright (C) 2016.

Institution
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Vitamin D is a versatile signaling molecule with an established role in the regulation of calcium homeostasis and bone health. In recent years the spectrum of vitamin D target organs has expanded and a reproductive role is supported by the presence of the vitamin D receptor (VDR) and the vitamin D metabolizing enzymes in the gonads, reproductive tract, and human spermatozoa. Interestingly, expression levels of VDR and the vitamin D inactivating enzyme CYP24A1 in human spermatozoa serve as positive predictive markers of semen quality and are higher expressed in spermatozoa from normal than infertile men. VDR mediates a non-genomic increase in intracellular calcium concentration, sperm motility, and induces the acrosome reaction. Furthermore, functional animal model studies have shown that vitamin D is important for sex steroid production, estrogen signaling, and semen quality. Cross-sectional clinical studies have supported the notion of a positive association between serum 25-hydroxyvitamin D (25-OHD) level and semen quality in both fertile and infertile men. However, it remains to be determined whether this association reflects a causal effect. The VDR is ubiquitously expressed and activated vitamin D is a regulator of insulin, aromatase, and osteocalcin. Hence, it is plausible that the influence of vitamin D on gonadal function may be mediated indirectly through other vitamin D regulated endocrine factors. Recent studies have indicated that vitamin D supplementation may be beneficial for couples in need of assisted reproductive techniques as high serum vitamin D levels were found to be associated with a higher chance of achieving pregnancy. Randomized clinical trials are needed to determine whether systemic changes in vitamin D metabolites can influence semen quality, fertility, and sex steroid production in infertile men. In this review known and possible future implications of vitamin D in human male reproduction function will be discussed. Copyright (C) 2016.
Comparison of clinical and serological differences according to the autoantibody cluster in women with systemic lupus erythematosus: results from the Korean lupus network (KORNET) registry


EBM Reviews - Cochrane Central Register of Controlled Trials


[Journal: Conference Abstract]

AN: CN-01292754  NEW

Background/Purpose: Individual autoantibodies are associated with the clinical features in patients with systemic lupus erythematosus (SLE). However, few studies have investigated differences in disease presentation based on autoantibody profiles in Asian patients with SLE. This study evaluated autoantibody clusters and compared the clinical and serological presentation and clinical outcome in Korean SLE patients. Methods: The Korean Lupus Network (KORNET) is a nationwide multicenter, hospital-based registry, set up to prospectively assess outcomes in Korean SLE patients. Of the 505 SLE patients enrolled in the KORNET registry from July 2014 to November 2015, the study group comprised 339 consecutive female SLE patients. Seven autoantibodies (anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, anti-La, lupus anticoagulant (LAC), and anti-cardiolipin antibody [aCL]) were selected for cluster analysis using the K-means cluster analysis procedure. Results: Three distinct autoantibody clusters were identified: cluster 1, anti-dsDNA and anti-Ro; cluster 2, anti-RNP; and cluster 3, anti-RNP, anti-Ro, and anti-La. Compared with patients in clusters 2 (n = 99) and 3 (n = 85), patients in cluster 1 (n = 155) had a shorter symptom duration before SLE diagnosis and higher incidence of biopsy-proven lupus nephritis. Patients in cluster 3 had a higher incidence of discoid rash, central nervous system
involvement, lupus pancreatitis, pulmonary arterial hypertension, Raynaud's phenomenon, and premature gonadal failure. In addition, patients in cluster 3 had the lowest proportion of mean prednisolone > 7.5 mg/day in the medication history. Conclusion: Autoantibody clusters were associated with the clinical features in women with SLE. Clustering autoantibodies could be a valuable approach for differentiating between various clinical subsets of SLE, and may help to guide prediction of the subsequent clinical course and organ damage in these patients.

Institution
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Publisher
John Wiley and Sons Inc.

Evaluation of radiation shielding protocols for patients undergoing computed tomography: a nationwide survey


EBM Reviews - Cochrane Central Register of Controlled Trials


[Journal: Conference Abstract]

AN: CN-01293480 NEW

Introduction & Objective: The substantial rise in use of computed tomography (CT) as a diagnostic imaging tool has contributed to increased patient exposure to high doses of ionizing radiation that can have adverse effects. Radiation shielding protocols have been demonstrated to reduce radiation exposure. In the United States (US), the ALARA (As Low As Reasonably Achievable) governing principle states that radiation dosages and radioactive material release should be as minimal as possible. We examined the utilization of protective shielding in adult patients receiving routine head, chest, or abdominopelvic CT scans in US hospitals. Materials and Methods: An online epidemiological survey was administered to randomly selected US hospitals with formal radiology departments. The survey included questions regarding dose-reduction shielding practices including eye, thyroid, breast, and gonadal shielding. Data were compiled and analyzed using REDCap electronic data capture software. Results: Among the 67 responding hospitals, 66 (98.5%) reported familiarity with the ALARA principle and 56 (83.6%) affirmed that shielding devices are beneficial to patients. However, only 40 (59.7%) institutions
reported using shielding devices for patients undergoing CT imaging. Of these institutions, 33 (82.5%) use shielding during head CT, 30 (75.0%) during chest CT, and 13 (32.5%) during abdominopelvic CT; 8 hospitals (20.5%) use devices for all three types of CT scans (Table 1). Figure 1 presents the geographic distribution of shielding protocols across the US. Conclusions: Although most hospitals are familiar with the ALARA principle and agree that CT shielding is a beneficial practice for radiation dose reduction, many do not utilize any form of shielding. Of hospitals that use CT shielding, the practice remains largely non-mandatory. (Figure presented) (Table presented).

Publisher
Mary Ann Liebert Inc.

207.
Effect of testosterone therapy combined with a very low caloric diet on fat mass in obese men with a low-to low-normal testosterone level: a randomized controlled trial
Fui MNT, Hoermann R, Dupuis P, Raval M, Zajac JD, Grossmann M
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Conference Abstract]
AN: CN-01294863 NEW
Effect of Testosterone Therapy Combined with a Very Low Caloric Diet on Fat Mass in Obese Men with a Low- to Low-Normal Testosterone Level: A Randomized Controlled Trial Context In men, obesity is strongly associated with low testosterone levels. Weight loss due to caloric restriction is associated with increases in circulating testosterone, and testosterone treatment reduces fat mass. However, whether combining testosterone treatment with caloric restriction reduces fat mass more so than caloric restriction alone is not known. Objective We hypothesised that testosterone treatment will reduce body fat mass more so than caloric restriction alone. Design, setting and participants We conducted a 56-week double-blind randomised placebo-controlled trial at a tertiary referral centre. We recruited 100 obese men (BMI > 30 kg/m<sup>2</sup>) aged 18-75 years with a low- to lownormal serum total testosterone level (average of 2 consecutive morning fasting levels of <12nmol/L [<346ng/dL]). Intervention All men underwent a weight-loss phase with a very low-calorie diet (providing approximately 600 kcal/ d)
for 10 weeks followed by reinstitution of normal foods with the aim of weight maintenance for the next 46 weeks. In addition, men were randomised in a concealed 1:1 allocation to receive 10-weekly intramuscular 1000 mg testosterone undecanoate or placebo injections for the 56-week duration of the study. Main outcome measures: The primary outcome was fat mass measured by DEXA. Secondary outcomes were visceral fat mass by abdominal CT and lean body mass by DEXA. Results Baseline characteristics of the 100 men were as follows: median [interquartile range] age 53.2 y [47.4-59.9y], BMI 37.4 kg/m^2 [34.7-41.2kg/m^2], fat mass 45.1kg [37.8-51.9kg] and total testosterone 7.1nmol/L [6.1-8.2nmol/L] (204ng/dL [175-237ng/dL]) by LCMS-MS. The study will be completed by November 2015 and results will be reported at the meeting Conclusions There is an epidemic of obesity and related functional hypogonadism yet testosterone treatment remains controversial. This trial will assess whether in middle-aged obese men with a low to low-normal testosterone, testosterone treatment has fat lowering effects beyond that achieved by caloric restriction alone.

Institution
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Publisher
Endocrine Society

208.
Effects of testosterone administration for 3 years on cognition in older men with low or low-normal testosterone levels: results from a randomized-controlled trial
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Conference Abstract]
AN: CN-01294884 NEW
Objective: To determine the effect of long-term testosterone administration on cognition in older men with low or low-normal testosterone levels. Methods: 308 men 60 years and older with low or low-normal testosterone levels (100-400 ng/dl; free testosterone <50 pg/mL) were randomized to receive 7.5 g of 1% testosterone gel or placebo gel daily for 3 years. The dose was adjusted to
achieve testosterone levels between 500 and 900 ng/dL. Cognitive function was evaluated using a comprehensive battery of standardized neuropsychological tests at baseline, 6 months, 18 months and 36 months. Results: 280 men who underwent cognitive function assessments constituted the analytic sample of which 140 men were randomized to receive testosterone while 140 men received placebo gels. Baseline characteristics were similar in both groups. Mean (SD) on-treatment serum total and free testosterone concentrations increased from 306 (65) to 568 (267) ng/dl and from 64 (18) to 105 (64) pg/ml, respectively, in the testosterone arm, but did not change significantly in the placebo group. No significant changes in spatial ability, verbal fluency, verbal memory or executive function were observed with testosterone administration compared with placebo; these results remained consistent after adjustment for age, education and baseline cognitive function. Multiple regression analysis did not show significant correlation between change in serum testosterone concentrations and change in cognitive function scores.

Conclusion: Testosterone administration for 36 months in older men with low or low-normal testosterone levels did not improve cognitive function.

Institution
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Publisher
Endocrine Society

Introduction: Testosterone therapy (TTh) is indicated for treating hypogonadal men with low serum testosterone (T) levels and related symptoms. However, T products administered as topical or parenteral T formulations are associated with inadvertent T transference, poor
compliance, and superphysiologic T levels in some patients. There is a need for T formulations that improve patient compliance, mitigate transference, and achieve more consistent serum T levels. LPCN 1021 is a novel oral T undecanoate formulation assessed in a Phase 3 (SOAR) trial that may avoid some of the undesirable attributes of non-oral T formulations. Long-term cardiovascular outcomes of TTh is unknown with studies of TTh and cardiovascular safety providing inconsistent results. Methods: SOAR is a randomized, active-controlled, 2-arm, 12-months, open-label, multicenter, dose-titration trial that included 314 hypogonadal (T<300ng/dl on 2 separate days) men between the ages of 18 and 80 years old. Participants were randomized to either LPCN 1021 (n=210) or Androgel 1.62% (n=104). Of the 314 randomized hypogonadal men, 164 (52%) of them had a comorbid condition of cardiovascular disorder (CVD+) at baseline. The LPCN 1021 dose could be titrated up (e.g. if T C<sub>ave</sub> 24h < 300 mg/dL) or down (e.g. if T C<sub>max</sub> was > 1500 mg/dL) at weeks 4 and 8 based on 24 h PK, if required. Androgel 1.62% was titrated based on manufacturer's instruction. Sexual function and mood changes were assessed by the Psychosexual Daily Questionnaire (PDQ) for 7 days preceding visits. In addition, quality of life (QoL) was assessed by the SF-36 questionnaire at weeks 1 and 52 (end of study, EOS). Results: Hypogonadal subjects with CVD+ (n=164; 52%) were significantly older (p<0.001), and had higher SHBG levels (p=0.002), and greater vitality (p=0.028); baseline T levels were comparable (p=NS). Men with CVD+ had worse erections (p=0.010) and more difficulty maintaining erections (p=0.001) compared to hypogonadal subjects without CVD at baseline. Treatment with LPCN 1021 resulted in greater reduction of LDL, cholesterol and triglycerides in hypogonadal subjects with CVD+ compared to those without CVD both at baseline (p=0.033, p=0.011 and p=0.091) and EOS (p=0.005, p<0.001 and p=0.014), respectively. Non-significant differences were observed for the same parameters with Androgel 1.62%. In addition, hypogonadal patients with CVD+ treated with LPCN 1021 had significant improvements at EOS compared to baseline for vitality (p=0.006), depressed mood (p<0.001), mental component summary (p=0.017), penile rigidity (p<0.001) and ability to maintain erections (p<0.001). Conclusions: Twice daily administration of oral LPCN 1021 improves psychosexual symptoms in hypogonadal men with or without CVD.

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Publisher
Endocrine Society
The role of testosterone in the utilization of iron in erythropoiesis
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Conference Abstract]
AN: CN-01294889  NEW

Since the syndrome of hypogonadotropic hypogonadism (HH) is associated with anemia and the administration of testosterone restores hematocrit to normal, we investigated the potential mechanisms which may contribute to it. We measured serum concentrations of erythropoietin, iron, iron binding capacity, transferrin (saturated and unsaturated), ferritin and hepcidin and the expression of ferroportin in peripheral blood mononuclear cells (MNC) of 94 men with type 2 diabetes. 44 men had HH (defined as free testosterone <5ng/dl along with low or normal LH concentrations) while 50 were eugonadal. Hematocrit concentrations were lower in hypogonadal men (41.2+/-3.8% vs. 43.8+/-3.2%, p=0.001). There were no differences in plasma concentrations of hepcidin, ferritin, erythropoietin, transferrin, iron or transferrin saturation or in ferroportin expression in MNC among hypogonadal and eugonadal men. Men with HH were randomized to testosterone treatment (200 mg i.m., every two weeks) or placebo (saline 1ml every 2 weeks) for 24 weeks. 20 men in testosterone group and 14 men in placebo group completed the study. Free testosterone concentrations increased from 4.5+/-1.3 to 13.8+/-4.1ng/dl (p<0.001) after testosterone therapy but did not change in placebo group. The hematocrit increased from 42.0+/-2.7% to 45.4+/-4.6% (p<0.001) but did not change after placebo (40.7+/-2.9% to 41.6+/-3.1%, p=0.22). There was a 30+/-7% decrease in plasma hepcidin (p=0.01) and 29+/-8% increase in erythropoietin concentrations (p<0.05) after testosterone therapy. There was no significant change in iron or ferritin concentrations but transferrin concentration increased by 21+/-7% and transferrin saturation decreased by 30+/-10% (p<0.01). Ferroportin mRNA expression in MNC increased by 70+/-13% (p<0.01) at 4 weeks and 15 weeks but came back to baseline at 24 weeks after testosterone therapy when the hematocrit normalized. There was no change in any of these parameters after placebo. We conclude that the administration of testosterone to restore normal testosterone concentration led to a significant increase in plasma erythropoietin concentrations, reduction in plasma hepcidin concentration, marked increase in ferroportin expression which was transient, a smaller but significant increase in transferrin and a small reduction in plasma iron concentrations. Clearly, therefore, the increase in hematocrit is supported by an increase in erythropoietin and an increase in iron transport.
through an increase in ferroportin. This increase is probably through the known suppression of hepcidin which suppresses ferroportin expression.

Institution
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Publisher
Endocrine Society

211.

Long-term safety and tolerability of oral testosterone (LPCN 1021) in hypogonadal men: results from the 52-week phase 3 study (soar trial)

EBM Reviews - Cochrane Central Register of Controlled Trials

[Journal: Conference Abstract]
AN: CN-01294890  NEW

Introduction and Objective: LPCN 1021 is a novel oral T undecanoate (TU) formulation, absorbed primarily via lymphatics bypassing the liver. LPCN 1021 previously has been shown to be safe and efficacious after 13 weeks in a randomized, active-controlled Phase 3 study.1 We report the long-term safety and consistency of LPCN 1021 in hypogonadal subjects who continued to receive treatment for up to 52 weeks. Methods: Hypogonadal patients (serum T levels < 300 ng/dL) were randomized in a 2:1 ratio to LPCN 1021 or AndroGel 1.62% (active control) and titrated to a successful dose of their assigned treatment. The LPCN 1021 dose was adjusted, if necessary, to achieve eugonadal T levels (300 to 1140 ng/dL); active control dosing followed the manufacturer's recommendations. Following the 13-week efficacy phase, subjects continued to receive their assigned study drug for up to 52 weeks. Subjects returned to the clinic at Weeks 26, 39, and 52 for safety assessments and to provide a 3 to 6 hour post dose blood sample. Safety assessments included an evaluation of adverse events (AEs), clinical laboratory tests, and physical examinations. Results: 210 subjects were randomized to LPCN 1021 and 105 to active control. Eugonadal T levels were restored with LPCN 1021 (Week 13 mean [SD] Cavg of 446
[171] ng/dL) and were reliably maintained through Week 52. AEs occurred in 67% of LPCN 1021 subjects and 65% of AndroGel 1.62% subjects. No hepatic, cardiac, or drug-related serious AEs occurred. Each of the gastrointestinal AEs reported occurred in 3% or fewer subjects with LPCN 1021. The most common drug-related AEs (ADRs) for LPCN 1021 and AndroGel 1.62% included acne (2.9% and 2.9% respectively), headache (0.5% and 3.8%, respectively), weight increase (2.4% and 0%, respectively), increased hematocrit (1.9% and 0%, respectively), liver enzyme level increased (1.4% and 0%, respectively), fatigue (0.5% vs 1.9%, respectively), and hypertension (0.5% vs 1.9%, respectively). All ADRs reported were mild or moderate in severity. Androgenic ADRs were uncommon in subjects receiving LPCN 1021 with no reports of sleep apnea or oily skin and 1% or fewer subjects reporting peripheral edema and polycythemia. Most lipid parameters (cholesterol, LDL, HDL, and TG) were comparable between treatment groups at Week 52. Liver enzymes were also generally similar between the treatment groups. Androgenic parameters, including hematocrit, hemoglobin, platelet, prothrombin, and PSA, showed no significant differences in change from baseline to end of study between treatments. Conclusions: LPCN 1021 was well tolerated and had a favorable safety profile in the longterm management of hypogonadal subjects. Notably, no hepatic safety concerns were identified and gastrointestinal AEs with oral LPCN 1021 were generally comparable to those with topically administered AndroGel 1.62%.

Institution
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Publisher
Endocrine Society

212.
Maximal oxygen uptake (VO$_{2}$) is markedly decreased in prader-willi syndrome (PWS)
Hirsch HJ, Gross I, Constantini N, Nice S, Pollak Y, Genstil L, Eldar-Geva T, Gross-Tsur V
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Conference Abstract]
AN: CN-01294895 NEW
Background: PWS, due to lack of expression of paternal genes in 15q11-13, is characterized by obesity, hypotonia, hypogonadism, abnormal body composition, and variable cognitive and behavioral disorders. Regimens to prevent morbid obesity in this population include a very restricted diet (800 kcal/day or less) and daily exercise. VO$_2$ max, the maximal amount of O$_2$ consumption during incremental exercise, is the single best measurement of cardiovascular fitness and maximal aerobic capacity. VO$_2$ max is an important measure in prescribing exercise regimens. Indirect methods using heart rate at rest and during exercise to estimate VO$_2$ max in normal individuals may not be accurate for PWS. Direct measurement of VO$_2$ max has not been previously reported in PWS.

Objectives:
Assess the efficacy of exercise in PWS by determining VO$_2$ max, anaerobic threshold, and other fitness components in young adults with PWS and compare the findings with a group of age and BMI-matched non-syndromic overweight controls.

Methods:
The study group consisted of 17 (12M, 5F) individuals ages 19-35 (28.6 +/- 4.9) years with PWS (10 deletion, 6 uniparental disomy, and 1 imprinting center defect). The control group (OC) consisted of 32 (22M, 10F) overweight/obese but otherwise healthy young adults of comparable ages 19-36 (29.3 +/- 5.2) years. BMI was similar in both groups: 19.4-38.1 (27.8 +/- 5) kg/m$^2$ for PWS and 21.1-48.1 (26.3 +/- 4.9) kg/m$^2$ for controls (NS). During a graded treadmill exercise test, VO$_2$ max was determined by direct measurements of oxygen consumption and CO$_2$ production using a metabolic analyzer (QUARK CPET, Cosmed, Italy). Maximal effort was reached within 8-14 minutes. Anaerobic threshold was determined by observing when the rise in VCO$_2$ was no longer parallel with the increase in VO$_2$ (Cardiopulmonary Exercise Training (CPET) V slope). Strength (hand dynamometer) and flexibility (sit and reach) tests were performed by all participants and a balance test was performed for the PWS group.

Results:
VO$_2$ max for PWS individuals was significantly lower than for OC (24.6 +/- 3.4 vs 46.5 +/- 12.2 ml/kg/min, p<0.001). VO$_2$ and pulse rate at the anaerobic threshold were significantly lower (20+/-2 vs 36.2 +/-10.5 ml/kg/min, p<0.001 and 130 +/- 20 vs 152 +/- 13 beats per minute, p<0.001) for PWS and OC, respectively. Maximal strength of both hands (36 +/- 4 vs. 91.4 +/- 21.2 kgm, p<0.001) and flexibility (15.2 +/- 9.5 vs. 26 +/- 11.1 cm, p=0.001) were significantly lower for PWS compared to OC.

Conclusions:
Exercise programs which do not take into account the significantly lower VO$_2$ max in PWS may fail to attain adequate energy expenditure in these individuals. Direct measurement of VO$_2$ max along with strength, flexibility, and balance assessment are needed to tailor appropriate exercise regimens in order to achieve more effective weight control in PWS as well as in other special need populations.

Institution
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Publisher
Endocrine Society
The androgen receptor (AR) CAG repeat length is not related to changes in androgen-responsive endpoints (AREs) in community-dwelling middle-aged and elderly men of white European origin: prospective results from the European Male Aging Study (EMAS).


EBM Reviews - Cochrane Central Register of Controlled Trials


[Journal: Conference Abstract]
AN: CN-01294913 NEW

Introduction: The Androgen Receptor (AR) tri-nucleotide CAG repeat length polymorphism has been proposed to be a genetic determinant of between-individual variations in androgen action on target tissue (1-9). However, most previous studies have been cross-sectional in design from single centres. Multi-centre studies investigating longitudinal changes in androgen-responsive endpoints (AREs) in relation to the AR CAG repeat length are lacking. Aim and setting: The aim of the study was to assess whether the AR CAG repeat length is associated with longitudinal change in AREs in a multi-centre European cohort study of middle-aged and elderly men (10-11).

Methods: 2228 men (mean+/−sd age at follow-up: 63+/−11 years) from 8 European countries comprised the analysis sample after exclusion of those with diagnosed diseases of the hypothalamic-pituitary-gonadal (HPG) axis. Phenotypic assessments undertaken included AREs, such as reproductive hormone levels, body composition, carbohydrate metabolism, hematological and cognitive parameters, and self-reported physical activity, sexual, physical and psychological symptoms and medical conditions. Follow-up measurements were performed a median of 4.3 years later. The AR CAG repeat length was measured using fluorescently-labeled PCR (12). The longitudinal association between relative change in AREs from baseline (dependent variables) and the AR CAG repeat length (independent variable) was assessed using regression analysis adjusting for age and center. The AR CAG repeat length was treated as a continuous linear and also categorical (6-20; 21-23; 24-39 repeats) predictor. Results: The distribution of the AR CAG repeat length (6-20: 581 men, 21-23: 667 men, 24-39: 639 men) was similar to previous studies.
in community-dwelling European men (9). Analysis of the AR CAG repeat length as a linear predictor of relative change in AREs revealed no significant associations after adjustment: overall sexual function (beta:-0.01, 95%CI:-0.07;0.04), hemoglobin (beta:-0.02, 95%CI:-0.07;0.03), estimated bone mineral density (beta:0.01, 95%CI:-0.04;0.05), waist circumference (beta:-0.04, 95%CI:-0.08;0.01), HOMA-IR (beta:0.01, 95%CI:-0.04;0.06) and physical performance (beta:-0.02, 95%CI:-0.07;0.02). Similar results were obtained, when the AR CAG repeat length was categorized into 3 groups. Conclusion: In this prospective study of community-dwelling middle-aged and elderly men, the AR CAG repeat length was not associated with changes in AREs. We conclude that in individuals with a functional HPG axis, variations in the AR CAG repeat length do not appear to impact on short-term changes in androgen-related physiological endpoints in the general population.

Institution
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Publisher
Endocrine Society

214.
Vitamin D and calcium as novel regulators of reproductive hormones and sex steroids in copenhagen bone gonadal study: a randomized clinical trial
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Conference Abstract]
AN: CN-01294934  NEW
Context: Newer studies have indicated that vitamin D may have more widespread effects than the classical effects on bone and calcium-phosphate homeostasis. The presence of the vitamin D receptor in the testis and male reproductive tract indicates a role for vitamin D in male reproduction Objective: To investigate changes in the reproductive, skeletal and endocrine organs following 5 months supplementation with high dose vitamin D and calcium or placebo in infertile men. Design: A single center, double blinded randomized clinical trial of 330 Danish infertile men with vitamin D insufficiency (serum 25-OHD < 50 nmol/l) conducted from 2011-2015.
Setting: Tertiary referral centre for andrology. Participants: All men were part of an infertile couple and were referred due to low semen quality. In total, 1421 infertile men were screened. 1090 men were excluded due to high vitamin D levels, azoospermia, serious associated comorbidities, medication or no desire to participate, yielding 330 men eligible for inclusion in the study. Of the 330 men who gave informed consent 309 showed up day 1 and started treatment with vitamin D + calcium or placebo. Main Outcome Measures: All 309 men underwent DXA scanning, delivered two semen samples and one blood sample prior to treatment start and again after 150 days intervention. The effect of one oral 300,000 IE cholecalciferol loading dose in addition to a daily 1400 IE cholecalciferol + 500 mg calcium dose for 5 months was compared with placebo on semen quality, clinical pregnancies, serum 25-hydroxyvitamin D, 1,25dihydroxyvitamin D, calcium ion, AMH, Inhibin B, LH, FSH and sex steroid levels. Results: More than 88% of the infertile men completed the study. Two semen analyses prior to the intervention and at follow up day 150 provide a reliable estimate of semen quality before and after the intervention. Serum analyses are being conducted currently using LCMS for vitamin D metabolites and validated ELISAs for sex steroids, AMH, Inhibin B, FSH and LH. The study will be un-blinded December 2015. Conclusions: This is the first randomized clinical trial investigating the effect of vitamin D supplementation to infertile men. This study will show whether supplementation with cholecalciferol and calcium influences reproductive function and changes the endocrine crosslink between bone and gonads in infertile men.

Institution
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Publisher
Endocrine Society

Peripheral makorin ring-finger protein-3 (MKRN3) levels in boys decline before the clinical onset of puberty
Varimo T, Hero M, Vaaralahti K, Dunkel L, Miettinen P, Raivio T
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Conference Abstract]
BACKGROUND: Makoring ring finger protein 3 (MKRN3) gene restrains the hypothalamic-pituitary-gonadal (HPG) axis and thereby controls the onset of puberty (1). In girls, peripheral levels of MKRN3 decline prior to the onset of puberty (2), whereas in boys the changes in serum MKRN3 levels before and during puberty have not been reported.

METHODS: This randomized controlled study included 30 peripubertal boys (age range 9.1-14.2 yrs) with idiopathic short stature (ISS) (3). Sixteen boys were treated with letrozole (2.5mg/d) for 2 yrs and 14 received placebo. Boys were followed up for 3 yrs, hormonal and MKRN3 levels were obtained with 6 mo intervals for 2 yrs, and analyzed using summary measures.

RESULTS: The boys showed an age-dependent decline in serum MKRN3 levels (mean regression coefficient - 6.6+/-7.2 pg/mL per year, P < 0.001), with no difference between the two groups. Importantly, MKRN3 levels declined before Tanner genital stage 2, but not thereafter (-29.3+/-27.5 vs -5.6+/-15.1 pg/mL per year) (P < 0.05). During Tanner genital stage 1, the rate of MKRN3 change correlated negatively with the rate of increases in testosterone (r= -0.4, n=28, P < 0.05), LH (r= -0.5, n=26, P < 0.01) and inhibin B (r= -0.44, n=26, P < 0.05) levels.

CONCLUSIONS: In boys, peripheral MKRN3 levels decrease prior to clinical onset of puberty in an inverse association with circulating markers of HPG axis activity. Inhibition of estrogen biosynthesis has no effect on circulating MKRN3 levels.

Institution
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Publisher
Endocrine Society

Neurokinin b receptor antagonism decreases LH and testosterone secretion in men
Skorupskaite K, George JT, Anderson RA
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Conference Abstract]
Background Hypothalamic neurons that co-secrete kisspeptin and neurokinin B (NKB) are central regulators of GnRH and thus gonadotropin (LH and FSH) secretion: men and women with loss-of-function mutations in NKB signalling show suppressed GnRH pulsatility and subsequently reduced gonadotropin secretion, which can be partially restored by exogenous kisspeptin. The availability of an NKB receptor antagonist allows exploration of the role of NKB in the regulation of the reproductive axis in healthy men. Methods Six healthy men aged 23-39 were administered NK3R antagonist, AZD4901, 80mg/day orally for 7 days with spot LH measurements on day -1, 2, 4 and 7. 10-minute blood sampling for 8 h was performed on day -1 and on the last day of treatment with NK3R antagonist for the analysis of pulsatile LH secretion by blinded deconvolution. Kisspeptin-10 (0.3 mug/kg iv bolus) was administered at 6 h on both days. Hormone concentrations were compared by t-test and ANOVA with Bonferroni multiple comparison post hoc analysis. Ethical approvals and informed consent were obtained. Results LH secretion decreased with NK3R antagonist administration (p=0.04), demonstrating a biphasic response: LH fell after 24 h of treatment (4.1 +/- 0.5 day -1 to 1.7 +/- 0.2 IU/l), then recovered (4.2 +/- 0.7 IU/l day 4) but was again decreased on day 7 (2.5 +/- 0.6 IU/l). Testosterone was consistently suppressed during 7 days of NK3R antagonist treatment (17.9 +/- 1.1 day -1, 5.6 +/- 1.5 at 24 hours, 10.1 +/- 1.2 day 4 and 8.9 +/- 0.7 nmol/l day 7, p<0.01 all vs day -1). LH pulse frequency was unchanged by NK3R antagonist (0.50 +/- 0.09 vs 0.47 +/- 0.07 pulses/h, ns), but LH secretory mass per pulse (5.9 +/- 1.5 vs 2.6 +/- 0.6 IU/l, p=0.03) and basal (nonpulsatile) LH secretion (35.0 +/- 6.6 vs 9.7 +/- 2.2 IU/l/6h, p=0.009) were markedly reduced. Serum testosterone recovered in all subjects 2 weeks later (19.8 +/- 1.2 nmol/l). The LH response to kisspeptin-10 was unaffected during NK3R antagonist administration (1 h post kisspeptin-10: 5.5 +/- 0.5 vs 5.7 +/- 0.5 IU/l with NK3R antagonist, ns). Conclusions Pharmacological NK3R antagonism reduced serum LH and testosterone concentrations, indicating an important role for NKB signalling in the regulation of gonadal activity in normal men. Kisspeptin is a key modulator of GnRH/LH pulse frequency: in contrast, NK3R antagonism did not affect this, but other aspects of the pulsatile nature of LH secretion were markedly reduced. The LH response to kisspeptin was maintained, supporting a predominantly hierarchical relationship whereby NKB is proximal to kisspeptin in the regulation of GnRH, but the pulse analysis suggests a more complex interaction between these neuropeptides. Manipulation of kisspeptin/NKB signalling to suppress hypothalamic-pituitary-gonadal axis has therapeutic potential for sex-steroid dependent disorders.

Institution
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Publisher
Endocrine Society
Proinflammatory cytokine infusion attenuates LH's feedforward on testosterone secretion: modulation by age

Veldhuis JD, Yang RY, Roelfsema F, Takahashi PY

EBM Reviews - Cochrane Central Register of Controlled Trials

[Journal: Conference Abstract]
AN: CN-01295203 NEW

Context. In the experimental animal, inflammatory signals quench luteinizing hormone's (LH) feedforward drive of testosterone (T) secretion and appear to impair gonadotropin-releasing hormone (GnRH)-LH output. The degree to which such suppressive effects operate in the human is not known. Objective. To test the hypothesis that interleukin-2 (IL2) impairs LH's feedforward drive on T and T's feedback inhibition of LH secretion in healthy men. Setting. Mayo Clinic's Center for Clinical and Translational Science. Participants. 35 healthy men, 17 young and 18 older. Interventions. Randomized prospective double-blind saline-controlled study of IL2 infusion in 2 doses with concurrent 10-min blood sampling for 24 h. Outcomes. Deconvolution analysis of LH and T secretion. Results. After saline injection, older compared with young men exhibited reduced LH feedforward drive on T secretion (P<0.001), and decreased T feedback inhibition of LH secretion (P<0.01). After IL2 injection, LH's feedforward onto T secretion declined markedly especially in young subjects (P<0.001). Concomitantly, IL2 potentiated T's proportional feedback on LH secretion especially in older volunteers. Conclusion. This investigation (a) confirms combined feedforward and feedback deficits in older relative to young men given saline, and (b) demonstrates: (1) joint mechanisms by which IL2 enforces biochemical hypogonadism, viz.: combined feedforward block and feedback amplification; and (2) unequal absolute inhibition of T and LH secretion by IL2 in young and older men. These outcomes establish that the male gonadal axis is susceptible to dual-site suppression by a prototypic inflammatory mediator. Thus, we postulate that selected interleukins might also enforce male hypogonadism in chronic systemic inflammation.

Institution
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Publisher
Endocrine Society
The effect of gonadal steroids on the natriuretic peptide system
Bachmann KN, Miller KK, Wang TJ, Finkelstein JS
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Conference Abstract]
AN: CN-01295228  NEW

Background: The natriuretic peptide (NP) hormonal system is an important determinant of blood pressure. Low NP levels are associated with hypertension and adverse cardiac remodeling. NP levels are much lower in healthy men compared to healthy women, suggesting that a relative NP deficiency in men might contribute to the higher risk of hypertension and cardiovascular disease observed in men. Prior observational studies suggest an inverse association between testosterone and N-terminal proBNP (BNP) in both sexes. Thus, we tested the hypothesis that testosterone supplementation reduces circulating BNP in men. Methods: We studied 362 healthy men (mean age 33 years) who were enrolled into one of 3 cohorts: 1) placebo GnRH agonist + placebo testosterone gel (controls, n=35); 2) GnRH agonist (goserelin acetate 3.6 mg monthly) + randomization to placebo gel or testosterone gel 1.25 g, 2.5 g, 5 g, or 10 g daily (n=167), and 3) GnRH agonist (goserelin acetate 3.6 mg monthly) + aromatase inhibitor (anastrazole 1 mg daily) + randomization to placebo gel or testosterone gel 1.25 g, 2.5 g, 5 g, or 10 g daily (n=160). At 12 weeks, we analyzed serum BNP, serum total testosterone, and serum estradiol levels. Results: As expected, mean levels of serum total testosterone and estradiol differed between testosterone dosage groups (p<0.0001), with higher levels in higher dosage groups. The range of estradiol levels was much narrower in the cohort that received an aromatase inhibitor compared to the cohorts that did not receive an aromatase inhibitor. BNP levels were negatively associated with serum total testosterone levels in the cohort that received an aromatase inhibitor (r = -0.21, p<0.009), in the cohorts that did not receive an aromatase inhibitor (r = -0.14, p<0.05), and in all cohorts combined (r = -0.17, p=0.001); differences remained significant after adjusting for age and BMI. In contrast, BNP levels were not associated with estradiol levels. In multivariable models including serum total testosterone, estradiol, age and BMI, BNP levels were associated negatively with serum total testosterone levels (partial r = -0.19, p=0.0005) but were not
associated with estradiol levels. Conclusions: In men randomized to receive varying doses of testosterone supplementation, there is an inverse association between circulating testosterone and BNP levels. In contrast, there is no clear association between estradiol and BNP, within the range of estradiol levels seen in men. Further investigation is needed to elucidate the mechanisms underlying the sex-specific differences in NP levels, a topic that has potentially important implications for sex-related disparities in hypertension and other cardiovascular disorders.

Institution
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Publisher
Endocrine Society

219.
Effect of testosterone therapy combined with a very low caloric diet on fat mass in obese men with a low-to low-normal testosterone level: a randomized controlled trial
Fui MNT, Prendergast L, Dupuis P, Raval M, Strauss BJ, Zajac JD, Grossmann M

EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Conference Abstract]
AN: CN-01295256 NEW
Background Obesity, is strongly associated with low testosterone in men. While both dietary restriction and testosterone treatment reduce body fat, whether a combination provides a more pronounced reduction in fat mass is unknown. Objective: We hypothesized that testosterone treatment augments diet-induced fat mass and prevents diet-induced loss of muscle mass.
Participants: Obese men 35-70y with a total testosterone level < 12.0 nmol/L (346 ng/dl).
Intervention: 100 participants receiving 10 weeks of a very low caloric diet (VLCD) followed by a weight maintenance diet were randomly assigned to 56 weeks of intramuscular testosterone undecanoate (n= 49) or matching placebo (n= 51). 82 men completed the study. Main Outcomes and Measures: The primary outcome measure was the difference in fat mass between testosterone- and placebo-treated men at study end (56 weeks) by dual-energy X-ray
absorptiometry (DXA). Secondary outcomes included change in lean mass (DXA), visceral fat
mixed effects model, determined the mean adjusted difference [95% confidence interval] between
groups during follow-up. Results: At the end of the VLCD phase, both men receiving testosterone
(T) and placebo (P) had lost similar amounts of body weight (T group -12.0kg [-14.5, -9.5]; P
group -13.5kg [-16.0, -11.0]), total fat mass (T group, -7.88kg [-9.70, -6.06]; P group -7.51kg [-
9.37, -5.65]) and visceral fat (T group -7,688mm² [-9,333, -6,044]; P group -6,590mm² [-8,267, -
4,912]), with p for between group differences all > 0.05. At study end, while both men receiving T
and P maintained their weight loss compared to baseline (T group -11.4kg [-13.9, -8.8]; P group
-10.9kg [-13.6, -8.1], T group compared to P group had greater reductions in total fat mass (mean
adjusted between group difference (MAD) -2.93kg [-5.71, -0.15], p=0.039), and in visceral fat MAD
-2,678mm² [-5,180, -176], p=0.036). While both groups had lost similar amounts of lean mass at
the end of the 10 week VLCD phase (T group -3.92kg [-5.27, -2.57]; P group -4.83kg [-6.21, -
3.45], p=0.36), during the weight maintenance phase, men treated with T regained lean mass
3.29kg [1.88, 4.70], p<0.001, in contrast to men receiving placebo, 0.81kg [-0.71, 2.32], p=0.29 so
that at study end, men receiving testosterone had an attenuated reduction in lean mass
compared to men receiving placebo, MAD3.38kg [1.32, 5.45], p=0.002. Conclusions: In this RCT
of obese men with lowered testosterone, testosterone treatment augmented the diet-induced loss
of total and visceral fat mass, and prevented the diet-induced loss of lean mass, without effect on
overall weight. Further studies should determine whether these metabolically favourable changes
translate into improved health outcomes.

Institution
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Publisher
Endocrine Society

Clinical and immunological characteristics of autoimmune addison's disease in Sweden: a
nationwide multicenter analysis of 660 patients
EBM Reviews - Cochrane Central Register of Controlled Trials
Autoimmune Addison's disease (AAD) is a rare disease and larger cohort studies are occasional. Deeper insights into clinical and immunological features are needed to optimize monitoring. To provide upgraded data regarding autoimmune comorbidities, autoantibody profiles, metabolic factors and replacement therapy we identified 660 patients with AAD utilizing the Swedish Addison Registry (SAR). Clinical data were analysed and autoantibodies in serum determined. 3627 individuals from the population-based survey Northern Sweden MONICA (MONItoring of Trends and Determinants of CArdiovascular Disease) served as controls when analyzing metabolic factors. The SAR cohort consisted of 59.4% women. The mean age at diagnosis was significantly higher for women (p<0.0001). The proportion of 21-hydroxylase (21-OH) autoantibody positive patients was 83.0%. The majority of patients (62%) had one or more associated autoimmune disease with a women to men ratio of 1.03:0.64 (p<0.0001). The most frequently associated disease among both women and men was hypothyroidism, which was more common among women than men (p<0.0001). Also hyperthyroidism (p=0.0028), hypogonadism (p=0.0015), and alopecia (p=0.0454) had a female preponderance. Regular hydrocortisone was used by 89% of patients; mean dose 28.1 mg/day (SD: 8.5). The mean hydrocortisone equivalent dose normalized to body surface was 14.8 mg/m²/day (SD: 4.4). Mineralocorticoid substitution was used in 88% of patients. BMI (p<0.0001) and the risk of hypertension (p=0.042) were significantly lower in patients with AAD compared with control subjects. No overall significant differences were found for the risk of type 2 diabetes or hyperlipidemia. However, a significant interaction between age and AAD was observed for hyperlipidemia (p=0.013); AAD patients <65 years but not >65 years had a higher risk of hyperlipidemia compared with control subjects. AAD patients are prone to develop other autoimmune conditions. Careful monitoring especially of clinically latent cases is warranted. The mean daily hydrocortisone dose in Swedish AAD patients is slightly higher than generally recommended but the patients do not have an overall unfavorable metabolic profile.

Institution
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Publisher
Endocrine Society
Luteinizing hormone releasing hormone agonists lower testosterone levels more than subcapsular orchiectomy: results from a randomized trial

Oestergren PB, Kistorp C, Fode M, Bennedbaek FN, Faber J, Sonksen J

EBM Reviews - Cochrane Central Register of Controlled Trials


[Journal: Conference Abstract]

AN: CN-01295287 NEW

Introduction & objectives Orchiectomy is considered the gold standard of androgen deprivation therapy (ADT). The aim of ADT is to lower serum testosterone (T) to castration levels, i.e. below 1.7nmol/l (50ng/dl). However, an even lower T level may result in longer time to disease progression and better overall survival and thus, a lower castration level of 0.7nmol/l (20ng/dl) has been proposed. We present data from a randomized trial (EudraCT 2013-002553-29) comparing androgen status after either subcapsular orchiectomy (SO) or the luteinizing hormone releasing hormone (LHRH) agonist, triptorelin (TRIP). Materials & methods Hormone naive men commencing ADT for advanced prostate cancer were randomized to either SO (n=29) or 24 week depot TRIP 22.5mg injections (n=29). Androgen status was measured by liquid chromatography tandem mass spectrometry prior to ADT commencement and after 12 and 24 weeks. Blood samples were collected between 8 and 9 a.m. with patients fasting. Results 58 men were recruited from September 2013 to March 2015, with complete data being available for 55 patients. Baseline characteristics were comparable between the groups regarding age, hormone levels and BMI. All patients achieved castration levels of T at week 12. T was higher after surgery at 12 weeks (median (IQR) 0.49nmol/l, (0.37-0.62)) as compared to TRIP (median (IQR) 0.30nmol/l, (0.30-0.37)) (p < 0.001). The difference remained significant at 24 weeks (p = 0.012), despite one patient on TRIP failing to reach castration levels. The proportion of patients having T levels below 0.7nmol/l was 77% and 97% at 12 weeks (chi<sup>2</sup> test p=0.076) and 92% and 89% at 24 weeks (chi<sup>2</sup> test p=1.00) in the SO and TRIP group, respectively. FSH and LH increased from baseline in the SO group to medians of 60.4 IU/l ((45.8- 71.4) and 32.3 IU/l (22.0-37.8), respectively, at 24 weeks (p < 0.001). FSH levels decreased in the TRIP group to a median of 4.6 IU/l (3.3-5.4), whereas LH levels reached the lower detection limit < 0.3 IU/l in nearly all patients (p < 0.001). Sulfated dehydroepiandrosterone, 17-hydroxyprogesterone, androstenedione and estradiol all decreased significantly in both groups (p < 0.05), no significant
between-group differences were apparent. Sex hormone-binding globulin was unchanged.

Conclusion Patients with advanced prostate cancer on LHRH agonists achieve lower levels of testosterone than those who undergo subcapsular orchiectomy. The clinical significance of this difference remains to be determined.

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Publisher

Endocrine Society

222.

Unexpectedly dramatic weight loss in a Prader-Willi syndrome patient treated by Liraglutide

Pirson N, Patricia E, Jean-Paul T

EBM Reviews - Cochrane Central Register of Controlled Trials


[Journal: Conference Abstract]

AN: CN-01295562  NEW

Prader-Willi syndrome is the most common genetic disorder responsible for a life-threatening obesity. The weight gain results mostly from hyperphagia, but its physiopathology remains unsettled. Hence, the treatment is generally poorly effective. Liraglutide is a Glugacon-Like Peptide (GLP)-1 analog approved for the treatment of type 2 diabetes and more recently for the treatment of the obesity. This medication induces generally a moderate weight loss resulting from enhanced satiety. We report the case of a 48-year-old man with a classical PWS associated with a super morbid obesity (W: 179.8 kg and H: 156 cm; BMI 73.9 kg/m<sup>2</sup>) and type 2 diabetes almost well controlled (HbA1c = 7.1%) with tritherapy (Metformine-Gliclazide-Sitagliptine). In addition to diabetes, obesity was complicated with arterial hypertension, sleep apnea syndrome and hypogonadism. At the first visit in our center, Sitagliptine was stopped for Liraglutide 1.2 mg/day to encourage weight loss. During the next three years, the weight loss was dramatic and continued over the years of treatment with Liraglutide (~90 kg /3 years) to reach a BMI of 37.4 kg/m<sup>2</sup>, below the threshold of morbid obesity at the most recent visit. In
parallel, glycemic control improved markedly allowing a reduction in the hypoglycemic treatment (HbA1c = 5.6%) despite the stop of gliclazide. To our best knowledge, few PWS patients treated by GLP-1 analogs have been reported in the literature. However, in these cases, the amplitude of weight loss was lower and the length of the follow up shorter. Since therapeutic options are limited and bariatric surgery controversial in this population, randomized controlled studies should be designed to assess the efficacy of GLP-1 analogs.

Institution
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Publisher
Taylor and Francis Ltd.

223.
Neuroendocrine phenotype, genetics and hormonal treatment outcome in idiopathic normosmic hypogonadism and Kallmann syndrome patients: a multicenter Belgian study

EBM Reviews - Cochrane Central Register of Controlled Trials

[Journal: Conference Abstract]
AN: CN-01295567  NEW
Aim: To study the clinical phenotype, the genetics and therapeutic responses in a series of 35 consecutive patients with hypogonadotropic hypogonadism and normosmia (nIHH) /hyposmia (KS). Methods: The study of the genes FGFR1 and KAL1 (anosmin), is performed in our center since 2013. Recently, a panel of genes is available for analysis of the following genes: KAL1, FGFR1, PROKR2, PROK2, CHD7, FGF8, KISS1, KISS1R, APR3, TACR3, GNRHR, GNRH1, NELF, WDR11, HS6ST1, SEMA3A. Results: the series includes 35 patients (32 H/3F, 18 +/- 9 years) belonging to 31 families. We have identified by olfactometry 26 nIHH and 9 KS. Brain MRI was performed in all patients: two patients had a malformation of Chiari I, two patients showed a partially empty sella, one patient had a cyst of the pouch of Rathke and another one had a cleft palate. Preliminary genetic analysis demonstrated a FGFR1 mutation in three patients and in a
family. Identified mutations were: c.1663 + 1 G > A, c.1025T > A (p.Leu342*) and c.937 - 1234C > T (new mutation: exon 8A of the isoform IIIb), An anosmin mutation was also identified in another patient: c.827-856 + 49delins, p.Ala276-asp286delinsGlyAsn. A last patient had a new mutation TAC3 c.238 + 1 G > A. concerning fertility outcomes, an oligospermia was obtained in 6/12 men treated with hCG and FSH. Hormonal treatment allowed the development of secondary sexual characters in all patients. The patient with FGFR1:c.937 - 1234C > T showed a reversibility of hypogonadism, after 4 years of treatment. Conclusions: Patients with nIHH FGFR1 mutation may also present with neuro developmental anomalies, which they should be screened for. The association of normosmic IHH and Chiari malformation is intriguing: it was reported just once in the literature (Kulmar & al. Pituitary 2010). We demonstrated hypogonadism reversibility in a patient with one FGFR1 mutation. Finally, we report two novel TAC3 and FGFR1 mutations.

Institution
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Publisher
Taylor and Francis Ltd.

Dynamics of changes in endocrine status in adolescents with lymphoma
Pak E, Kit O, Frantsiyants E, Dmitrieva V, Kozyuk O, Lysenko I, Vladimirova L
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Conference Abstract]
AN: CN-01295971  NEW
Background: The purpose of the study was to analyze the endocrine status of patients with Hodgkin lymphoma (HL) before treatment and the effect of chemotherapy on sex, pituitary and glucocorticoid hormones. Methods: Gonadal function, its regulation by tropic pituitary hormones and levels of prolactin and cortisol were studied by radioimmunoassay in 32 HL patients aged 12-21 years receiving chemotherapy. Results: Before therapy females showed estradiol decreased by 10 times compared with the norm in follicular and luteal phases of the cycle, with testosterone increase by 3.7 times in phase I and by 10 times in phase II of the cycle. Follicle-stimulating hormone (FSH) was 10 times lower than the norm. Luteinizing hormone in the luteal phase was
similar to the norm in all disease stages, and in the follicular phase it was decreased by 15 times in patients with stage III-IV disease, compared with the norm. Male patients, especially those with stage III-IV disease, showed low testosterone levels in the blood before treatment. Significant overproduction of estradiol was observed, especially in stages III-IV. FSH levels in stage III-IV patients were 11 times lower than the norm; cortisol content did not change in stages I-II, and in stages III-IV it was 2.5 times higher than the norm. Prolactin and progesterone levels were similar to the norm. Conclusions: HL development in adolescents is accompanied by significant changes in levels of sex and pituitary hormones and cortisol depending on the disease stage. Chemotherapy provides high antitumor effect and normalizes the levels of circulating hormones that have changed before the treatment.

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Publisher
Oxford University Press

225.
Obesity and hyperglycemia in Korean men with klinefelter syndrome: the Korean endocrine society registry

EBM Reviews - Cochrane Central Register of Controlled Trials

[Journal: Article]
AN: CN-01300482 NEW

Background: The aim of this study was to investigate the prevalence of obesity in Korean men with Klinefelter syndrome (KS) and the associated risk factors for obesity and hyperglycemia.

Methods: Data were collected retrospectively from medical records from 11 university hospitals in Korea between 1994 and 2014. Subjects aged >18 years with newly diagnosed KS were enrolled. The following parameters were recorded at baseline before treatment: chief complaint, height, weight, fasting glucose level, lipid panel, blood pressure, testosterone, luteinizing hormone, follicle-stimulating hormone, karyotyping patterns, and history of hypertension, diabetes, and dyslipidemia. Results: Data were analyzed from 376 of 544 initially enrolled
patients. The rate of the 47 XXY chromosomal pattern was 94.1%. The prevalence of obesity (body mass index >25 kg/m²) in Korean men with KS was 42.6%. The testosterone level was an independent risk factor for obesity and hyperglycemia. Conclusion: Obesity is common in Korean men with KS. Hypogonadism in patients with KS was associated with obesity and hyperglycemia. Copyright (C) 2016 Korean Endocrine Society.

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Publisher
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226.
Frequency of severe iatrogenic hyperprolactinaemia with atypical long acting and oral antipsychotics: paliperidone, risperidone, olanzapine, quetiapine and aripiprazole

EBM Reviews - Cochrane Central Register of Controlled Trials

[Journal: Conference Abstract]
AN: CN-01303826 NEW

Background: Iatrogenic hyperprolactinaemia (IHPRL) is a common but heterogeneous side effect that has been more frequently related with some antipsychotic (APS) drugs like haloperidol, risperidone, amisulpride and paliperidone. Increased awareness between clinicians and a careful attention about some severe physical risk is needed. IHPRL frequency and symptoms could be underestimated without routine exploration. Short-term symptoms include amenorrhea, galactorrhea and sexual dysfunction (decrease of libido and erectile difficulties related to hypogonadism). Medium and long-term symptoms related to estrogen decrease like low bone mass density, hipogonadism, praecox menopause, some types of cancer risk increase (breast and endometrial), cardiovascular risk increase, immune system disorders lipids and cognitive dysfunction could be observed. Routinely explore sexual dysfunction is recommended due to possible poor patient tolerance and low compliance. Severity of IHPRL (mild <25 ng/ml; moderate
25-75 ng/ml; severe >100 ng/ml) must be taken into account in order to avoid clinical consequences and follow treatment strategies. Published consensus states that special care for elderly, child and adolescents and patients with PRI levels >50 ng/ml should be taken. Objective: To evaluate the frequency and severity of hyperprolactinemia associated to different APS, including oral and longacting in clinical settings. Methods: Multicentre and observational cross-sectional study. Adult patients treated with either ILD or oral paliperidone, risperidone, olanzapine, aripiprazole and oral quetiapine for at least 4 weeks and with no other PRL-rising treatment were included at clinically approved dosages. Hyperprolactinaemia was defined as 25 ng/ml in women or 20 ng/ml in men. Patients under more than one antipsychotic treatment were excluded. Results: 363 patients suffering for severe mental disorders (psychosis or bipolar disorder) were evaluated. Oral paliperidone was associated with the higher frequency of severe hyperprolactinaemia (>100 ng/ml): 46.4% (mean dosage 7.6 mg/day) followed by paliperidone ILD (26.8%; 125 mg/monthly); risperidone ILD (23.1%; 71 mg/15 days); oral risperidone (19.4%; 4.7 mg/day); olanzapine ILD (8.3%; 338 mg/monthly); quetiapine (3.2%; 466 mg/day) and oral olanzapine (1.5%; 12.5 mg/day). Aripiprazol did not show any severe IHPRL (15 mg/day). Conclusion: Prolactin levels should be checked in all patients receiving antipsychotics at baseline although praecox symptoms (amenorrhea-galactorrhea) could not be present in order to determine severity of IHPRL and not underestimate other tardive symptoms sometimes severe (osteooporosis, increased of cardiovascular/cancer risk. Intervention strategies (dosage decrease, drug substitution, dopaminergic agonist) should be approached in all moderate/severe hyperprolactinaemia. A possible prolactinoma should be investigated in patients with PRL levels >100 ng/ml with special attention to patients with breast/endometrial cancer history. Densitometry should be prescribed for males >50 years old, amenorrhea >6 months or praecox menopause to avoid fractures risk. This frequency of severe IHPRL must be taken in consideration when choosing a long-term antipsychotic for patients, given the important clinical consequences associated to severe sustained hyperprolactinaemia.

Institution
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Publisher
Elsevier B.V.
Utility of a single serum testosterone measurement to determine response to topical testosterone replacement in hypogonadal men.

EBM Reviews - Cochrane Central Register of Controlled Trials
Current Medical Research and Opinion. 32 (2) (pp 263-269). 2016. Date of Publication: 01 Feb 2016. 2016.
[Journal: Article]
AN: CN-01193093 NEW

Objective: To evaluate the utility of single serum testosterone measurement in patients receiving transdermal testosterone therapy.

Research design and methods: Data were from an open-label, 120 day, multi-center titration trial in androgen-deficient men receiving an initial daily dose of 60 mg testosterone (testosterone topical solution 2%) applied to axillae (30 mg/axilla). Average concentration (Cavg) of serum testosterone (TT) was determined on days 15, 60, and 120; doses were adjusted to maintain normal Cavg (300-1050 ng/dL [10.4-36.4 nmol/L]). Accuracy of single serum TT measurements (2, 4, 8, 12, 16, and 20 hours post-dose) was assessed in patients with Cavg TT within and below (<300 ng/dL [<10.4 nmol/L]) the normal range. Clinical trial registration: Clinicaltrials.gov - NCT00702650. Main outcome measure: Serum testosterone levels.

Results: In patients with normal Cavg (n = 85), 79% to 92% had serum testosterone levels within normal range 2, 4, 8, 12, 16, and 20 hours post-dose; significant effects of time post-dose for single testosterone measurement accuracy (P = 0.01) were observed: testing accuracy peaked 4-8 hours post-dose and tapered ~16 hours post-dose. In 28/63 instances with low Cavg TT throughout the study a normal 2 hour serum TT level was observed. The average percentage (across all days) of discordant results between Cavg (<300 ng/dL [<10.4 nmol/L]) and single serum TT measurements (300-1050 ng/dL [10.4-36.4 nmol/L]) declined with increasing time from dose application (44% at 2 hours, 38% at 4 hours, 22% at 8 hours, 3% at 16 hours).

Conclusions: Reliance on a single serum testosterone measurement to determine the need for dose adjustment of testosterone topical solution 2% may lead clinicians to change the dose unnecessarily, or alternatively, not increase the dose when necessary. The results reported here are limited to testosterone topical solution 2% and may not be applicable to other topical agents.

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Publisher
Taylor and Francis Ltd (E-mail: healthcare.enquiries@informa.com)
Prevalence and prognosis of a low serum testosterone in men with type 2 diabetes: the Fremantle Diabetes Study Phase II.

EBM Reviews - Cochrane Central Register of Controlled Trials

[Journal: Article]
AN: CN-01196132 NEW

Background: Because published studies have usually involved imprecise assays and selected patients with limited additional data and follow-up, the consequences of a low serum testosterone in diabetes are unclear. This study assessed the prevalence, associates and prognosis of a low testosterone in community-dwelling men with type 2 diabetes. Design: Longitudinal observational study. Patients: 788 men (mean +/- SD age: 65.8 +/- 11.3 years) followed for 4.0 +/- 1.1 years.
Measurements: Serum testosterone, SHBG, erectile dysfunction (ED; Sexual Health Inventory for Men score <22), anaemia (haemoglobin <130 g/l), all-cause mortality. Results: The mean +/- SD total serum testosterone by liquid chromatography/mass spectrometry was 13.1 +/- 5.9 nmol/l (30.6% <10 nmol/l). Most men with a total testosterone <10 nmol/l (67.0%) had a normal/low serum LH. Serum testosterone was independently associated with anaemia (P < 0.001), but not ED (P = 0.80), in logistic regression models. The optimal cut-point (Youden Index) for anaemia was 9.8 nmol/l (sensitivity 53.6%, specificity 75.4%). During the follow-up, 102 men (12.9%) died. There was a U-shaped relationship between total serum testosterone quintiles and death (P = 0.003, log rank test). The middle quintile (>11.1 to <13.7 nmol/l) had the lowest risk and there was a 78% increased risk for highest (>16.9 nmol/l) vs lowest (<8.6 nmol/l) quintile in Cox proportional hazards modelling (P = 0.036). Free serum testosterone and SHBG quintiles were not associated with death. Conclusions: These data provide some support for the general conventional serum testosterone <10 nmol/l cut-point in identifying an increased risk of anaemia and the subsequent death in men with type 2 diabetes, but indicate that high-normal levels are also an adverse prognostic indicator. Copyright (C) 2016 John Wiley & Sons Ltd

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Publisher
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Effects of developmental exposure to bisphenol A and ethinyl estradiol on spatial navigational learning and memory in painted turtles (Chrysemys picta).

EBM Reviews - Cochrane Central Register of Controlled Trials
Hormones and Behavior. 85 (pp 48-55), 2016. Date of Publication: 01 Sep 2016. 2016.

Developmental exposure of turtles and other reptiles to endocrine disrupting chemicals (EDCs), including bisphenol A (BPA) and ethinyl estradiol (EE2, estrogen present in birth control pills), can induce partial to full gonadal sex-reversal in males. No prior studies have considered whether in ovo exposure to EDCs disrupts normal brain sexual differentiation. Yet, rodent model studies indicate early exposure to these chemicals disturbs sexually selected behavioral traits, including spatial navigational learning and memory. Thus, we sought to determine whether developmental exposure of painted turtles (Chrysemys picta) to BPA and EE2 results in sex-dependent behavioral changes. At developmental stage 17, turtles incubated at 26°C (male-inducing temperature) were treated with 1) BPA High (100 mug/mL), 2) BPA Low (0.01 mug/mL), 3) EE2 (0.2 mug/mL), or 4) vehicle or no vehicle control groups. Five months after hatching, turtles were tested with a spatial navigational test that included four food containers, only one of which was baited with food. Each turtle was randomly assigned one container that did not change over the trial period. Each individual was tested for 14 consecutive days. Results show developmental exposure to BPA High and EE2 improved spatial navigational learning and memory, as evidenced by increased number of times spent in the correct target zone and greater likelihood of solving the maze compared to control turtles. This study is the first to show that in addition to overriding temperature sex determination (TSD) of the male gonad, these EDCs may induce sex-dependent behavioral changes in turtles. Copyright (C) 2016 Elsevier Inc.

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Academic Press Inc. (E-mail: apjcs@harcourt.com)
Dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history.

EBM Reviews - Cochrane Central Register of Controlled Trials

[Journal: Review]
AN: CN-01197235 NEW

Background: Hyperprolactinemia is the presence of abnormally high circulating levels of prolactin. Idiopathic hyperprolactinemia is the term used when no cause of prolactin hypersecretion can be identified and it is causally related to the development of miscarriage in pregnant women, especially women who have a history of recurrent miscarriage. A possible mechanism is that high levels of prolactin affect the function of the ovaries, resulting in a luteal phase defect and miscarriage. A dopamine agonist is a compound with high efficacy in lowering prolactin levels and restoring gonadal function. Objectives: To assess the effectiveness and safety of different types of dopamine agonists in preventing future miscarriage given to women with idiopathic hyperprolactinemia and a history of recurrent miscarriage. Search methods: We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 June 2016) and reference lists of retrieved studies. Selection criteria: Randomized controlled trials (RCTs) in all languages examining the effect of dopamine agonists on preventing future miscarriage. Women who had idiopathic hyperprolactinemia with a history of recurrent miscarriages were eligible for inclusion in this review. Comparisons planned included: dopamine agonists alone versus placebo/no treatment; and dopamine agonists combined with other therapy versus other therapy alone. Data collection and analysis: Two review authors independently assessed a single trial for inclusion, evaluated trial quality and extracted data. Data were checked for accuracy. Main results: One study (recruiting 48 women with idiopathic hyperprolactinemia) met our inclusion criteria; 46 women (42 pregnancies - 4/46 women did not conceive during the study period) were included in the analysis. The study compared the use of a dopamine agonist (bromocriptine, 2.5 mg to 5.0 mg/day until the end of the ninth week of gestation) versus a no-treatment control. The study was judged as being at a high risk of bias. It was not possible to carry out meta-analysis due to insufficient data. The study reported both of this review's primary outcomes of miscarriage and live birth. Results from this single study suggest that, compared to no treatment, oral bromocriptine was effective in preventing future miscarriage (risk ratio (RR) 0.28, 95% confidence interval (CI) 0.09 to 0.87, 46 participants (low-quality evidence)) in women with idiopathic hyperprolactinemia. There was no clear difference with regard to the other primary outcome of live births (RR 1.50, 95% CI 0.93 to 2.42, 46 participants (very low-quality evidence)). There was
no difference with regard to this review's secondary outcome of conception (RR 0.92, 95% CI 0.77 to 1.09, 46 participants (very low-quality evidence)) between the group of women who received dopamine (21 out of 24 women conceived) and women in the no-treatment group (21 out of 22 women conceived). The included study only reported the serum prolactin levels in pregnant women and therefore the data could not be analyzed in this review. No other secondary outcomes relevant to this review were reported; adverse effects for women (nausea, vomiting, headache, vertigo, fatigue, hypotension, arrhythmia, and psychotic symptoms) and infants (birth defects, low birthweight, and developmental disabilities) were not reported. We downgraded the quality of the evidence for risk of bias in the one trial contributing outcome data (no description of allocation concealment, lack of blinding and possible reporting bias) and for imprecision (all effect estimates were based on small sample size, miscarriage was based on few events, and the 95% CIs of live birth and conception cross the line of no effect). Authors' conclusions: Currently, there is insufficient evidence (from a single randomized trial with a small sample size, and judged to be at high risk of bias) to evaluate the effectiveness of dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and a history of recurrent miscarriage. We assessed outcomes using GRADE methodology. Miscarriage was assessed as low quality due to risk of bias concerns in the one trial contributing data (no description of allocation concealment, lack of blinding and possible reporting bias) and to imprecision (effect estimates were based on small sample size and few events). Live births and conception were assessed as of very low quality due to the same risk of bias concerns in study design and to imprecision (with a wide 95% CI consistent with either benefit or harm), and a small sample size. There were no data relating to adverse effects of the intervention for either the mother or her baby. Further high-quality research in this area is warranted. There is a need for well-designed, larger RCTs to confirm and extend the findings of the trial reviewed here. Many questions remain unanswered. Some important considerations for future research include, the need for well-designed RCTs with large sample sizes, and for those studies to consider important outcomes (including adverse effects for both the mother and her baby). Future studies should examine the effectiveness and safety of various dopamine agonists including bromocriptine, cabergoline and quinagolide.

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Publisher
John Wiley and Sons Ltd (Southern Gate, Chichester, West Sussex PO19 8SQ, United Kingdom)
Testosterone supplementation in adult males with cutaneous injury.

Fagin AM, Pape K

EBM Reviews - Cochrane Central Register of Controlled Trials

CONFERENCE END: 2016 May 6, 48th Annual Meeting of the American Burn Association Las Vegas, NV United States.,

[Journal: Conference Abstract]

AN: CN-01160574  UPDATE

Introduction: It has been well established that burn and other cutaneous injuries have long range and prolonged effects on multiple systems within the human body. Methods: We present a case series of 3 adult men treated for cutaneous injuries (43% TBSA burn, 2 initial and 1 recurrent necrotizing soft tissue infection). All 3 men were found throughout their hospital course to have low motivation and a flat affect with poor oral intake. They were also non-compliant with therapies and each had some evidence of difficult healing. Testosterone was checked in each patient.

Results: Testosterone levels in all 3 patients were found to be consistent with prepubescent Tanner Stage 2, typical in ages 9-11 years. Testosterone replacement was undertaken by depot injection in 2 men and testosterone topical gel in one. After supplementation, all 3 men were found to be more willing to work with therapy with more responsibility taken for their own care. Also, wounds were noted to be improved after supplementation.

Conclusions: Testosterone is the primary male androgen. It is made in the testes primarily with a small amount produced in the adrenal medulla. Free testosterone is the active hormone in the plasma that enacts downstream effects. Most studies of the effects of burn on the hypothalamic-pituitary-gonadal (HPG) axis have been in animal models. The pro-inflammatory cytokines produced after significant burn injury have been shown to have a negative effect on the HPG axis and thus depress the production of testosterone (1). This can cause long ranging affects such as lean muscle mass loss, depressed affect, and loss of interests/energy/strength. Additionally anabolic steroids, such as testosterone, directly stimulate the healing process (2) so decreased levels can significantly affect the body's ability to heal a cutaneous insult. The loss of lean muscle mass after burn injury is related to increased morbidity and mortality. Studies suggest that pharmacologic agents improve muscle protein balance, and effects depend on patient's age, dosage, and probably time after burn (3).

Our case series suggests that testosterone is important for healing and improved outcomes for men after significant cutaneous injury. It raises more questions than it answers. When should we check testosterone levels? How soon and in what way should we supplement testosterone in the
patient? When do we stop? How should we monitor to determine appropriate replacement? These are all questions that need to be answered with a randomized controlled trial within the burn patient population. Applicability of Research to Practice: With further research to answer these remaining questions, care of the adult male with depressed testosterone production may be changed to allow for improved wound and psychosocial outcomes.

Institution
A.M. Fagin
Publisher
Lippincott Williams and Wilkins

232.
A Combined Therapy with Myo-Inositol and D-Chiro-Inositol Improves Endocrine Parameters and Insulin Resistance in PCOS Young Overweight Women.
Benelli E, Del Ghianda S, Di Cosmo C, Tonacchera M
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Article]
AN: CN-01177087 NEW
Introduction. We evaluated the effects of a therapy that combines myo-inositol (MI) and D-chiro-inositol (DCI) in young overweight women affected by polycystic ovary syndrome (PCOS), characterized by oligo- or anovulation and hyperandrogenism, correlated to insulin resistance.
Methods. We enrolled 46 patients affected by PCOS and, randomly, we assigned them to two groups, A and B, treated, respectively, with the association of MI plus DCI, in a 40: 1 ratio, or with placebo (folic acid) for six months. Thus, we analyzed pretreatment and posttreatment FSH, LH, 17-beta-Estradiol, Sex Hormone Binding Globulin, androstenedione, free testosterone, dehydroepiandrosterone sulphate, HOMA index, and fasting glucose and insulin. Results. We recorded a statistically significant reduction of LH, free testosterone, fasting insulin, and HOMA index only in the group treated with the combined therapy of MI plus DCI; in the same patients, we observed a statistically significant increase of 17-beta-Estradiol levels. Conclusions. The combined therapy of MI plus DCI is effective in improving endocrine and metabolic parameters in young obese PCOS affected women.
Institution
Significant and reversible reductions in testosterone levels were observed with AZD4901 in both preclinical and clinical testing. A comprehensive population pharmacokinetic/pharmacodynamic (PK/PD) modeling of AZD4901 concentration and testosterone relationship from 3 phase 1 studies was performed using NONMEM to support dose selection for phase 2a development. A 2-compartment model with first-order absorption and first-order elimination best described AZD4901 PK. Circadian rhythm of baseline testosterone concentrations was well described by a cosine function. An indirect response model with inhibition of testosterone production was used to link the AZD4901 concentration to testosterone response. The AZD4901 concentration to yield 50% maximum testosterone suppression (IC50) was estimated to be 230 ng/mL. Based on simulations, following 40 mg twice daily (BID) treatment, the AZD4901 steady-state trough concentration will be much higher compared to 80 mg once daily (QD). The AZD4901 concentration time above IC50 after 40 mg BID is 84% of the time of the dosing interval compared to only 49% after 80 mg QD. The mean predicted testosterone concentrations at steady state are lower and overall less variable over 24 hours for 40 mg BID dosing compared to 80 mg QD dosing. Population PK and PK/PD analyses demonstrated that AZD4901 40 mg BID is a better dosing strategy to more consistently suppress testosterone during the entire dosing interval. Consequently, 40 mg BID dosing was suggested in a phase 2a trial in females with polycystic ovary syndrome, and the trial resulted in a positive outcome as shown by significant testosterone decrease compared to placebo.
Abstracts of the 38th Annual Scientific Meeting of the Indonesian Urological Association.
Anonymous

EBM Reviews - Cochrane Central Register of Controlled Trials

BJU international. 117(no pagination):CONFERENCE START: 2015 Nov 4 CONFERENCE END: 2015 Nov 7, 38th Annual Scientific Meeting of the Indonesian Urological Association Bali India.,

[Journal: Conference Review]

AN: CN-01167586 NEW

The proceedings contain 42 papers. The topics discussed include: pediatric advance care planning: physician experience, confidence and education in raising difficult discussions; central venous catheter associated blood stream infection in neonatal intensive care unit - prediction and prevention; identification of health risk behaviors among adolescent refugees resettling in Western Australia; quick-wee: catching urine samples quickly from infants in the pediatric emergency department; PREMM: preterm early massage by the mother - the effects of massage in very preterm infants; does written dietary advice improve the ingestion of non-allergic nuts in children with existing nut allergies? - a randomized controlled trial; epidemiology of intussusception in New Zealand pre rotavirus vaccination; response to growth hormone therapy and gonadal pathology in 45,X/46,XY females; oration - Howard Williams 2016 disability at the crossroads: improving the care of children with cerebral palsy; and the parental immunization needs and attitudes (PINA) survey in hospital pediatric clinics (PINA-H) and community maternal and child health centers (PINA-C) in Melbourne.

Publisher
Blackwell Publishing Ltd
Re: Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men with Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial.
Rai S, Ramasamy R
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Note]
AN: CN-01161917 NEW
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Publisher
Elsevier

236.
Abstracts of the 38th Annual Scientific Meeting of the Indonesian Urological Association.
Anonymous
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Conference Review]
AN: CN-01165868 NEW
The proceedings contain 42 papers. The topics discussed include: pediatric advance care planning: physician experience, confidence and education in raising difficult discussions; central venous catheter associated blood stream infection in neonatal intensive care unit - prediction and prevention; identification of health risk behaviors among adolescent refugees resettling in Western Australia; quick-wee: catching urine samples quickly from infants in the pediatric emergency department; PREMM: preterm early massage by the mother - the effects of massage in very preterm infants; does written dietary advice improve the ingestion of non-allergic nuts in children with existing nut allergies? - a randomized controlled trial; epidemiology of intussusception in New Zealand pre rotavirus vaccination; response to growth hormone therapy and gonadal pathology in 45,X/46,XY females; oration - Howard Williams 2016 disability at the crossroads: improving the care of children with cerebral palsy; and the parental immunization
needs and attitudes (PINA) survey in hospital pediatric clinics (PINA-H) and community maternal and child health centers (PINA-C) in Melbourne.

Publisher
Blackwell Publishing Ltd

237.
Testosterone gel improved sexual function, but not walk distance or fatigue, in older men with low testosterone: Commentary.
Hamidi O, Montori VM
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Note]
AN: CN-01158458 NEW
Publisher
American College of Physicians (190 N. Indepnence Mall West, Philadelphia PA 19106-1572, United States)

238.
Androgens and cardiovascular risk.
Yeap BB
EBM Reviews - Cochrane Central Register of Controlled Trials
[Journal: Conference Abstract]
AN: CN-01160362 NEW
Ageing is accompanied by a reduction in circulating testosterone (T), and progressive accumulation of medical morbidities. There is ongoing debate as to whether low T contributes to ill-health, particularly to increased risk of cardiovascular disease, as opposed to being a
biomarker for its presence. Despite this uncertainty, prescriptions for T are rising on a background of concern over potential adverse effects. Observational studies show lower risk of cardiovascular events in older men with higher T concentrations. In longitudinal analyses from the Western Australian Health In Men Study (HIMS) we have shown that optimal circulating T predicts survival in older men, and that higher T concentrations are independently associated with reduced incidence of stroke. Furthermore, in HIMS men with higher concentrations of the more potent androgen dihydrotestosterone (DHT) experienced lower mortality from ischaemic heart disease. Concern has been raised following the Testosterone in Older Men with Mobility Limitations (TOM) trial, which was terminated due to excess cardiovascular adverse events reported in the T treatment arm. However, no such signal was seen in a comparable study of T in intermediate-frail and frail older men. Of note, these and other randomised controlled trials (RCTs) of T supplementation have been underpowered for the outcome of cardiovascular events. Recent metaanalyses generally have not shown an excess of cardiovascular adverse events to be associated with T therapy. Retrospective studies of prescription databases have produced controversial and conflicting results. Thus additional RCTs are required to clarify the role of T supplementation to modulate cardiovascular risk in older men in the absence of pituitary or testicular disease. T replacement therapy should be considered in androgen deficient men, with evaluation of potential benefits and risks.

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Publisher
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239.
Associations between endogenous sex hormones and MRI structural changes in patients with symptomatic knee osteoarthritis.

EBM Reviews - Cochrane Central Register of Controlled Trials
Purpose: The increased prevalence of knee osteoarthritis (OA) in postmenopausal women suggests involvement of endogenous sex hormones in its pathogenesis. However, the effects of these hormones on knee OA structures remain controversial. This study aimed to describe the associations between serum levels of estrogen, progesterone and testosterone and knee MRI structural changes in both males and females with symptomatic knee OA.

Methods: 200 participants (mean age 63.0 +/- 7.3 years) with symptomatic knee OA were selected from a randomized controlled trial of vitamin D supplementation for knee OA. Serum levels of estradiol, progesterone, testosterone and sex hormone binding globin (SHBG) were measured using commercial ELISA kits at baseline and 24 months later. Knee magnetic resonance images (MRIs) were obtained on a 1.5T whole body 3D MRI unit at baseline and 24 months. Tibial cartilage volume was measured using manual segmentation of T1-weighted fat saturated MRI. Cartilage defects were graded on T1- and T2-weighted images using a modified Outerbridge scoring system (0e4). Bone marrow lesions (BMLs) and effusion-synovitis volume BMLs and effusion-synovitis were measured on T2-weighted fat saturated FSE images using a modified Whole-Organ Magnetic Resonance Imaging scoring system (grade 0e3). Knee pain was assessed using a 100mm visual analogue scale (VAS). Analyses were performed using linear mixed-effects model with terms for age, body mass index, sex hormone concentration, and randomization. Longitudinal temporal relationships were further explored by adding interaction terms between sex hormones and age to the model.

Results: 107 males and 93 females were included. There were no demographic difference between the two sexes. Mean estradiol and progesterone levels were comparable for males and females, while testosterone levels were significantly higher for males (3.5 +/- 1.5 versus 0.4 +/- 0.4, p < 0.01) and SHBG levels were significantly higher for females (34.0 +/- 15.3 versus 52.3 +/- 27.8, p < 0.01). For males, no consistent associations were observed between sex hormones and structural changes or VAS pain. For females, progesterone quarters were significantly associated with cartilage volume (beta = 0.12 per quarter, p = 0.01). Estradiol levels were associated with lower BML scores (beta = -0.45 per quarter, p = 0.03). Estradiol (beta = -1.26 per quarter, p = 0.05), progesterone (beta = -1.60 per quarter, p < 0.01) and testosterone (beta = -1.49 per quarter, p = 0.02) levels were inversely associated with effusion-synovitis volume. Neither estradiol nor progesterone were significantly associated with VAS pain score for females. For males, testosterone quarters were associated with a lower VAS pain (b = -3.90 per quarter, p = 0.02). The interaction terms between different sex hormones and age were not statistically significant when they were added to the mixed-effect model.

Conclusions: For females, endogenous estradiol, progesterone and testosterone may be protective for joint structural changes in knee OA. In contrast, there were no significant
associations between sex hormones and joint structural changes in male patients. This may at least in part explain observed sex differences in knee OA prevalence. (Table Presented).

Institution

Publisher
W.B. Saunders Ltd

240.
Pulsatile gonadotropin-releasing hormone therapy is associated with earlier spermatogenesis compared to combined gonadotropin therapy in patients with congenital hypogonadotropic hypogonadism.

Mao JF; Liu ZX; Nie M; Wang X; Xu HL; Huang BK; Zheng JJ; Min L; Kaiser UB; Wu XY. OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Asian Journal of Andrology. , 2016 Dec 27.
[Journal Article]
UI: 28051040
Both pulsatile gonadotropin-releasing hormone (GnRH) infusion and combined gonadotropin therapy (human chorionic gonadotropin and human menopausal gonadotropin [HCG/HMG]) are effective to induce spermatogenesis in male patients with congenital hypogonadotropic hypogonadism (CHH). However, evidence is lacking as to which treatment strategy is better. This retrospective cohort study included 202 patients with CHH: twenty had received pulsatile GnRH and 182 had received HCG/HMG. Patients had received therapy for at least 12 months. The total follow-up time was 15.6 +/- 5.0 months (range: 12-27 months) for the GnRH group and 28.7 +/- 13.0 months (range: 12-66 months) for the HCG/HMG group. The median time to first sperm appearance was 6 months (95% confidence interval [CI]: 1.6-10.4) in the GnRH group versus 18 months (95% CI: 16.4-20.0) in the HCG/HMG group (P < 0.001). The median time to achieve sperm concentrations >=5 x 10^6 ml^-1 was 14 months (95% CI: 5.8-22.2) in the GnRH group versus 27 months (95% CI: 18.9-35.1) in the HCG/HMG group (P < 0.001), and the median time to concentrations >=10 x 10^6 ml^-1 was 18 months (95% CI: 10.0-26.0) in the GnRH group versus 39 months (95% CI unknown) in the HCG/HMG group. Compared to the GnRH group, the HCG/HMG group required longer treatment periods to achieve testicular sizes of >=4 ml, >=8 ml, >=12 ml, and >=16 ml. Sperm motility (a + b + c percentage) evaluated in semen samples with
concentrations >1 x 10^6 ml^-1 was 43.7% +/- 20.4% (16 samples) in the GnRH group versus 43.2% +/- 18.1% (153 samples) in the HCG/HMG group (P = 0.921). Notably, during follow-up, the GnRH group had lower serum testosterone levels than the HCG/HMG group (8.3 +/- 4.6 vs 16.2 +/- 8.2 nmol l^-1 , P < 0.001). Our study found that pulsatile GnRH therapy was associated with earlier spermatogenesis and larger testicular size compared to combined gonadotropin therapy. Additional prospective randomized studies would be required to confirm these findings.

Status
Publisher
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Effect of Testosterone Replacement Therapy on Cognitive Performance and Depression in Men with Testosterone Deficiency Syndrome.

Jung HJ; Shin HS.

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PURPOSE: We aimed to evaluate the effect of testosterone replacement therapy (TRT) on cognitive function and depression in men with testosterone deficiency syndrome.

MATERIALS AND METHODS: We carried out a prospective, placebo-controlled trial involving 106 men with total testosterone levels <3.3 ng/mL and symptoms of hypogonadism. Based on whether the patients received TRT (injection with 1,000 mg testosterone undecanoate) or a placebo (advice to modify lifestyle), the study population was divided into a TRT group (n=54) and a control group (n=52).

RESULTS: The age among patients in the TRT and control groups was 56.7 +/-12.6 years and 57.8 +/-11.4 years, respectively (p> 0.05). At baseline, no significant differences between the TRT and control groups were noted regarding serum testosterone or prostate-specific antigen levels, or regarding the scores for aging symptoms (Aging Males' Symptoms scale), erectile function (5-item International Index of Erectile Function questionnaire), cognitive function (Korean Mini-Mental State Examination), and depression (Beck Depression Inventory). At 8 months after intervention total serum testosterone levels and erectile function scores had significantly increased (p<0.05), whereas the scores for aging symptoms and depression had significantly decreased (p<0.05) in the TRT group; no significant improvement in any parameters was noted for the control group. Notably, significant improvement in cognitive function was noted among patients with cognitive impairment at baseline (cognitive function score <25) who received TRT.

CONCLUSIONS: TRT may be considered in men with testosterone deficiency syndrome if low testosterone levels are associated with depression or cognitive impairment.

Status
In-Data-Review
Authors Full Name
Central precocious puberty (CPP) develops due to premature activation of the hypothalamic-pituitary-gonadal (HPG) axis, resulting in early pubertal changes and rapid bone maturation. CPP is associated with lower adult height and increased risk for development of psychological problems. Standard treatment of CPP is based on postponement of pubertal development by blockade of the HPG axis with gonadotropin releasing hormone analogs (GnRHa) leading to abolition of gonadal sex hormones synthesis. Whereas the hormonal and auxological effects of GnRHa are well-researched, there is a lack of knowledge whether GnRHa treatment influences psychological functioning of treated children, despite the fact that prevention of psychological problems is used as one of the main reasons for treatment initiation. In the present study we seek to address this issue by exploring differences in cognitive function, behavior, emotional reactivity, and psychosocial problems between GnRHa treated CPP girls and age-matched controls. Fifteen girls with idiopathic CPP; median age 10.4 years, treated with slow-release GnRHa (triptorelin acetate-Decapeptyl SR 11.25) and 15 age-matched controls, were assessed with a
comprehensive test battery consisting of paper and pencil tests, computerized tasks, behavioral paradigms, heart rate variability, and questionnaires filled in by the children's parents. Both groups showed very similar scores with regard to cognitive performance, behavioral and psychosocial problems. Compared to controls, treated girls displayed significantly higher emotional reactivity (p = 0.016; Cohen's d = 1.04) on one of the two emotional reactivity task conditions. Unexpectedly, the CPP group showed significantly lower resting heart rates than the controls (p = 0.004; Cohen's d = 1.03); lower heart rate was associated with longer treatment duration (r = -0.582, p = 0.037). The results suggest that GnRHa treated CPP girls do not differ in their cognitive or psychosocial functioning from age matched controls. However, they might process emotional stimuli differently. The unexpected finding of lower heart rate that was associated with longer duration of the treatment should be further explored by methods appropriate for assessment of cardiac health.

Status
PubMed-not-MEDLINE

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Metabolic Syndrome in Childhood: Rare Case of Alstrom Syndrome with Blindness.
Ahmad A; D'Souza B; Yadav C; Agarwal A; Kumar A; Nandini M; D'Souza V; Poornima AM; Kamath N.
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
[Journal Article]
UI: 27605748
Alstrom's syndrome (AS) is a rare autosomal recessive ciliopathic condition affecting 1:10,00,000 children. It's a single gene disorder of ALMS1 on chromosome 2 with multisystem involvement with cone-rod retinal dystrophy causing juvenile blindness, obesity, insulin resistance, type 2
Diabetes mellitus, hypogonadism and sensorineural hearing loss. Till now only 800 patients with this disorder has been identified so far. In this report, we describe the case of a 9-year old male boy from south India. He had been initially referred for polyphagia, polyuria, polydipsia, generalized weakness from 1 weeks. On examination he was demonstrated features suggestive of AS, including blindness, obesity, type 2 diabetes, altered lipid profile, hypogonadism, acanthosis nigricans, seborrheic dermatitis, right ear discharge and episodes of respiratory tract infections. So, diagnosis of AS is critical as it can easily be overlooked because of the many features associated with metabolic syndrome starting at age 7, a relatively early age.

Status
PubMed-not-MEDLINE

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Date Created
20160908
Year of Publication
2016
The effect of Bongardia Chrysogonum on prostate tissue in a rat model of STZ-induced diabetes. Dokuyucu R; Gozukara KH; Ozcan O; Sefil NK; Nacar A; Dokuyucu A; Inci M. OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present Springerplus. 5(1):1322, 2016. [Journal Article] UI: 27563517

BACKGROUND: Bongardia chrysogonum is widely used in Turkey for treating urinary tract infections and prostate hypertrophy, and it also has potent hypoglycemic effects and aids glucose homeostasis. Because of the inflammatory conditions in diabetes mellitus (DM), the prostate tissue of men with diabetes is particularly susceptible to developing hypoplasia, and DM produces characteristic pathological changes in prostate tissue. Here, we examined the effects of B. chrysogonum on the prostate tissue of rats with streptozotocin (STZ)-induced diabetes.

RESULTS: The glucose levels were statistically significantly higher in the diabetic rats than in healthy controls (P < 0.001). Further, they were significantly lower in the healthy and diabetic rats administered B. chrysogonum than in the untreated diabetic rats (P < 0.001 and 0.05, respectively). The total cholesterol levels were significantly lower in the healthy rats administered B. chrysogonum than the healthy controls (P < 0.05) and diabetic rats (P < 0.01). They were also significantly lower in the diabetic rats administered B. chrysogonum than those that were left untreated (P < 0.05). The testosterone levels were significantly lower in the untreated diabetic rats than in the controls (untreated ones and those administered B. chrysogonum) and diabetic rats administered the herb (P < 0.001, 0.05 and 0.01, respectively). The oxidative stress index was significantly higher in the untreated diabetic rats than the healthy controls (P < 0.05). It was also significantly lower in the healthy and diabetic groups treated with B. chrysogonum than the untreated diabetic rats (P < 0.05). Histological examination showed no changes in the prostate tissue of the non-diabetic rats. In the diabetic group, the glandular lumens were filled with cellular debris and leucocytic infiltrate, and the glandular epithelium was degenerated and thickened. In the diabetic group treated with B. chrysogonum, the epithelium was better preserved and less debris was seen in the glandular lumen.
CONCLUSION: To our knowledge, this is the first study to histologically prove the effects of B. chrysogonum on prostate tissue in diabetes. Our findings may be useful in developing B. chrysogonum into a therapeutic agent against diabetes and benign prostate hyperplasia.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4980850

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20160826

Year of Publication
2016

245.
Testicular pathology, gonadal and epididymal sperm reserves of Yankasa rams infected with experimental Trypanosoma brucei brucei and Trypanosoma evansi.
Wada YA; Oniye SJ; Rekwot PI; Okubanjo OO.
AIM: The study was conducted to evaluate the pathological effects of trypanosomosis on the testes, gonadal, and epididymal sperm reserves of Yankasa rams for 98 days.

MATERIALS AND METHODS: A total of 16 Yankasa rams, aged between 24 and 30 months and weighed between 22 and 25 kg, were acclimatized for a period of 2-months in a clean fly proof house and were adequately fed and given water ad-libitum. Of the 16 rams, 12 that were clinically fit for the experiment at the end of the acclimatization period were randomly divided into four groups: Groups I, II, III, and IV, each having 3 rams. Groups I and II were each challenged singly with experimental Trypanosoma brucei brucei (Federer strain) and Trypanosoma evansi (Sokoto strain), respectively, while Group III was challenged with mixed T. brucei brucei and T. evansi parasites (50% of each species in the infective inoculum) and Group IV was left as an uninfected control. Each infected ram received 2 mL of the infected blood containing 2x10^6 trypomastigotes via the jugular vein, while the control group received 2 mL each, normal saline.

RESULTS: All the infected rams developed clinical signs typical of trypanosomosis at varying pre-patent periods. The gross lesions observed in the infected rams in Group II were moderate and more severe in those of Groups I and III. Histological sections of the testes of infected rams (Groups I, II, and III) showed moderate (T. evansi-infected group) to severe (mixed and T. brucei brucei-infected groups) testicular degenerations with reduction in number of spermatogenic cell layers, degenerated seminiferous tubules, congested interlobular spaces, loss of tissue architecture with significant (p<0.01) depletion, and loss of gonadal and epididymal sperm reserves in Groups I and III in comparison to Group II and the control Group IV. No observable clinical signs and histopathological lesions were found in those rams of the control Group IV.

CONCLUSION: The study concluded that trypanosomosis due to experimental T. brucei brucei or T. evansi or mixed infections (of both parasites) caused testicular damage, decreased epididymal and gonadal sperm reserves and an important cause of infertility in Yankasa rams.

Status
PubMed-not-MEDLINE

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A Combined Therapy with Myo-Inositol and D-Chiro-Inositol Improves Endocrine Parameters and Insulin Resistance in PCOS Young Overweight Women.

Benelli E; Del Ghianda S; Di Cosmo C; Tonacchera M.

OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

[Journal Article]
UI: 27493664

Introduction. We evaluated the effects of a therapy that combines myo-inositol (MI) and D-chiro-inositol (DCI) in young overweight women affected by polycystic ovary syndrome (PCOS), characterized by oligo- or anovulation and hyperandrogenism, correlated to insulin resistance.

Methods. We enrolled 46 patients affected by PCOS and, randomly, we assigned them to two groups, A and B, treated, respectively, with the association of MI plus DCI, in a 40:1 ratio, or with placebo (folic acid) for six months. Thus, we analyzed pretreatment and posttreatment FSH, LH, 17-beta-Estradiol, Sex Hormone Binding Globulin, androstenedione, free testosterone, dehydroepiandrosterone sulphate, HOMA index, and fasting glucose and insulin. Results. We recorded a statistically significant reduction of LH, free testosterone, fasting insulin, and HOMA index only in the group treated with the combined therapy of MI plus DCI; in the same patients, we observed a statistically significant increase of 17-beta-Estradiol levels. Conclusions. The combined therapy of MI plus DCI is effective in improving endocrine and metabolic parameters in young obese PCOS affected women.
247.
Anti-spermatogenic activities of Taraxacum officinale whole plant and leaves aqueous extracts.
Tahtamouni LH; Al-Khateeb RA; Abdellatif RN; Al-Mazaydeh ZA; Yasin SR; Al-Gharabli S; Elkarmi AZ.
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Veterinary Research Forum. 7(2):89-97, 2016 Spring.
[Journal Article]
UI: 27482352
Taraxacum officinale has been used in Jordan folk medicine to treat male infertility. A recent study has proved a contradictory effect of the whole plant aqueous extract. The aim of the current study was to determine if the leaves of T. officinale have similar anti-fertility activities, and whether this effect is mediated through the regulation of spermatogonial stem cells (SSCs). Fifty adult male rats were divided into five groups. Two groups were gavaged with 1/10 of LD50 of T. officinale whole plant (1.06 g kg(-1) body weight) or leaves (2.30 g kg(-1) body weight) aqueous extract; while two groups were gavaged with 1/20 of LD50 of T. officinale whole plant (2.13 g kg(-1)) or leaves (4.60 g kg(-1)) extract. The control group received distilled water. Oral administration of T. officinale (whole plant and leaves aqueous extract) caused a significant decrease in testis and seminal vesicle weight, a reduction in serum testosterone concentration, impaired sperm parameters, and a decrease in pregnancy parameters. Testicular histology of treated rats showed structural changes such as hypoplasia of germ cells, reduction in the thickness of germinal epithelium, arrest of spermatogenesis at spermatid stage (late maturation arrest) and reduction in the number of Leydig cells. Gene expression levels of two SSCs markers (GFRalpha1 and CSF1) responsible for self-renewal were relatively counter-balanced. In conclusion, T. officinale whole plant and leaves aqueous extracts changed the gene expression of two SSCs markers leading to the imbalance between spermatogonia self-renewal and differentiation causing late maturation arrest.

Status
PubMed-not-MEDLINE

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Primary ovarian insufficiency: different approaches in three cases and a review of literature.

Moreira AM; Spritzer PM.

OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present Endocrinology, Diabetes & Metabolism Case Reports. 2016:160026, 2016.

[Journal Article]

UI: 27252868

UNLABELLED: Primary ovarian insufficiency (POI) is the condition of intermittent or permanent gonadal insufficiency that occurs in women before the age of 40. We describe three cases of POI referred to the outpatient endocrinology clinic of a university hospital. The three patients met diagnostic criteria for POI and were managed by specific approaches tailored to individualized goals. In the first case, the main concern was fertility and the reproductive prognosis. The second patient was a carrier of a common genetic cause of POI: premutation of the FMR1 gene. The third case was a patient diagnosed with a POI and established osteoporosis, a common complication of estrogen deprivation. This study reports the treatment and follow-up of these cases, with an emphasis on relevant aspects of individualized management, alongside a brief literature review.

LEARNING POINTS: A diagnosis of POI should be considered in patients presenting with amenorrhea or irregular menses and high serum follicle-stimulating hormone (FSH) levels before age 40 years. Patients with POI without an established cause, especially in familial cases, should be tested for FMR1 mutations. Estrogen/progestin replacement therapy is indicated since diagnosis until at least the estimated age of menopause, and is the cornerstone for maintaining the good health of breast and urogenital tract and for primary or secondary osteoporosis prevention in POI. Fertility should be managed through an individualized approach based on patient possibilities, such as egg or embryo donation and ovarian cryopreservation; pregnancy
can occur spontaneously in a minority of cases. Women with POI should be carefully monitored for cardiovascular risk factors.

Status
PubMed-not-MEDLINE

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20160602

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2016
and DVT/PE. We evaluated the incidence of DVT and PE in men who were prescribed TRT for low serum total testosterone (sTT) levels.

METHODS: This is a retrospective cohort study, conducted using data obtained from the Veterans Affairs Informatics and Computing Infrastructure. We compared the incidence of DVT/PE between those who received TRT and subsequently had normal on-treatment sTT levels (Gp1), those who received TRT but continued to have low on-treatment sTT (Gp2), and those who did not receive TRT (Gp3). Those with prior history of DVT/PE, cancer, hypercoagulable state, and chronic anticoagulation were excluded.

RESULTS: The final cohort consisted of 71,407 subjects with low baseline sTT. Of these, 10,854 did not receive TRT (Gp3) and 60,553 received TRT. Of those who received TRT, 38,362 achieved normal sTT (Gp1) while 22,191 continued to have low sTT (Gp2). The incidence of DVT/PE was 0.5%, 0.4%, and 0.4% in Gp1, Gp2, and Gp3, respectively. Univariate, multivariate, and stabilized inverse probability of treatment weights analyses showed no statistically significant difference in DVT/PE-free survival between the various groups.

CONCLUSIONS: This study did not detect a significant association between testosterone replacement therapy and risk of DVT/PE in adult men with low sTT who were at low to moderate baseline risk of DVT/PE.

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MEDLINE
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250.
Outcome of intracytoplasmic sperm injection using fresh and cryopreserved-thawed testicular spermatozoa in 83 azoospermic men with Klinefelter syndrome.
Vicdan K; Akarsu C; Sozen E; Buluc B; Vicdan A; Yilmaz Y; Biberoglu K.
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
[Journal Article]
UI: 27785898
AIM: To report the outcome of intracytoplasmic sperm injection (ICSI) cycles using fresh or cryopreserved-thawed testicular spermatozoa of men with Klinefelter syndrome (KS).
METHODS: Medical records of 83 azoospermic men with KS who underwent testicular sperm extraction (TESE) were reviewed. The clinical parameters for predicting sperm retrieval and fertilization, implantation, pregnancy and live birth rates of ICSI cycles in these patients were evaluated.
RESULTS: A total of 88 TESE procedures were performed with sperm retrieval rates of 39.8% per cycle (35/88) and 42.1% per patient (35/83). None of the studied clinical parameters were found to be informative in predicting successful sperm recovery. A total of 41 embryo transfer cycles were carried out using fresh testicular spermatozoa in 30, cryopreserved-thawed spermatozoa in 10 and cryopreserved-thawed embryo replacement in one. The fertilization and clinical pregnancy rates were comparable at 52.7% and 51.6% with fresh and 48.3% and 60% with cryopreserved-thawed testicular spermatozoa groups, respectively. Twenty-two clinical
pregnancies were obtained, including 14 singletons, five twins, two triplets and one quadruplet and ended with the delivery of 13 singletons and six twins. In total, out of 25 delivered fetuses, four died (3 female, 1 male) following delivery and 21 newborns (14 female, 7 male) were healthy with a female to male ratio of 2:1. Conclusions We concluded that no clinical or laboratory parameter predicts the presence of spermatozoa in patients with KS, except the TESE procedure itself. The use of fresh or cryopreserved-thawed spermatozoa on ICSI cycle outcomes are equally successful in patients with KS.

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Status

MEDLINE

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20161027

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2016

251.
Dosage of Sex Chromosomal Genes in Blood Deposited on Filter Paper for Neonatal Screening of Sex Chromosome Aneuploidy.
Campos-Acevedo LD; Ibarra-Ramirez M; de Jesus Lugo-Trampe J; de Jesus Zamudio-Osuna M; Torres-Munoz I; Del Roble Velasco-Campos M; Rojas-Patlan L; Rodriguez-Sanchez IP; Martinez-de-Villarreal LE.
AIMS: In this study, we examined the doses of the stature homeobox (SHOX), vesicle-associated membrane protein 7 (VAMP7), and SRY genes to establish a protocol for using peripheral blood samples deposited on filter paper for the screening of sex chromosome aneuploidy in neonates. We also measured correlations with karyotypes to assess this method as a neonatal screening strategy.

MATERIALS AND METHODS: This was an observational, descriptive, comparative blind study. Thirty-two healthy young adults (17 women, 15 men; age, >=18 years), four patients with known sex chromosome aneuploidy (positive control group), and 1000 healthy newborns were included. Gene dosages were determined using quantitative real-time polymerase chain reaction (RT-PCR). Values with standard deviations (SDs) of three or more were considered abnormal.

RESULTS: Men and women differed in the gene dosage of the SRY gene. Cases with Turner syndrome showed values below 3 SDs for SHOX and VAMP7 genes, and cases with Klinefelter syndrome showed values above 3 SDs for SHOX and VAMP7 genes. Two suspected cases of sex chromosome aneuploidy were diagnosed using our neonatal screening strategy; these cases were confirmed as Turner syndrome and 47,XYY syndrome by karyotyping.

CONCLUSIONS: Our data establish a basis for the determination of chromosomal sex and neonatal screening of sex chromosome aneuploidy using RT-PCR.
Testosterone treatment and risk of venous thromboembolism: population based case-control study.

Martinez C; Suissa S; Rietbrock S; Katholing A; Freedman B; Cohen AT; Handelsman DJ. OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

[Journal Article. Multicenter Study]

UI: 27903495

OBJECTIVE: To determine the risk of venous thromboembolism associated with use of testosterone treatment in men, focusing particularly on the timing of the risk.
DESIGN: Population based case-control study

SETTING: 370 general practices in UK primary care with linked hospital discharge diagnoses and in-hospital procedures and information on all cause mortality.

PARTICIPANTS: 19215 patients with confirmed venous thromboembolism (comprising deep venous thrombosis and pulmonary embolism) and 909530 age matched controls from source population including more than 2.22 million men between January 2001 and May 2013.

EXPOSURE OF INTEREST: Three mutually exclusive testosterone exposure groups were identified: current treatment, recent (but not current) treatment, and no treatment in the previous two years. Current treatment was subdivided into duration of more or less than six months.

MAIN OUTCOME MEASURE: Rate ratios of venous thromboembolism in association with current testosterone treatment compared with no treatment were estimated using conditional logistic regression and adjusted for comorbidities and all matching factors.

RESULTS: The adjusted rate ratio of venous thromboembolism was 1.25 (95% confidence interval 0.94 to 1.66) for current versus no testosterone treatment. In the first six months of testosterone treatment, the rate ratio of venous thromboembolism was 1.63 (1.12 to 2.37), corresponding to 10.0 (1.9 to 21.6) additional venous thromboembolisms above the base rate of 15.8 per 10000 person years. The rate ratio after more than six months' treatment was 1.00 (0.68 to 1.47), and after treatment cessation it was 0.68 (0.43 to 1.07). Increased rate ratios within the first six months of treatment were observed in all strata: the rate ratio was 1.52 (0.94 to 2.46) for patients with pathological hypogonadism and 1.88 (1.02 to 3.45) for those without it, and 1.41 (0.82 to 2.41) for those with a known risk factor for venous thromboembolism and 1.91 (1.13 to 3.23) for those without one.

CONCLUSIONS: Starting testosterone treatment was associated with an increased risk of venous thromboembolism, which peaked within six months and declined thereafter.

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Status
MEDLINE
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Distinctive pattern of expression of spermatogenic molecular markers in testes of azoospermic men with non-mosaic Klinefelter syndrome.

Kleiman SE; Yogev L; Lehavi O; Yavetz H; Hauser R.

OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present


[Journal Article]

UI: 26995389

PURPOSE: Mature sperm cells can be found in testicular specimens extracted from azoospermic men with non-mosaic Klinefelter syndrome (KS). The present study evaluates the expression of various known molecular markers of spermatogenesis in a population of men with KS and assesses the ability of those markers to predict spermatogenesis.
METHODS: Two groups of men with non-obstructive azoospermia who underwent testicular sperm-retrieval procedures were included in the study: 31 had non-mosaic KS (KS group) and 91 had normal karyotype (NK group). Each group was subdivided into mixed atrophy (containing some mature sperm cells) or Sertoli cell only syndrome according to testicular histology and cytology observations. Semi-quantitative histological morphometric analysis (interstitial hyperplasia and hyalinization, tubules with cells and abnormal thickness of the basement membrane) and expression of spermatogenetic markers (DAZ, RBM, BOLL, and CDY1) were evaluated and compared among those subgroups.

RESULTS: Clear differences in the histological morphometry and spermatogenetic marker expression were noted between the KS and NK groups. There was a significant difference in the expression of spermatogenetic markers between the subgroups of the NK group (as expected), while no difference could be discerned between the two subgroups in the KS group.

CONCLUSION: We conclude that molecular spermatogenetic markers have a pattern of expression in men with KS that is distinctively different from that of men with NK, and that it precludes and limits their use for predicting spermatogenesis in the former. It is suggested that this difference might be due to the specific highly abnormal histological morphometric parameters in KS specimens.

Status
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PMID
Testosterone undecanoate improves lipid profile in patients with type 1 diabetes and hypogonadotrophic hypogonadism.

Chillaron JJ; Fernandez-Miro M; Albareda M; Fontsere S; Colom C; Vila L; Pedro-Botet J; Flores Le-Roux JA.

OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

[Journal Article. Multicenter Study. Randomized Controlled Trial]
UI: 27452372

Testosterone deficiency (Td) has been associated with the metabolic syndrome. Few studies have evaluated this condition in type 1 diabetes (T1D). The primary aim of this study was to evaluate the effectiveness of testosterone undecanoate (TU) on insulin sensitivity, glycemic control, anthropometric parameters, blood pressure and lipid profile in patients with Td and T1D.

We performed a randomized placebo-controlled multicenter study.

INCLUSION CRITERIA: a) age >= 18 years; b) autoimmune diabetes; c) Td (total testosterone <10 nmol/L or calculated free testosterone <225 pmol/L and low/normal LH; d) ability to sign informed consent; e) comply with the study protocol.

EXCLUSION CRITERIA: a) pituitary tumor, empty sella, hyperprolactinemia, panhypopituitarism or secondary hypogonadism; b) contraindications for treatment with testosterone undecanoate (TU); c) patients who did not agree to sign their informed consent. Six patients were randomly assigned to testosterone undecanoate (TU) treatment and 7 to placebo with the following dosing schedule: baseline, 6 weeks and 16 weeks. Blood test, anthropometric parameters, blood pressure and insulin sensitivity were determined at baseline, 6, 16 and 22 weeks. No differences were observed regarding insulin sensitivity, HbA1c or basal glucose, anthropometric parameters or blood pressure. At 22 weeks, the decrease in total cholesterol was 37.4 +/- 27.5 mg/dL in the TU group compared with an increase of 13.2 +/- 17.8 mg/dL in the placebo group (P<0.005), and
LDL cholesterol concentration decreased 30.2 +/- 22.1 mg/dL, compared with an increase of 10.5 +/- 13.4 mg/dL in the placebo group (P=0.004). We conclude that treatment with TU in patients with T1D and Td improves lipid profile, with no effects on metabolic control or anthropometric parameters.

In Kallmann syndrome (KS), congenital hypogonadism is associated with olfactory impairment. To evaluate flavor perception-related disability in KS patients, 30 patients with KS, 12 with normosmic hypogonadism (nIHH), 24 with acquired anosmia (AA), and 58 healthy controls entered the study. All participants completed questionnaires concerning dietary habits, olfaction-related quality of life (QoL), and self-determined olfactory, flavor, and taste abilities prior to undergoing standardized olfactometry and gustometry. Each subject underwent flavor testing, using orally administered aqueous aromatic solutions, identifying 21 different compounds by choosing each out of 5 alternative items. Flavor score (FS) was calculated as the sum of correct
answers (range 0-21). Flavor perception by self-assessment was similar between KS, nIHH, and controls, and was mostly reduced only in AA. FS was similar between KS (5.4 +/- 1.4) and AA (6.4 +/- 1.9), and lower than in nIHH (16.2 +/- 2.4, p < 0.001) and controls (16.8 +/- 1.7, p < 0.0001). FS showed strong reproducibility, and correlated with olfactory scores in the overall population. KS and AA patients identified aromatics eliciting trigeminal stimulation better than pure odorants. Olfaction-related QoL was more impaired in AA than in KS. We report significant flavor impairment in KS. This contrasts with routine clinic evidence; KS patients, in contrast with AA, do not complain of flavor perception impairment, perhaps owing to the congenital nature of the dysfunction. Flavor perception impairment should be considered a specific KS disability, because of important detrimental effects on physical and mental health and on QoL. KS patients should also be advised of this impairment in order to prevent accidental and life-threatening events.

Status
MEDLINE

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Testofen, a specialised Trigonella foenum-graecum seed extract reduces age-related symptoms of androgen decrease, increases testosterone levels and improves sexual function in healthy aging males in a double-blind randomised clinical study.

Rao A; Steels E; Inder WJ; Abraham S; Vitetta L.

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[Journal Article. Randomized Controlled Trial]

UI: 26791805

This study examined the effect of Testofen, a specialised Trigonella foenum-graecum seed extract on the symptoms of possible androgen deficiency, sexual function and serum androgen concentrations in healthy aging males. This was a double-blind, randomised, placebo-controlled trial involving 120 healthy men aged between 43 and 70 years of age. The active treatment was standardised Trigonella foenum-graecum seed extract at a dose of 600mg/day for 12 weeks. The primary outcome measure was the change in the Aging Male Symptom questionnaire (AMS), a measure of possible androgen deficiency symptoms; secondary outcome measures were sexual function and serum testosterone. There was a significant decrease in AMS score over time and between the active and placebo groups. Sexual function improved, including number of morning erections and frequency of sexual activity. Both total serum testosterone and free testosterone
increased compared to placebo after 12 weeks of active treatment. Trigonella foenum-graecum seed extract is a safe and effective treatment for reducing symptoms of possible androgen deficiency, improves sexual function and increases serum testosterone in healthy middle-aged and older men.

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257.
Oxytocin, testosterone, and human social cognition. [Review]
Crespi BJ.
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[Journal Article. Research Support, Non-U.S. Gov't. Review]
UI: 25631363
I describe an integrative social-evolutionary model for the adaptive significance of the human oxytocinergic system. The model is based on a role for this hormone in the generation and maintenance of social familiarity and affiliation across five homologous, functionally similar, and sequentially co-opted contexts: mothers with offspring, female and male mates, kin groups,
individuals with reciprocity partners, and individuals within cooperating and competing social groups defined by culture. In each situation, oxytocin motivates, mediates and rewards the cognitive and behavioural processes that underlie the formation and dynamics of a more or less stable social group, and promotes a relationship between two or more individuals. Such relationships may be positive (eliciting neurological reward, reducing anxiety and thus indicating fitness-enhancing effects), or negative (increasing anxiety and distress, and thus motivating attempts to alleviate a problematic, fitness-reducing social situation). I also present evidence that testosterone exhibits opposite effects from oxytocin on diverse aspects of cognition and behaviour, most generally by favouring self-oriented, asocial and antisocial behaviours. I apply this model for effects of oxytocin and testosterone to understanding human psychological disorders centrally involving social behaviour. Reduced oxytocin and higher testosterone levels have been associated with under-developed social cognition, especially in autism. By contrast, some combination of oxytocin increased above normal levels, and lower testosterone, has been reported in a notable number of studies of schizophrenia, bipolar disorder and depression, and, in some cases, higher oxytocin involves maladaptively 'hyper-developed' social cognition in these conditions. This pattern of findings suggests that human social cognition and behaviour are structured, in part, by joint and opposing effects of oxytocin and testosterone, and that extremes of such joint effects partially mediate risks and phenotypes of autism and psychotic-affective conditions. These considerations have direct implications for the development of therapies for alleviating disorders of social cognition, and for understanding how such disorders are associated with the evolution of human cognitive-affective architecture.

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20160406
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2016
Effect of Sleep Extension on the Subsequent Testosterone, Cortisol and Prolactin Responses to Total Sleep Deprivation and Recovery.

Arnal PJ; Drogou C; Sauvet F; Regnauld J; Dispersyn G; Faraut B; Millet GY; Leger D; Gomez-Merino D; Chennaoui M.

OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present


Total sleep deprivation (TSD) in humans is associated with altered hormonal levels, which may have clinical relevance. Less is known about the effect of an extended sleep period before TSD on these hormonal changes. Fourteen subjects participated in two experimental counterbalanced conditions (randomised cross-over design): extended sleep (21.00-07.00 h time in bed, EXT) and habitual sleep (22.30-07.00 h time in bed, HAB). For each condition, subjects performed two consecutive phases: six nights of either EXT or HAB. These nights were followed by 3 days in the sleep laboratory with blood sampling at 07.00 and 17.00 h at baseline (B-07.00 and B-17.00), after 24 and 34 h of continuous awakening (24 h-CA, 34 h-CA) and after one night of recovery sleep (R-07.00 and R-17.00) to assess testosterone, cortisol, prolactin and catecholamines concentrations. At 24 h of awakening, testosterone, cortisol and prolactin concentrations were significantly lower compared to B-07.00 and recovered basal levels after recovery sleep at R-07.00 (P < 0.001 for all). However, no change was observed at 34 h of awakening compared to B-17.00. No effect of sleep extension was observed on testosterone, cortisol and catecholamines concentrations at 24 and 34 h of awakening. However, prolactin concentration was significantly lower in EXT at B-07.00 and R-07.00 compared to HAB (P < 0.05, P < 0.001, respectively). In conclusion, 24 h of awakening inhibited gonadal and adrenal responses in healthy young subjects and this was not observed at 34 h of awakening. Six nights of sleep extension is not sufficient to limit decreased concentrations of testosterone and cortisol at 24 h of awakening but may have an impact on prolactin concentration.

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259.
Treatment for osteoporosis in people with s-thalassaemia. [Review]
Bhardwaj A; Swe KM; Sinha NK; Osunkwo I.
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Cochrane Database of Systematic Reviews. 3:CD010429, 2016 Mar 10.
UI: 26964506

BACKGROUND: Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. Osteoporosis represents an important cause of morbidity in people with beta-thalassaemia and its pathogenesis is multifactorial. Factors include bone marrow expansion due to ineffective erythropoiesis, resulting in reduced trabecular bone tissue with cortical thinning; endocrine dysfunction secondary to excessive iron loading, leading to increased bone turnover; and lastly, a predisposition to physical inactivity due to disease complications with a subsequent reduction in optimal bone mineralization. A number of therapeutic strategies have been applied to treat osteoporosis in people with beta-thalassaemia, which include bisphosphonates, with or without, hormone replacement therapy. There are various forms of bisphosphonates, such as clodronate, pamidronate, alendronate and zoledronic acid. Other treatments include calcitonin, calcium, zinc supplementation, hydroxyurea and hormone replacement therapy for preventing hypogonadism.
OBJECTIVES: To review the evidence on the efficacy and safety of treatment for osteoporosis in people with beta-thalassaemia.

SEARCH METHODS: We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings. Date of most recent search: 04 February 2016.

SELECTION CRITERIA: Randomised, placebo-controlled trials in people with thalassaemia with a bone mineral density z score of less than -2 standard deviations for: children less than 15 years old; adult males (15 to 50 years old); and all pre-menopausal females above 15 years and a bone mineral density t score of less than -2.5 standard deviations for post-menopausal females and males above 50 years old.

DATA COLLECTION AND ANALYSIS: Two review authors assessed the eligibility and risk of bias of the included trials, extracted and analysed data and completed the review. We summarised results using risk ratios or rate ratios for dichotomous data and mean differences for continuous data. We combined trial results where appropriate.

MAIN RESULTS: Four trials (with 211 participants) were included; three trials investigated the effect of bisphosphonate therapies and one trial investigated the effect of zinc supplementation. Only one trial was judged to be of good quality (low risk of bias); the remaining trials had a high or unclear risk of bias in at least one key domain. One trial (data not available for analysis) assessing the effect of neridronate (118 participants) reported significant increases in favour of the bisphosphonate group for bone mineral density at the lumbar spine and hip at both six and 12 months. For the femoral neck, a significant difference was noted at 12 months only. A further trial (25 participants) assessed the effect of alendronate and clodronate and found that after two years, bone mineral density increased significantly in the alendronate and clodronate groups as compared to placebo at the lumbar spine, mean difference 0.14 g/cm(2) (95% confidence interval 0.05 to 0.22) and at the femoral neck, mean difference 0.40 g/cm(2) (95% confidence interval 0.22 to 0.57). One 12-month trial (26 participants) assessed the effects of different doses of pamidronate (30 mg versus 60 mg) and found a significant difference in bone mineral density in favour of the 60 mg dose at the lumbar spine and forearm, mean difference 0.43 g/cm(2) (95% CI 0.10 to 0.76), mean difference 0.87 g/cm(2) (95% CI 0.23 to 1.51), respectively, but not at the femoral neck. In a zinc sulphate supplementation trial (42 participants), bone mineral density increased significantly compared to placebo at the lumbar spine after 12 months (37 participants), mean difference 0.15 g/cm(2) (95% confidence interval 0.10 to 0.20) and after 18 months (32 participants), mean difference 0.34 g/cm(2) (95% confidence interval 0.28 to 0.40). The same was true for bone mineral density at the hip after 12 months, mean difference 0.15 g/cm(2) (95% confidence interval 0.11 to 0.19) and after 18 months, mean difference 0.26 g/cm(2) (95% confidence interval 0.21 to 0.31). Fractures were not observed in one trial and not reported in
three trials. There were no major adverse effects reported in two of the bisphosphonate trials; in the neridronate trial there was a reduction noted in the use of analgesic drugs and in the reported back pain score in favour of bisphosphonate treatment. Adverse effects were not reported in the trial of different doses of pamidronate or the zinc supplementation trial.

AUTHORS' CONCLUSIONS: There is evidence to indicate an increase in bone mineral density at the femoral neck, lumbar spine and forearm after administration of bisphosphonates and at the lumbar spine and hip after zinc sulphate supplementation. The authors recommend that further long-term randomised control trials on different bisphosphonates and zinc supplementation therapies in people with beta-thalassaemia and osteoporosis are undertaken.

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260.
Testosterone Replacement Therapy and the Cardiovascular System. [Review]
Naderi S.
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Current Atherosclerosis Reports. 18(4):19, 2016 Apr.
[Journal Article. Review]
UI: 26932226
As testosterone replacement therapy (TRT) has emerged as a commonly prescribed therapy for symptomatic low testosterone, conflicting data have been reported in terms of both its efficacy and potential adverse outcomes. One of the most controversial associations has been that of TRT and cardiovascular morbidity and mortality. This review briefly provides background on the
history of TRT, the indications for TRT, and the data behind TRT for symptomatic low testosterone. It then specifically delves into the rather limited data for cardiovascular outcomes of those with low endogenous testosterone and those who receive TRT. The available body of literature strongly suggests that more work, by way of clinical trials, needs to be done to better understand the impact of testosterone and TRT on the cardiovascular system.

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261.

Sperm Retrieval in Adolescents and Young Adults with Klinefelter Syndrome: A Prospective, Pilot Study.

Nahata L; Yu RN; Paltiel HJ; Chow JS; Logvinenko T; Rosoklija I; Cohen LE.

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[Clinical Trial. Journal Article. Research Support, Non-U.S. Gov't]

UI: 26746120

OBJECTIVE: To assess sperm retrieval rates in adolescents and young adults with Klinefelter syndrome, with the ultimate goal of improving fertility in this population. Secondary aims were to evaluate other clinical characteristics of the cohort and identify predictors of sperm retrieval.

STUDY DESIGN: Patients 12-25 years of age with Klinefelter syndrome (47,XXY) were recruited at the Boston Children's Hospital. Physical examination, biochemical evaluation, scrotal ultrasonography, and semen analysis were performed. Neurocognitive data were collected. Microdissection sperm extraction (unilateral micro-testicular sperm extraction) was offered to
individuals with no sperm in their ejaculates. Given the small sample size, analysis was primarily
descriptive.

RESULTS: Fifteen patients were enrolled. None had sperm in their ejaculates. Ten patients
underwent unilateral micro-testicular sperm extraction. Sperm retrieval rate was 50%. From a
neurocognitive standpoint, subjects reported problems with peers, conduct, and overall
difficulties. Incidentally, one-third of the patients were found to have testicular microlithiasis and
17% of subjects with renal ultrasound imaging had bilateral renal medullary nephrocalcinosis.

CONCLUSIONS: This pilot study suggests that sperm retrieval rates in adolescents and young
adults with Klinefelter syndrome are comparable with those reported in older men. However,
larger studies are needed to confirm our findings. The clinical significance of the scrotal and renal
ultrasound findings merits further investigation.

TRIAL REGISTRATION: ClinicalTrials.gov: NCT01817296.

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20160229
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2016
The Cardiovascular Trial of the Testosterone Trials: rationale, design, and baseline data of a clinical trial using computed tomographic imaging to assess the progression of coronary atherosclerosis.

Abd Alamir M; Ellenberg SS; Swerdloff RS; Wenger NK; Mohler ER 3rd; Lewis CE; Barrett-Conner E; Nakanishi R; Darabian S; Alani A; Matsumoto S; Nezarat N; Snyder PJ; Budoff MJ.

BACKGROUND: Data from prior studies have yielded inconsistent results on the association of serum testosterone levels with the risk for cardiovascular disease. There are no clinical trial data on the effects of testosterone replacement therapy on plaque progression.

OBJECTIVE: We designed a study to investigate the effect of testosterone therapy on coronary artery plaque progression using serial coronary computed tomographic angiography (CCTA). In this paper, we describe the study design, methods, and characteristics of the study population.

METHODS: The Cardiovascular Trial of the Testosterone Trials (TTrials; NCT00799617) is a double-blind, placebo-controlled trial of 1 year of testosterone therapy in men 65 years or older with clinical manifestations of androgen deficiency and unequivocally low serum testosterone concentrations (<275ng/dl). CCTA performed at baseline and after 12 months of therapy will determine the effects of testosterone on the progression of the total volume of noncalcified plaques. All scans are evaluated at a central reading center by an investigator blinded to treatment assignment.

RESULTS: A total of 165 men were enrolled. The average age is 71.1 years, and the average BMI is 30.7. About 9% of men had a history of myocardial infarction, 6% angina, and 10% coronary artery revascularization. A majority reported hypertension and/or high cholesterol; 31.8% reported diabetes. Total noncalcified plaque at baseline showed a slight but nonsignificant trend toward lower plaque volume with higher serum testosterone concentrations (P=0.12).

CONCLUSION: The Cardiovascular Trial will test the hypothesis that testosterone therapy inhibits coronary plaque progression, as assessed by serial CCTA.

Status

MEDLINE

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The Effects of Gonadotropin Replacement Therapy on Metabolic Parameters and Body Composition in Men with Idiopathic Hypogonadotropic Hypogonadism.

Bayram F; Elbuken G; Korkmaz C; Aydogdu A; Karaca Z; Cakir I.

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[Clinical Trial. Journal Article]

UI: 26485362

Testosterone replacement therapy (TRT) in idiopathic hypogonadotrophic hypogonadism (IHH) slows the process of metabolic syndrome (MetS), diabetes mellitus, and cardiovascular diseases...
by its inversing effects on insulin resistance, dyslipidemia, and blood pressure. Since there are not enough data regarding the effects of gonadotropin replacement therapy (GRT), we aimed to investigate the impact of GRT on MetS parameters in IHH patients. Sixteen patients with IHH and 20 age and body mass index (BMI)-matched healthy controls were enrolled into the study. Patients were evaluated at baseline and 6 months after the GRT. Sex hormones, insulin like growth factor-1, prolactin, insulin, C-reactive protein (CRP), homocysteine, and lipid levels were measured at baseline and after the treatment. Anthropometric measurements, including BMI, body fat ratio (BFR), fat free mass (FFM), waist circumference, and waist-to-hip ratio (WHR), were also performed. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index was calculated. Body fat ratio, triglyceride, HOMA-IR, and CRP levels were higher, whereas bone age, fat free mass, and creatinine levels were lower in the patients with hypogonadism. HOMA-IR indices and basal insulin levels decreased significantly after 6 months of GRT compared with baseline levels. Triglyceride levels, and BFRs diminished significantly by an accompanying decline in WHR. FFM of the patients increased following the GRT. No significant changes were detected in CRP, homocysteine, total and LDL-cholesterol levels. Similar to TRT, hCG treatment decreases HOMA-IR, triglyceride levels, BFR and WHRs, and increases FFM in patients with IHH.

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Year of Publication
Boule gene expression underpins the meiotic arrest in spermatogenesis in male rainbow trout (Oncorhynchus mykiss) exposed to DEHP and butachlor.

Ahmadivand S; Farahmand H; Teimoori-Toolabi L; Mirvaghefi A; Eagderi S; Geerinckx T; Shokrpoor S; Rahmati-Holasoo H.

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[Journal Article]
UI: 26027538

Boule, the ancestor of the DAZ (Deleted in AZoospermia) gene family, in most organisms is mainly involved in male meiosis. The present study investigates the effects of the plasticizer DEHP (50mg/kg body weight) and herbicide butachlor (0.39mg/L) on male rainbow trout (Oncorhynchus mykiss) for a 10-day period in two independent experiments. The results showed that plasma testosterone (T) concentrations were significantly lower in fish exposed to either DEHP or butachlor compared to the control fish (P<0.05). Fish showed a significantly elevated hepatosomatic index (HSI) in the butachlor treatment (P<0.05). However, no significant difference was observed in HSI values in the DEHP treatment (P>0.05). In addition, no significant differences were found in the gonadosomatic index (GSI) in both DEHP and butachlor treatments (P>0.05). Histologically, testes of male trout in the control groups were well differentiated and filled with large numbers of cystic structures containing spermatozoa. In contrast, the testes of male trout contained mostly spermatocytes with few spermatozoa in both treated group, suggesting that DEHP and butachlor may inhibit the progression of meiosis. Also, boule gene expression was significantly lower in the testes of male trout affected by DEHP and butachlor in comparison with their control groups (P<0.05), which confirmed the meiotic arrest in affected trout. Based on the results, the present study demonstrated that DEHP and butachlor can inhibit the progression of spermatogenesis in male trout, potentially by causing an arrest of meiosis, maybe due to down-regulation of boule gene expression through T and/or IGF1 via ERK1/2 signaling in T-independent pathways. In addition, these results confirmed that boule can be considered as a predictive marker to assess meiotic efficiency.

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Oestrogens are Not Related to Emotional Processing: a Study of Regional Brain Activity in Female-to-Male Transsexuals Under Gonadal Suppression.

Soleman RS; Staphorsius AS; Cohen-Kettenis PT; Lambalk CB; Veltman DJ; van Trotsenburg MA; Hompes PG; Drent ML; de Ronde WP; Kreukels BP.
Although the prevailing opinion is that emotional processes are influenced by sex hormones, the literature is still inconclusive. The aim of the current study was to examine the effects of gonadal suppression on brain activity during affective picture processing. Twenty-one female-to-male (FtM) transsexuals and 19 control women were recruited and underwent functional magnetic resonance imaging scanning while rating emotional pictures adapted from the International Affective Picture System. The gonadal hormone production of the FtMs was suppressed for 8 weeks, the control group did not receive any treatment before scanning. Under gonadal suppression, FtMs showed less brain activation in the superior temporal lobe compared with female controls during perception of positive affective pictures. Regression analysis showed that during processing of positive affective images, brain activity within the right superior temporal lobe was not correlated with levels of estradiol, luteinizing hormone, and follicle-stimulating hormone. In the absence of associations with hormonal levels, the difference in activation in the superior temporal lobe during positive emotional stimuli between FtMs and control women may be attributed to a priori differences between the 2 groups. Future studies should clarify if these differences are a result of atypical sexual differentiation of the brain in FtMs.
Novel Uses for the Anabolic Androgenic Steroids Nandrolone and Oxandrolone in the Management of Male Health.

Wu C., Kovac J.R.

Embase

Current Urology Reports. 17 (10) (no pagination), 2016. Article Number: 72. Date of Publication: 01 Oct 2016.

[Review]

AN: 611711667

There has recently been renewed interest in novel clinical applications of the anabolic-androgenic steroid (AAS) testosterone and its synthetic derivatives, particularly given with the rising popularity of testosterone supplementation therapy (TST) for the treatment of male hypogonadism. In this manuscript, we provide a brief review of the history of AAS and discuss clinical applications of two of the more well-known AAS: nandrolone and oxandrolone. Both
agents exhibit favorable myotrophic/androgenic ratios and have been investigated for
effectiveness in numerous disease states. We also provide a brief synopsis of selective androgen
receptor modulators (SARMs) and postulate how these orally active, non-aromatizing, tissue-
selective agents might be used in contemporary andrology. Currently, the applications of
testosterone alternatives in hypogonadism are limited. However, it is tempting to speculate that
these agents may one day become accepted as alternatives, or adjuncts, to the treatment of male
hypogonadism.


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2016

267.
A novel nomogram for prediction of spermatogenic improvement following empiric medical
therapy for moderate-severe oligospermia.
Barazani Y., Polackwich A.S., Sabanegh E.S.

Embase
The Canadian journal of urology. 23 (1) (pp 8135-8140), 2016. Date of Publication: 01 Feb 2016.
[Article]
AN: 616094576

INTRODUCTION: To identify pre-treatment clinical variables and hormonal responses predictive
of successful spermatogenic response to empiric medical therapy (EMT), then to create a
nomogram to guide clinical therapy.  MATERIALS AND METHODS: All men who had been
treated at our institution with EMT for moderate-severe oligospermia (<= 10 million sperm/mL) from 2003 to 2014 were included in our study. Men with hypogonadotropic hypogonadism, azoospermia, or those who had varicocelectomy or had received fertility altering medications within 6 months of initiating EMT were excluded, as well as those who did not obtain a follow up semen analysis. Pre-treatment clinical variables, hormonal responses, and spermatogenic responses were assessed. Success was defined by improvements in baseline sperm concentrations as follows: (1) cryptospermia to >= 0.3 million/mL, (2) > 100% increase in sperm concentration for men with baseline concentration < 1 million/mL, or (3) a 30% increase in sperm concentration for men with a baseline concentration between 1-10 million/mL. We performed univariate analysis to evaluate for predictors of success. The Wilcoxon rank sum test was used for continuous variables and the Fisher's exact test was used for categorical variables. Multivariable logistic regression was then used to build a nomogram.

RESULTS: We identified 107 men who were treated with EMT for oligospermia (<= 10 million sperm/mL) who met our inclusion criteria. Forty-five men (42%) exhibited a poor spermatogenic response to EMT and 62 men (58%) exhibited a good response. Univariate analysis did not identify significant differences in any variable between the two groups. Multivariate analysis did identify predictive combinations which allowed the development of a nomogram with a high concordance index (0.78) for predicting spermatogenic response to EMT.

CONCLUSIONS: While none of the individual pre-treatment clinical variables or hormonal responses were predictive of success following EMT, analysis of multiple factors in concert yielded a clinically useful nomogram with a high concordance index.


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Year of Publication 2016

Purpose of review Male hormones can significantly impact a man's quality of life. Recently, there has been controversy with the use of testosterone and its impact on a man's quality of life. These controversies include testosterone's effect on cardiovascular disease, benign prostatic hyperplasia, prostate cancer, and fertility. The purpose of this manuscript is to further evaluate mainly testosterone's effect in these controversial areas as well as testosterone's overall effect on a man's quality of life. Recent findings Recent findings suggest that testosterone does not increase a man's risk of developing benign prostatic hyperplasia or prostate cancer. Men with low testosterone levels are more likely to suffer a cardiovascular event and develop insulin resistance. Exogenous testosterone is a natural contraceptive and men desiring to preserve their fertility should use mechanisms to raise their own natural endogenous testosterone production. Summary Although testosterone deficiency can significantly impair a man's quality of life, testosterone therapy has been shown to significantly improve many of these qualities, such as depression, bone mineral density, energy, libido, erectile function, muscle mass, insulin resistance, and lower urinary tract symptoms. Testosterone therapy can be administered safely to symptomatic hypogonadal men.

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Publisher Lippincott Williams and Wilkins (E-mail: agents@lww.com)

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Year of Publication 2016
Denosumab is really effective in the treatment of osteoporosis secondary to hypogonadism in prostate carcinoma patients? A prospective randomized multicenter international study.

Doria C., Leali P.T., Solla F., Maestretti G., Balsano M., Scarpa R.M.

Embase
Clinical Cases in Mineral and Bone Metabolism. 13 (3) (pp 195-199), 2016. Date of Publication: 2016.

[Article]
AN: 615509207

Introduction: Osteoporosis is a complication of androgen deprivation therapy (ADT) in men with prostate carcinoma. The best defense against osteoporosis in prostate cancer is to identify patients with a high risk for fracture during the first clinical visit, select an effective anti-osteoporosis agent, and advise the patient to change his lifestyle and diet to prevent further bone loss. New agents include denosumab, a human monoclonal antibody that inhibits the RANK ligand (RANKL). RANKL promotes the formation, activity, and survival of osteoclasts and, thus, supports the breakdown of bone. Purpose: This is a multicenter, randomized, double-blind prospective study on use of denosumab versus alendronate in the therapy of secondary osteoporosis related to ADT in prostate cancer patients in three European countries (Italy, France, Switzerland). Patients and methods: In this 24-month observation study we enrolled 234 patients with diagnosis of osteoporosis underwent ADT for prostate cancer. All patients aged >=55 years and had a dual-energy X-ray absorptiometry (DEXA) T-score <-1.0 (hip or spine, measured within last 2 years) and >= 1 fragility fracture. Patients were randomly assigned 1:1 to receive denosumab 60 mg subcutaneously every 6 months or alendronate (70 mg weekly) for 2 years. All patient received supplemental Vitamin D (600 IU per day) and supplemental calcium to maintain a calcium intake of 1200 mg per day. Effectiveness of therapy in both groups (denosumab group and alendronate group) was assessed by changes in bone turnover markers (BTMs), Bone Mineral Density (BMD), fracture incidence, Visual Analogue Scale (VAS) score for back pain, and Short Form-8 (SF-8TM) health survey score for health-related quality of life (HRQoL). Percent changes from baseline in BTMs and BMD were assessed using the paired t test; a P-value 0.05). Mean changes in BMD at final follow-up differed significantly between two groups. BMD changes at the lumbar spine at 24 months were 5.6% with denosumab vs -1.1% with alendronate (P<0.001). New vertebral fractures developed in fewer patients in the denosumab group than in the alendronate group during the 24-month period, although this difference was not significant (P=0.10). Back pain significantly (P<0.001) improved from baseline at all time points during the study in both study groups. SF-8 health survey scores significantly
improved following treatment with both drugs. Incidence of adverse drug reactions were similar in both groups. Conclusion: In our study denosumab and alendronate showed similar clinical efficacy in the therapy of ADT-related osteoporosis in men with prostate carcinoma; both drugs provided significant improvements in back pain and general health conditions. Denosumab showed significant increase of BTMs and BMD than alendronate with lower rate of new vertebral fractures.

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INPROCESS

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20170423

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2016

Kisspeptin levels in idiopathic hypogonadotropic hypogonadism diagnosed male patients and its relation with glucose-insulin dynamic.
Oztin H., Cagiltay E., Caglayan S., Kaplan M., Akpak Y.K., Karaca N., Tiglioglu M.

Embase
Gynecological Endocrinology. 32 (12) (pp 991-994), 2016. Date of Publication: 01 Dec 2016.
[Article]
AN: 612075802

Male hypogonadism is defined as the deficiency of testosterone or sperm production synthesized by testicles or the deficiency of both. The reasons for hypogonadism may be primary, meaning testicular or secondary, meaning hypothalamic or hypophyseal. In hypogonadotropic hypogonadism (HH), there is inadequacy in gonadotropic hormones due to hypothalamic or hypophyseal
reasons. Gonadotropin-releasing hormone (GnRH) is an important stimulant in releasing follicular stimulant hormone (FSH), mainly luteinizing hormone (LH). GnRH omitted is under the effect of many hormonal or stimulating factors. Kisspeptin is present in many places of the body, mostly in hypothalamic anteroventral periventricular nucleus and arcuate nucleus. Kisspeptin has a suppressor effect on the metastasis of many tumors such as breast cancer and malign melanoma metastases, and is called "metastin" for this reason. Kisspeptin is a strong stimulant of GnRH. In idiopathic hypogonadotropic hypogonadism (IHH) etiology, there is gonadotropic hormone release indeficiency which cannot be clearly described. A total of 30 male hypogonatropic hypogonadism diagnosed patients over 30 years of age who have applied to Haydarpasa Education Hospital Endocrinology and Metabolic Diseases Service were included in the study. Compared to the control group, the effect of kisspeptin on male patients with hypogonatropic hypogonadism and on insulin resistance developing in hypogonadism patients was investigated in our study. A statistically significant difference was detected between average kisspeptin measurements of the groups (p < 0.01). Kisspeptin measurement of the cases in the patient group were detected significantly high. No statistically significant relation was detected among kisspeptin and LH/FSH levels. Although a positive low relation was detected between kisspeptin measurements of patient group cases and homeostasis model assessment of insulin resistance (HOMA-IR) measurements, this relation was statistically insignificant. When the patient and control groups were compared for HOMA-IR, no statistically significant difference was detected. The reason for high kisspeptin levels in the patient group compared to the control group makes us consider that there may be a GPR54 resistance or GnRH neuronal transfer pathway defect. When patients and control groups were compared for HOMA-IR, the difference was not statistically significant. It is considered that kisspeptin is one of the reasons for hypogonatropic hypogonadism and has less effect on insulin resistance.

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Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy.
Embase
The Medical journal of Australia. 205 (4) (pp 173-178), 2016. Date of Publication: 15 Aug 2016. [Article]
AN: 615394335
INTRODUCTION: This article, Part 1 of the Endocrine Society of Australia's position statement on male hypogonadism, focuses on assessment of male hypogonadism, including the indications for testosterone therapy. (Part 2 will deal with treatment and therapeutic considerations.) MAIN RECOMMENDATIONS: Key points and recommendations are: Pathological hypogonadism arises due to diseases of the hypothalamus or pituitary gland (hypogonadotropic hypogonadism) or testes (hypergonadotropic hypogonadism). It is a clinical diagnosis with a pathological basis, confirmed by hormone assays. Hormonal assessment is based on measurement of circulating testosterone, luteinising hormone (LH) and follicle-stimulating hormone (FSH) concentrations. Measurement of sex hormone-binding globulin levels can be informative, but use of calculated free testosterone is not recommended for clinical decision making. Testosterone replacement therapy is warranted in men with pathological hypogonadism, regardless of age. Currently, there are limited data from high-quality randomised controlled trials with clinically meaningful outcomes to justify testosterone treatment in older men, usually with chronic disease, who have low circulating testosterone levels but without hypothalamic, pituitary or testicular disease. Obesity,
metabolic syndrome and type 2 diabetes are associated with lowering of circulating testosterone level, but without elevation of LH and FSH levels. Whether these are non-specific consequences of non-reproductive disorders or a correctable deficiency state is unknown, but clear evidence for efficacy and safety of testosterone therapy in this setting is lacking. Glucocorticoid and opioid use is associated with possibly reversible reductions in circulating testosterone level, without elevation of LH and FSH levels. Where continuation of glucocorticoid or opioid therapy is necessary, review by an endocrinologist may be warranted. Changes in management as result of the position statement: Men with pathological hypogonadism should be identified and considered for testosterone therapy, while further research is needed to clarify whether there is a role for testosterone in these other settings.

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272.
Acute protease supplementation effects on muscle damage and recovery across consecutive days of cycle racing.

Shing C.M., Chong S., Driller M.W., Fell J.W.

Embase

European journal of sport science. 16 (2) (pp 206-212), 2016. Date of Publication: 2016.

[Article]

AN: 615318222
Bromelain, a mixture of proteases obtained from pineapples, has been demonstrated to reduce exercise-induced muscle damage and inflammation, enhancing recovery. This investigation aimed to establish if markers of muscle damage and testosterone were influenced by acute bromelain supplementation in competitive cyclists taking part in a six-day cycle stage race.

Fifteen highly trained cyclists [age: 22, [Formula: see text] = 1.2 years, height: 1.79, [Formula: see text] = 0.01 m, body mass: 68.69, [Formula: see text] = 1.97 kg] were supplemented with either bromelain (1000 mg.day(-1)) (n = 8) or a placebo (n = 7) across six days of competitive racing in a randomised, double-blind, placebo-controlled trial. Blood was collected from each cyclist on days one, three and six of racing and analysed for creatine kinase (CK), myoglobin, lactate dehydrogenase (LDH) and testosterone. CK activity (P < 0.001, d = 17.4-18.8), LDH activity (P < 0.004, d = 0.5-2.5) and myoglobin concentration (P < 0.007, d = 3.4-4.8) were elevated from pre-race on days three and six of racing in both groups. Testosterone concentrations were significantly lower on the final day of racing (P = 0.03, d = 1.3) and there was a trend for bromelain to maintain testosterone concentrations across the race period (P = 0.05, d = 1.04-1.70) when compared to placebo. Fatigue rating was lower in the bromelain group on day four of racing (P = 0.01). Consecutive days of competitive cycling were associated with increased markers of muscle damage and a reduction in circulating testosterone across the race period. Bromelain supplementation reduced subjective feelings of fatigue and was associated with a trend to maintain testosterone concentration.


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20170414
Year of Publication
2016

273.
Acute severe male hypo-testosteronemia affects central motor command in humans.
Purpose: To indirectly evaluate the effect of androgens on neuromuscular system in humans we analyzed if an induced short-term hypogonadal state (serum total testosterone-TT < 2.3 ng/ml) may affect central drive to skeletal muscle and/or muscle neuro-mechanical performance.

Methods: We compared voluntary and electrically evoked muscle sEMG signals from biceps brachii in nine hypogonadal male volunteers (Hypo) and in ten healthy controls (Cont). Serum TT and dihydrotestosterone (DHT) were assayed. Results: With respect to Hypo, Cont exhibited significantly higher median frequency content (MDF) at any angular velocity; normalized MDF [95.9% (SD = 23.3) vs 73.8% (SD = 9.3)]; muscle fiber conduction velocity (CV) from lowest to highest angular velocities; initial MDF at fatigue test [91.78 Hz (SD = 22.03) vs 70.94 Hz (SD = 11.06)] as well as was the normalized slope [-0.64 (SD = 0.14 vs -0.5 (SD = 0.11)]. In the non-fatigued state, Hypo showed a slower single twitches time to peak (TTP). In Cont, half relaxation time (HRT) decreased after fatigue while increased in Hypo (p < 0.05 between groups). A significant correlation between both TT and dihydrotestosterone with MDF and CV was found during voluntary contractions only. Conclusions: A brief exposure to very low serum TT concentration in males seem to determine a reduced excitability of the NM system which, in turn, would favor a predominant recruitment of slow twitch MUs.
Introduction: Part 1 of this position statement dealt with the assessment of male hypogonadism, including the indications for testosterone therapy. This article, Part 2, focuses on treatment and therapeutic considerations for male hypogonadism and identifies key questions for future research. Main recommendations: Key points and recommendations are: Excess cardiovascular events have been reported in some but not all studies of older men without pathological hypogonadism who were given testosterone treatment. Additional studies are needed to clarify whether testosterone therapy influences cardiovascular risk. Testosterone is the native hormone that should be replaced in men being treated for pathological hypogonadism. Convenient and cost-effective treatment modalities include depot intramuscular injection and transdermal administration (gel, cream or liquid formulations). Monitoring of testosterone therapy is recommended for efficacy and safety, focusing on ameliorating symptoms, restoring virilisation,
avoiding polycythaemia and maintaining or improving bone mineral density. Treatment aims to relieve an individual's symptoms and signs of androgen deficiency by administering standard doses and maintaining circulating testosterone levels within the reference interval for eugonadal men. Evaluation for cardiovascular disease and prostate cancer risks should be undertaken as appropriate for eugonadal men of similar age. Nevertheless, when there is a reasonable possibility of substantive pre-existing prostate disease, digital rectal examination and prostate-specific antigen testing should be performed before commencing testosterone treatment.

Changes in management as result of the position statement: Treatment aims to relieve symptoms and signs of androgen deficiency, using convenient and effective formulations of testosterone. Therapy should be monitored for efficacy and safety.

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Publisher Australasian Medical Publishing Co. Ltd (E-mail: ampco@ampco.com.au)

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Year of Publication 2016
Salivary testosterone responses to a physical and psychological stimulus and subsequent effects on physical performance in healthy adults.

Crewther B.T., Kilduff L.P., Finn C., Scott P., Cook C.J.

Embase

Hormones. 15 (2) (pp 248-255), 2016. Date of Publication: April-June 2016.

[Article]

AN: 611042457

OBJECTIVE: To address the rapid influence of testosterone (T) on neuromuscular performance, we compared the T and physical performance responses of adults exposed to a physical and psychological stimulus. DESIGN: A group of healthy men (n=12) and women (n=14) each completed three treatments using a randomised, crossover design: exercise involving five x ten-second cycle sprints, viewing a video clip with aggressive content and a control session. Salivary T concentrations, hand-grip strength (HGS) and countermovement jump peak power (CMJ PP) were assessed before and 15 minutes after each session. RESULTS: The relative changes in T (17+/−29%) and CMJ PP (-0.1+/−4.4%) following sprint exercise were superior to the aggressive video (-6.3+/−19%, -2.2+/−5.9%) and control (-4.8+/−23%, -2.8+/−4.4%) treatments, respectively (p <=0.05). Pre-treatment T levels correlated (r=−0.58 to -0.61, p <0.05) with the T responses of men (sprint exercise) and women (sprint exercise, aggressive video), but no variables were significantly correlated with the relative changes in HGS or CMJ PP. CONCLUSIONS: Sprint exercise promoted a general rise in T and maintained CMJ PP, relative to the video and control treatments. In both sexes, those individuals with higher pre-test T levels tended to produce smaller T responses to one or more treatments. These data highlight the importance of stimulus selection and individual predispositions when attempting to acutely modify T and associated physical performance. Copyright © 2016, Hellenic Endocrine Society. All rights reserved.

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Predicting low testosterone in aging men: A systematic review.
Embase
[Article]
AN: 612310541

Background: Physicians diagnose and treat suspected hypogonadism in older men by extrapolating from the defined clinical entity of hypogonadism found in younger men. We conducted a systematic review to estimate the accuracy of clinical symptoms and signs for predicting low testosterone among aging men. Methods: We searched the MEDLINE and Embase databases (January 1966 to July 2014) for studies that compared clinical features with a measurement of serum testosterone in men. Three of the authors independently reviewed articles for inclusion, assessed quality and extracted data. Results: Among 6053 articles identified, 40 met the inclusion criteria. The prevalence of low testosterone ranged between 2% and 77%. Threshold testosterone levels used for reference standards also varied substantially. The summary likelihood ratio associated with decreased libido was 1.6 (95% confidence interval [CI] 1.3- 1.9), and the likelihood ratio for absence of this finding was 0.72 (95% CI 0.58-0.85). The likelihood ratio associated with the presence of erectile dysfunction was 1.5 (95% CI 1.3-1.8) and with absence of erectile dysfunction was 0.83 (95% CI 0.76-0.91). Of the multiple-item instruments, the ANDROTEST showed both the most favourable positive likelihood ratio (range 1.9-2.2) and the most favourable negative likelihood ratio (range 0.37-0.49). Interpretation: We
found weak correlation between signs, symptoms and testosterone levels, uncertainty about what threshold testosterone levels should be considered low for aging men and wide variation in estimated prevalence of the condition. It is therefore difficult to extrapolate the method of diagnosing pathologic hypogonadism in younger men to clinical decisions regarding age-related testosterone decline in aging men. Copyright © 2016 Joule Inc. or its licensors.


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Publisher Canadian Medical Association (1867 Alta Vista Drive, Ottawa K1G5W8, Canada)

Date Created 20161005
Year of Publication 2016


Embase


[Article]
Objective: Hyperprolactinaemia as a side effect of dopamine receptor blockers is common in patients with schizophrenia and other psychotic disorders and may lead to amenorrhea, galactorrhoea, hypogonadism, subfertility and osteoporosis. The aim of our study was to determine whether hyperprolactinaemia occurs also in patients with schizophrenia and other psychotic disorders prior to any antipsychotic treatment. Methods: Serum prolactin, thyroid-stimulating hormone (TSH), triiodothyronine (T3), free tetraiodothyronine (FT4) and cortisol levels were measured in 40 newly diagnosed, drug naive, patients with schizophrenia and other psychotic disorders and in 40 age and gender matched healthy subjects. Results: The median prolactin value was 12.5 ng/ml (range: 2-38 ng/ml) for patients and 8.6 ng/ml (range: 4-17.6 ng/ml) for healthy subjects (p = 0.011). Patients had lower levels of T3 compared to healthy controls (mean: 1.08 ng/ml, SD: 0.16 vs. 1.18 ng/ml, 0.18, respectively; p = 0.008). Serum TSH, FT4 and cortisol levels were similar between the two groups. Multiple regression analysis revealed that the difference in serum prolactin values was independent of thyroid function (TSH, FT4, T3) and serum cortisol levels. Conclusions: A higher serum prolactin level was found in drug naive, newly diagnosed patients with schizophrenia and other psychotic disorders compared to healthy controls, prior to starting any antipsychotic treatment. Copyright © 2016 Informa UK Limited, trading as Taylor & Francis Group.

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Year of Publication
Effects of aging on the male reproductive system.
Gunes S., Hekim G.N.T., Arslan M.A., Asci R.
Embase
[Review]
AN: 608269612
The study aims to discuss the effects of aging on the male reproductive system. A systematic review was performed using PubMed from 1980 to 2014. Aging is a natural process comprising of irreversible changes due to a myriad of endogenous and environmental factors at the level of all organs and systems. In modern life, as more couples choose to postpone having a child due to various socioeconomic reasons, research for understanding the effects of aging on the reproductive system has gained an increased importance. Paternal aging also causes genetic and epigenetic changes in spermatozoa, which impair male reproductive functions through their adverse effects on sperm quality and count as, well as, on sexual organs and the hypothalamic-pituitary-gonadal axis. Hormone production, spermatogenesis, and testes undergo changes as a man ages. These small changes lead to decrease in both the quality and quantity of spermatozoa. The offspring of older fathers show high prevalence of genetic abnormalities, childhood cancers, and several neuropsychiatric disorders. In addition, the latest advances in assisted reproductive techniques give older men a chance to have a child even with poor semen parameters. Further studies should investigate the onset of gonadal senescence and its effects on aging men. Copyright © 2016, Springer Science+Business Media New York.
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Testosterone treatment and risk of venous thromboembolism: Population based case-control study.
Martinez C., Suissa S., Rietbrock S., Katholing A., Freedman B., Cohen A.T., Handelsman D.J.
Embase
[Article]
AN: 613492711
Objective: To determine the risk of venous thromboembolism associated with use of testosterone treatment in men, focusing particularly on the timing of the risk. Design: Population based case-control study. Setting: 370 general practices in UK primary care with linked hospital discharge diagnoses and in-hospital procedures and information on all cause mortality. Participants: 19 215 patients with confirmed venous thromboembolism (comprising deep venous thrombosis and pulmonary embolism) and 909 530 age matched controls from source population including more than 2.22 million men between January 2001 and May 2013. Exposure of interest: Three mutually exclusive testosterone exposure groups were identified: current treatment, recent (but not current) treatment, and no treatment in the previous two years. Current treatment was subdivided into duration of more or less than six months. Main outcome measure: Rate ratios of venous thromboembolism in association with current testosterone treatment compared with no treatment were estimated using conditional logistic regression and adjusted for comorbidities and all matching factors. Results: The adjusted rate ratio of venous thromboembolism was 1.25 (95% confidence interval 0.94 to 1.66) for current versus no testosterone treatment. In the first six months of testosterone treatment, the rate ratio of venous thromboembolism was 1.63 (1.12 to 2.37), corresponding to 10.0 (1.9 to 21.6) additional venous thromboembolisms above the base
rate of 15.8 per 10 000 person years. The rate ratio after more than six months' treatment was 1.00 (0.68 to 1.47), and after treatment cessation it was 0.68 (0.43 to 1.07). Increased rate ratios within the first six months of treatment were observed in all strata: the rate ratio was 1.52 (0.94 to 2.46) for patients with pathological hypogonadism and 1.88 (1.02 to 3.45) for those without it, and 1.41 (0.82 to 2.41) for those with a known risk factor for venous thromboembolism and 1.91 (1.13 to 3.23) for those without one. Conclusions: Starting testosterone treatment was associated with an increased risk of venous thromboembolism, which peaked within six months and declined thereafter.

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280.
The Potential of Gonadal Hormone Signalling Pathways as Therapeutics for Dementia.
Dementia is an ever-expanding problem facing an ageing society. Currently, there is a sharp paucity of treatment strategies. It has long been known that sex hormones, namely 17beta-estradiol and testosterone, possess neuroprotective- and cognitive-enhancing qualities. However, certain lacunae in the knowledge underlying their molecular mechanisms have delayed their use as treatment strategies in dementia. With recent advancements in pharmacology and molecular biology, especially in the development of safer selective oestrogen receptor modulators and the recent discovery of the small-molecule brain-derived neurotrophic factor receptor agonist, 7,8-dihydroxyflavone, the exploitation of these signalling pathways for clinical use has become possible. This review aims to adumbrate the evidence and hurdles underscoring the use of sex hormones in the treatment of dementia as well as discussing some direction that is required to advance the translation of evidence into practise. Copyright © 2016, Springer Science+Business Media New York.
Incidence of pituitary dysfunction following traumatic brain injury: A prospective study from a regional neurosurgical centre.

Alavi S.A., Tan C.L., Menon D.K., Simpson H.L., Hutchinson P.J.

Embase

British Journal of Neurosurgery. 30 (3) (pp 302-306), 2016. Date of Publication: 03 May 2016.

[Article]

AN: 607083117

Patients with traumatic brain injury (TBI) may develop pituitary dysfunction. Although, there is now increasing awareness of and investigations into such post-traumatic hypopituitarism (PTHP), the exact prevalence and incidence remain uncertain. Here, we aim to identify the incidence of PTHP in a selected population of TBI patients deemed at risk of PTHP at a regional neurosurgical centre in the UK. A total of 105 patients have been assessed in two cohorts: (i) 58 patients in serial cohort and (ii) 47 patients in cross-sectional late cohort. We found that in serial cohort, 10.3% (6/58) of TBI patients had abnormalities of the pituitary-adrenal axis in the acute phase (Day 0-7 post injury). In comparison, in cross-sectional late cohort, 21.3% (10/47) of the patients developed dysfunction in at least one of their pituitary axes at 6 months or more post-TBI, with hypogonadotrophic hypogonadism being the most common. Twenty-two patients from these two cohorts had their growth hormone assessment at 12 months or more post-TBI and 9.1% (2/22) were found to have growth hormone deficiency. Our results suggest that PTHP is a common condition amongst sufferers of TBI, and appropriate measures should be taken to detect and manage it. Copyright © 2015 Taylor & Francis.

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Publisher

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Gonadal differentiation has a determinative influence on sex development in human embryos. Disorders of sexual development (DSD) have been associated with persistent embryonal differentiation stages. Between 1998 and 2015, 139 female patients with various (DSD) underwent operations at the Scientific Center of Obstetrics, Gynaecology and Perynatology in Moscow, Russia. Clinical investigations included karyotyping, ultrasound imaging, hormonal measurement and investigations of gonadal morphology. The male characteristics in the embryo are imposed by testicular hormones. When these are absent or inactive, the fetus may be arrested at between developmental stages, or stay on indifferent stage and become phenotypically female. A systematic analysis of gonadal morphology in DSD patients and a literature review revealed some controversies and led us to formulate a new hypothesis about sex differentiation. Proliferation of the mesonephric system (tubules and corpuscles) in the gonads stimulates the masculinization of gonads to testis. Sustentacular Sertoli cells of the testes are derived from mesonephric excretory tubules, while interstitial Leydig cells are derived from the original mesenchyme of the mesonephros. According to the new hypothesis, the original mesonephric cells (tubules and corpuscles) potentially persist in the ovarian parenchyma. In female gonads, some mesonephric excretory tubules regress and lose the tubular structure, but form ovarian theca interna and externa, becoming analogous to the sustentacular Sertoli cells in the testis. The ovarian interstitial Leydig cells are derived from intertubal mesenchyme of the mesonephros, similar to what occurs in male gonads (testis). Surprisingly, the leading determinative factor in sexual differentiation of the gonads is the mesonephros, represented by the embryonic urinary system. Copyright © 2016 Taylor & Francis Group, LLC.
Withdrawal of dopamine agonist therapy in prolactinomas: In which patients and when?
Dogansen S.C., Selcukbiricik O.S., Tanrikulu S., Yarman S.

Embase
Pituitary. 19 (3) (pp 303-310), 2016. Date of Publication: 01 Jun 2016.

Purpose: The aim of the study was to assess the effect of dopamine agonist (DA) withdrawal, the current recurrence rate of hyperprolactinemia, and possible factors that predict recurrence in patients with prolactinoma. Methods: We evaluated DA withdrawal in 67 patients with prolactinoma (50 female/17 male) who received DA treatment for at least 2 years and showed normalization of prolactin (PRL) levels and tumor disappearance or >=50 % tumor shrinkage, retrospectively. Accordingly, patients were divided into two groups as remission and recurrence groups, and factors that predict recurrence were evaluated. Results: The overall remission rate was 46 %; the remission ratios were 65 % in microprolactinomas and 36 % in macroprolactinomas. Remission rates were 39 % in the bromocriptine withdrawal group and 55 % in the cabergoline withdrawal group. The maximum tumor diameter and baseline PRL levels were significantly higher in the recurrence group (p = 0.001 and p = 0.003, respectively). The mean duration of DA therapy was significantly longer in the remission group (88.7 +/- 48.1 and 66.7 +/- 30.4 months, respectively, p = 0.026). The mean time to recurrence was 5.3 +/- 3.2 months. The mean PRL levels at recurrence time were significantly lower than baseline PRL levels (p = 0.001).
Conclusion: The most important predictors of recurrence were maximum tumor diameter and baseline PRL levels in this study. The remission rate in our study group was higher, which was thought to be associated with the longer duration of DA treatment and that our patients were selected according to certain criteria. Despite these positive results, close monitoring is necessary for detection of early and late recurrence, especially within the first year after DA withdrawal. Copyright © 2016, Springer Science+Business Media New York.


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Year of Publication 2016

284.
A beneficial effect of estradiol on blood pressure, not on glucose and lipids levels in women with Turner syndrome.
Irzyniec T.J., Jez W.
Embase
Arterial Hypertension. 20 (4) (pp 206-210), 2016. Date of Publication: 29 Dec 2016.
[Article]
AN: 614992063
Introduction. Turner syndrome (TS) is the form of gonadal malfunction. Arterial hypertension, elevated LDL and glucose and decreased HDL levels are characteristic of TS-women. Hormone therapy is a treatment for short stature and sex hormone deficits. Hormonal replacement therapy (HRT) reduces the risk of cardiovascular diseases. A large percentage of TS-women do not
comply with doctors’ orders regarding HRT. The analysis of 17beta estradiol (E2) levels and the assessment of blood pressure, lipid and carbohydrate metabolisms in TS-women it is possible to state whether HRT decreases the risk of cardiovascular diseases? Material and methods. The group of 95 TS-women, who declared HRT, were investigated. The information about HRT was collected during the anamnesis. E2, total cholesterol (TC), high (HDL) and low (LDL) density lipoproteins, triglycerides (TG) and glucose were assessed. Patients were divided into subgroups with E2 >= 110 pmol/L (n = 34) (HE) and < 110 pmol/L (n = 61) (LE) respectively. Results. Arterial hypertension was diagnosed in 26.3%. The groups did not differ in systolic 119 +/- 20 versus 118 +/- 14 and diastolic 82 +/- 13 versus 80 +/- 10 mm Hg blood pressure. Despite the higher concentrations of E2 in HE, no differences were found in weights, lipids and glucose concentrations. Negative correlations between E2 and body mass (r = -0.25, p = 0.04) and diastolic blood pressure (r = -0.28, p = 0.02) as well as positive between E2 and glucose (r = 0.24, p < 0.05) were observed only in HE. No correlations between E2 and lipids were found. Conclusions. 1. Only 1/3 TS-women, who declare HRT, have a satisfactory level of E2. 2. In TS-women HRT does not affect glucose and lipid metabolisms. 3. Negative correlation between E2 and diastolic blood pressure in TS-women suggest beneficial effect of estrogens in hypertension.
Provocative stimulation of the hypothalamic-pituitary-testicular axis in men with spinal cord injury. 
Bauman W.A., La Fountaine M.F., Cirnigliaro C.M., Kirshblum S.C., Spungen A.M.
Embase
Spinal Cord. 54 (11) (pp 961-966), 2016. Date of Publication: 01 Nov 2016.
[Article]
AN: 610082710
Study design: Prospective study.
Objective: To determine the integrity of the hypothalamic-pituitary-testicular axis in healthy men with spinal cord injury (SCI).
Methods: Thirty healthy men with chronic SCI (37+/−10 years) and thirty-eight able-bodied (AB) controls (36+/−10 years) participated. Gonadotropin-releasing hormone (GnRH; 100 mug IV) was administered to determine gonadotropin release, and human chorionic gonadotropin (hCG; 4000 IU IM) was administered to determine testosterone (T) secretion. Responses to stimulation were categorized as 'responder' or 'non-responder' by clinical criteria. Single factor ANOVA with repeated measures was performed to identify group differences.
Results: The proportion of responders to pituitary GnRH stimulation was similar in the SCI group (22 subjects (73%) for the follicular-stimulating hormone (FSH) and 23 subjects (76%) for the luteinizing hormone (LH) to that of the AB group. The SCI-responder group had an increased FSH response after stimulation compared with the AB-responder group (P<0.05). The SCI-responder group had a greater LH area under the curve to GnRH stimulation than the AB-responder group (P=0.06). The peak FSH response was at 60 min and the peak LH response at 30 min, regardless of group designation. All groups had similar increases in serum T concentration to hCG stimulation.
Conclusions: The pituitary response to stimulation in healthy men with SCI revealed an augmented FSH response; LH response only trended higher. The testicular response to provocative stimulation was similar in hypogonadal and eugonadal subjects and in GnRH responders and non-responders. These findings suggest a lack of hypothalamic drive of pituitary gonadotropin release in healthy people with chronic SCI.

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The correlation between highly sensitive C-reactive protein levels and erectile function among men with late-onset hypogonadism.


Aging Male. 19 (4) (pp 239-243), 2016. Date of Publication: 01 Oct 2016.

We investigated the correlation between highly sensitive C-reactive protein (hs-CRP) levels and erectile function, and assessed the clinical role of hs-CRP levels in men with late-onset hypogonadism (LOH) syndrome. For 77 participants, we assessed Sexual Health Inventory for men (SHIM) score, Aging Male Symptoms (AMS) score and International Prostate Symptom Score (IPSS). We also evaluated free testosterone (FT), hs-CRP, total cholesterol, triglyceride levels, high density lipoprotein cholesterol, hemoglobin A1c, body mass index, waist size and blood pressure. We attempted to identify parameters correlated with SHIM score and to determine the factors affecting cardiovascular risk based on hs-CRP levels. A Spearman rank correlation test revealed that age, AMS score, IPSS and hs-CRP levels were significantly correlated with SHIM score. Age-adjusted analysis revealed that hs-CRP and IPSS were the
independent factors affecting SHIM score ($r = -0.304$ and $-0.322$, respectively). Seventeen patients belonged to the moderate to high risk group for cardiovascular disease, whereas the remaining 60 belonged to the low risk group. Age, FT value and SHIM score showed significant differences between the two groups. A multivariate regression analysis demonstrated that SHIM score was an independent factor affecting cardiovascular risk (OR: 0.796; 95%CI: 0.637-0.995).

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287.
Serum testosterone and cognitive function in ageing male: Updating the evidence.
Giagulli V.A., Guastamacchia E., Licchelli B., Triggiani V.

Embase
Recent Patents on Endocrine, Metabolic and Immune Drug Discovery. 10 (1) (pp 22-30), 2016.
Date of Publication: 2016.

[Article]
AN: 613959872

Background: Testosterone (T) deficit, either in prepubertal or postpubertal form of hypogonadism, seems to play a key role in impairing cognitive function, including memory, attention, language and visuospatial abilities, especially in elderly men Objective: Several studies have recently showed the association between low serum T levels and important cognitive dysfunctions in ageing male as well as in subjects suffering from Alzheimer's disease (AD), mild cognitive impairment (MCI) and even depression, suggesting that T could exert an active neuro protective
Methods: By searching PubMed and recent patents (ranging from 2010 to 2015), we identified several observational and intervention studies dealing with T and cognitive function in adult and ageing men. Findings were reviewed, thoroughly examined and, finally, summarized herein. Results: Although a large number of studies have been carried out so far, conclusive evidence cannot be drawn, in particular, for cognitive disorders in males. Conversely, T supplementation has been suggested for depressive syndrome in young and ageing men. To date, no clinical data have been carried out on cognitive dysfunctions employing the quoted patents in men. Conclusions: Studies aiming to evaluate the role of serum T and its supplementation in adult and ageing men with T deficiency syndrome need to be encouraged, given that subjects affected by overt hypogonadism, either in prepubertal (i.e. Klinefelter syndrome) or postpubertal forms (chemical castration in subjects affected by prostate cancer), often complain of cognitive dysfunction, and seem to considerably benefit from T replacement therapy.

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20170117

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2016

Identification of late-onset hypogonadism in middle-aged and elderly men from a community of China.

Embase
In this study, we investigated the essential criteria for late-onset hypogonadism (LOH) syndrome based on the presence of symptoms associated with low testosterone levels in Han Chinese men. Blood tests for total testosterone (TT) and sex hormone-binding globulin (SHBG) were performed, and the aging male symptoms (AMS) questionnaire was conducted in a randomly selected cohort composed of 944 Chinese men aged 40 to 79 years from nine urban communities. Three sexual symptoms (decreased ability/frequency of sexual activity, decreased number of morning erections, and decreased libido) were confirmed to be related to the total and free testosterone levels. The thresholds for TT were approximately 12.55 nmol l^{-1} for a decreased ability/frequency to perform sex, 12.55 nmol l^{-1} for decreased frequency of morning erections, and 14.35 nmol l^{-1} for decreased sexual desire. The calculated free testosterone (CFT) thresholds for these three sexual symptoms were 281.14, 264.90, and 287.21 pmol l^{-1}, respectively. TT <13.21 nmol l^{-1} (OR = 1.4, 95%CI: 1.0-1.9, P = 0.037) or CFT <268.89 pmol l^{-1} (OR = 1.5, 95%CI: 1.1-20, P = 0.020) was associated with an increase in the aforementioned three sexual symptoms. The prevalence of LOH was 9.1% under the criteria, including all three sexual symptoms with TT levels <13.21 nmol l^{-1} and CFT levels <268.89 pmol l^{-1}. Our results may improve the diagnostic accuracy of LOH in older men. Copyright © 2016 AJA, SIMM & SJTU.

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2016
Pituitary morphovolumetric changes in Alstrom syndrome.
Embase
Journal of Neuroradiology. 43 (3) (pp 195-199), 2016. Date of Publication: 01 Jun 2016.
[Article]
AN: 607335851
Purpose: Alstrom syndrome (AS) is a rare monogenic ciliopathy characterized by cone-code dystrophy, leading to early blindness, and obesity. Early endocrinological dysfunctions, especially growth hormone deficiency and hypogonadism, are detected in about half of AS patients. This MRI study investigates the presence of pituitary gland abnormalities in a large cohort of AS patients. Methods: Pituitary morphological changes (gland flattening with partial or total empty sella) were evaluated on midsagittal high-resolution T1-weighted images of 32 AS patients (mean-age 23.2 +/- 9.4 years; range: 6-45, 15 females) and 21 unrelated healthy subjects (mean age 23.2 +/- 11.2 years; range: 6-43; 10 females). Results: Among AS patients, 11/32 (34%) had total empty sella and 6/32 (19%) partial empty sella, while 3/21 (14%) of controls had partial empty sella and none presented with total empty sella (P < 0.005). AS patients harboring a total or partial empty sella did not differ from those with normal pituitary gland for gender (P = 0.98), BMI (P = 0.10) or visual impairment (P = 0.21), while the presence of empty sella was associated with an older age (P = 0.007) being especially frequent above the age of 30. Conclusions: Total or partial empty sella appears commonly during the course of AS. Pituitary gland flattening might represent the morphological underpinning of subtle endocrinologic dysfunctions and raises the need to further investigate the pituitary function in this rare ciliopathy.
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Male fertility potential alteration in rheumatic diseases: a systematic review.
Tiseo B.C., Cocuzza M., Bonfa E., Srougi M., Silva C.A.
Embase
International braz j urol : official journal of the Brazilian Society of Urology. 42 (1) (pp 11-21), 2016. Date of Publication: 01 Jan 2016.
[Review]
AN: 614863461
BACKGROUND: Improved targeted therapies for rheumatic diseases were developed recently resulting in a better prognosis for affected patients. Nowadays, patients are living longer and with improved quality of life, including fertility potential. These patients are affected by impaired reproductive function and the causes are often multifactorial related to particularities of each disease. This review highlights how rheumatic diseases and their management affect testicular function and male fertility. MATERIALS AND METHODS: A systematic review of literature of all published data after 1970 was conducted. Data was collected about fertility abnormalities in male patients with systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, ankylosing spondylitis, Behcet disease and gout. Two independent researchers carried out the search in online databases.
RESULTS: A total of 19 articles were included addressing the following diseases: 7 systemic lupus erythematosus, 6 Behcet disease, 4 ankylosing spondylitis, 2 rheumatoid arthritis, 2
dermatomyositis and one gout. Systemic lupus erythematosus clearly affects gonadal function impairing spermatogenesis mainly due to antisperm antibodies and cyclophosphamide therapy. Behcet disease, gout and ankylosing spondylitis patients, including those under anti-TNF therapy in the latter disease, do not seem to have reduced fertility whereas in dermatomyositis, the fertility potential is hampered by disease activity and by alkylating agents. Data regarding rheumatoid arthritis is scarce, gonadal dysfunction observed as consequence of disease activity and antisperm antibodies.

CONCLUSIONS: Reduced fertility potential is not uncommon. Its frequency and severity vary among the different rheumatic diseases. Permanent infertility is rare and often associated with alkylating agent therapy.


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291.
The effect of epilepsy and antiepileptic drugs on sexual, reproductive and gonadal health of adults with epilepsy.
Hamed S.A.

Embase
[Review]
AN: 609209564
ABSTRACT: Epilepsy is a common chronic medical illness. Hyposexuality is the most frequent abnormality in men and women with epilepsy. In men with epilepsy, hypoandrogenimia, hypogonadism and sperm abnormalities are common. Testicular atrophy was also infrequently reported. In women with epilepsy, hyperandrogenism, polycystic ovaries (PCOs) and PCO syndrome are frequent. Decreased serum free testosterone, dehydroepiandrosterone levels, free androgen index and free testosterone/leutinizing hormone (LH) ratio and increased sex hormone binding globulin, estradiol, prolactin, LH, follicle stimulating hormone (FSH) levels and LH/FSH ratio are common with epilepsy. Disturbance of central and/or peripheral control of hypothalamic-pituitary-gonadal axis and alteration of central neurotransmitters (GABA, glutamate and serotonin) by epileptic discharges or antiepileptic drugs (AEDs), direct gonadal toxicity by AEDs and psychiatric/psychosocial factors are all incriminated in sexual, reproductive and gonadal abnormalities associated with epilepsy. Patients may benefit from multidisplinary evaluation, tight seizure control, change the AED, androgen therapy, genital vasodilators, L-carnitine supplementation and psychotherapy. Copyright © 2016 Informa UK Limited, trading as Taylor & Francis Group.

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20160704

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292.
Relationship of each anterior pituitary hormone deficiency to the size of non-functioning pituitary adenoma in the hospitalized patients.
Mukai K., Kitamura T., Tamada D., Murata M., Otsuki M., Shimomura I.

Embase
Non-functioning pituitary adenoma (NFPA) is often associated with hypopituitarism. Diagnosis of hypopituitarism is important because of its poor prognosis and low quality of life. Among hypopituitarism, it is difficult to diagnose secondary adrenocortical insufficiency and GH deficiency without hormone stimulation test. Therefore, the aim of our study was to identify patients with NFPA who require more careful endocrinological examination. We examined the relationship between NFPA size and the prevalence of each hypopituitarism or the response of each anterior pituitary hormone by insulin tolerance test, LHRH test and TRH test. We studied 63 patients with NFPA admitted for evaluation of pituitary function and surgical indication. They were classified into three groups by tumor diameter. The prevalence of GH deficiency, male secondary hypogonadism, secondary hypothyroidism and PRL deficiency were higher in the group of larger tumor diameter (p<0.0001, p<0.05, p<0.05 and p<0.05, respectively). However, that of secondary adrenocortical insufficiency only tended to be higher (p=0.07). In the group with small NFPA (less than 20 mm), the prevalence of secondary adrenocortical insufficiency was 38% although those of GH deficiency, male secondary hypogonadism, secondary hypothyroidism and PRL deficiency were 0%, 0% and 8% and 9%, respectively. Anterior pituitary hormone responses except TSH had significantly negative correlation with tumor diameter (ACTH: r=-0.40, GH: r=-0.57, LH: r=-0.69, FSH: r=-0.46, PRL: r=-0.36). The results suggested physicians should proactively suspect GH deficiency, male secondary hypogonadism and secondary hypothyroidism in patients with larger NFPA. On the other hand, adrenocortical function should be examined even in patients with small NFPA. Copyright © 2016 The Japan Endocrine Society.
The most effective anti-inflammatory drugs used to treat patients with airways disease are topical glucocorticosteroids (GCs). These act on virtually all cells within the airway to suppress airway inflammation or prevent the recruitment of inflammatory cells into the airway. They also have profound effects on airway structural cells to reverse the effects of disease on their function. Glucorticosteroids act via specific receptors—the glucocorticosteroid receptor (GR)—which are a member of the nuclear receptor family. As such, many of the important actions of GCs are to modulate gene transcription through a number of distinct and complementary mechanisms. Targets genes include most inflammatory mediators such as chemokines, cytokines, growth factors and their receptors. GCs delivered by the inhaled route are very effective for most patients and have few systemic side effects. However, in some patients, even high doses of topical or even systemic GCs fail to control their disease. A number of mechanisms relating to inflammation have been reported to be responsible for the failure of these patients to respond correctly to GCs and these provide insight into GC actions within the airways. In these patients, the side-effect profile of GCs prevent continued use of high doses and new drugs are needed for these patients. Targeting the defective pathways associated with GC function in these patients may also reactivate GC responsiveness. Copyright © Springer International Publishing AG 2016.
Hypogonadism attributable to males with metabolic syndrome was observed in automechanics occupationally exposed to mixed chemicals accompanied by oxidative stress (OS). We evaluated association between testosterone, OS biomarkers, enzymatic and non-enzymatic antioxidants in normal weight automechanics in Ibadan. This was a prospective cross sectional study involving 100 normal weight males aged 18 - 60 years. They were 50 automechanics in Ibadan, age and anthropometry matched with 50 eugonadic males from University College Hospital and environs (controls). Demographic, anthropometry, social habits and dietary history were obtained by standard methods. Blood (10mL) was collected and serum/plasma was used for biochemical analyses. Enzymatic antioxidants (catalase, glutathione peroxidase, superoxide dismutase (SOD) and glutathione -S- transferase (GST); non-enzymatic antioxidants (reduced glutathione (GSH), selenium and zinc), OS biomarkers (hydrogen peroxide (H2O2), malondialdehyde (MDA), total antioxidant capacity (TAC), total plasma peroxides (TPP) and oxidative Stress index (OSI) were estimated spectrophotometrically. Testosterone was assayed by enzyme immunoassay method (Dialab, Austria). Student's t-test, Chi-square test and multiple regression were used for comparisons, associations and relationships respectively, which were significant at P<0.05. Testosterone, TPP, OSI, GST, MDA, H2O2, selenium and zinc concentrations were significantly higher while catalase and SOD concentrations were lower in automechanics than controls (P<0.05). However, testosterone levels in both groups were within the normal reference interval. TAC, OSI and GSH had significantly negative relationship while TPP had positive relationship with years at occupation in automechanics only (P<0.05). Automechanics may have OS but not hypogonadism probably due to increased antioxidant intake. Copyright © 2016, Ibadan Biomedical Communications Group. All rights reserved.
295.

Endogenous, very small embryonic-like stem cells: Critical review, therapeutic potential and a look ahead.

Bhartiya D., Shaikh A., Anand S., Patel H., Kapoor S., Sriraman K., Parte S., Unni S.

Embase

Human Reproduction Update. 23 (1) (pp 1-36), 2016. Date of Publication: 2016.

[Article]

AN: 614355774

BACKGROUND: Both pluripotent very small embryonic-like stem cells (VSELs) and induced pluripotent stem (iPS) cells were reported in 2006. In 2012, a Nobel Prize was awarded for iPS technology whereas even today the very existence of VSELs is not well accepted. The underlying reason is that VSELs exist in low numbers, remain dormant under homeostatic conditions, are very small in size and do not pellet down at 250-280g. The VSELs maintain life-long tissue homeostasis, serve as a backup pool for adult stem cells and are mobilized under stress conditions. An imbalance in VSELs function (uncontrolled proliferation) may result in cancer.

SEARCH METHODS: The electronic database 'Medline/Pubmed' was systematically searched with the subject heading term 'very small embryonic-like stem cells'. OBJECTIVE AND RATIONALE: The most primitive stem cells that undergo asymmetric cell divisions to self-renew and give rise to progenitors still remain elusive in the hematopoietic system and testes, while the presence of stem cells in ovary is still being debated. We propose to review the available literature on VSELs, the methods of their isolation and characterization, their ontogeny, how they
compare with embryonic stem (ES) cells, primordial germ cells (PGCs) and iPS cells, and their role in maintaining tissue homeostasis. The review includes a look ahead on how VSELs will result in paradigm shifts in basic reproductive biology. OUTCOMES: Adult tissue-specific stem cells including hematopoietic, spermatogONial, ovarian and mesenchymal stem cells have good proliferation potential and are indeed committed progenitors (with cytoplasmic OCT-4), which arise by asymmetric cell divisions of pluripotent VSELs (with nuclear OCT-4). VSELs are the most primitive stem cells and postulated to be an overlapping population with the PGCs. Rather than migrating only to the gonads, PGCs migrate and survive in various adult body organs throughout life as VSELs. VSELs express both pluripotent and PGC-specific markers and are epigenetically and developmentally more mature compared with ES cells obtained from the inner cell mass of a blastocyst-stage embryo. As a result, VSELs readily differentiate into three embryonic germ layers and spontaneously give rise to both sperm and oocytes in vitro. Like PGCs, VSELs do not divide readily in culture, nor produce teratoma or integrate in the developing embryo. But this property of being relatively quiescent allows endogenous VSELs to survive various kinds of toxic insults. VSELs that survive oncotherapy can be targeted to induce endogenous regeneration of non-functional gonads. Transplanting healthy niche (mesenchymal) cells have resulted in improved gonadal function and live births. WIDER IMPLICATIONS: Being quiescent, VSELs possibly do not accumulate genomic (nuclear or mitochondrial) mutations and thus may be ideal endogenous, pluripotent stem cell candidates for regenerative and reproductive medicine. The presence of VSELs in adult gonads and the fact that they survive oncotherapy may obviate the need to bank gonadal tissue for fertility preservation prior to oncotherapy. VSELs and their ability to undergo spermatogenesis/ne-oogenesis in the presence of a healthy niche will help identify newer strategies toward fertility restoration in cancer survivors, delaying menopause and also enabling aged mothers to have better quality eggs. Copyright © The Author 2016.

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Publisher
Oxford University Press (E-mail: jnl.info@oup.co.uk)
Effect of metformin on semen quality.
Banihani S.A.
Embase
[Review]
AN: 614565949
Various studies have linked metformin, a universally antidiabetic drug, with semen quality; however, such a direct link has not been established. This review systematically addresses and summarizes the effect of metformin on semen quality, particularly sperm function. We searched the MEDLINE electronic database for English articles and abstracts containing the key words 'metformin' and 'sperm', and relevant articles were reviewed. In summary, metformin appears to have improved and provided positive impact on sperm quality. This effect may be due to the ability of metformin to reduce oxidative stress and lipid peroxidation, enhance 5'-AMP activated protein kinase activity, and restore the normal levels of pituitary-gonadal hormones. However, further clinical research is still necessary to confirm such effect. Copyright © 2016, Faculdade de Ciencias Farmaceuticas (Biblioteca). All rights reserved.
Iron overload detection using pituitary and hepatic MRI in thalassemic patients having short stature and hypogonadism.
Embase
Endocrine Research. 41 (2) (pp 81-88), 2016. Date of Publication: 02 Apr 2016.
[Article]
AN: 607520936
ABSTRACT: Objective: to assess the growth and pubertal development among a group of patients with beta-Thalassemia Major (beta-TM) and to evaluate the role of the pituitary gland and liver MRI signal intensity (SI) reduction in assessing and predicting the clinical severity of growth and pubertal dysfunctions. Methods: Thirty-eight patients with beta-TM were examined and divided into two groups: Group I patients were of normal height and puberty and Group II patients had short statures and hypogonadism. Laboratory investigations included serum ferritin, LH, FSH, prolactin, TSH, and basal and dynamic growth hormones. Pituitary and liver MRIs were performed to assess the pituitary to fat (P/F) and liver to muscle (L/M) signal intensities (SI), respectively. Fifteen healthy and sex- and age-matched subjects were included as controls. Results: Both patient groups had significantly elevated serum ferritin and significantly decreased prolactin and IGF1 compared to control subjects. Group II showed a significant reduction in LH, FSH, and IGF1 and a significant increase in ferritin in comparison with Group I and the control group, and it had a highly significant reduction in both P/F and L/M SI in comparison with Group I (p<0.001 and 0.008, respectively). The reduced P/F ratio was significantly correlated with FSH and LH, and a cutoff for a P/F ratio >=0.94 was obtained to differentiate between Group I and II. Conclusion: MRI in conjunction with the P/F signal intensity ratio is a useful and noninvasive tool for the early diagnosis of pituitary iron overload. Copyright © 2016 Taylor & Francis.
Controversial effects of exogenous testosterone on cardiovascular diseases.
Al-Khazaali A., Arora R., Muttar S.
Embase
American Journal of Therapeutics. 23 (6) (pp e1504-e1513), 2016. Date of Publication: 28 Nov 2016.
[Article]
AN: 61333906
The use of testosterone (T) among men aged 40 years or older was increased more than 3 times from 0.81% in 2001 to 2.91% in 2011. Until recently, the majority of the studies did not show any increased cardiovascular (CV) risk by using T in male patients with hypogonadism. What is more, some studies had observed a protective effect of using T against CV diseases. However, in 2010, a randomized clinical trial (RCT) was intended to study the advantage of T gel in older men with limitations in mobility; the study was stopped due to unexpected high prevalence of CV adverse outcome. These findings were confirmed by 2 other studies published in November of 2013 and January of 2014. Consequently, the Food and Drug Administration (FDA) had announced in January 2014 that it will reassess the safety of those treatments. Meanwhile, the agency had not reached to a definitive conclusion that FDA-approved testosterone therapy raises the risk of stroke, heart attack, or death. A report released in the broadcast of the NBC Nightly News in
September of this year that the FDA says there's little evidence that T boosting drugs taken by millions of American men are actually effective. NBC notes that the agency also pointed out that it was not convinced that they carry serious risk either. The condition has been marketed as low 'T', and the medications are offered to help with low sex drive and fatigue among some men, notes NBC. The European Medicines Agency EMA's Pharmacovigilance Risk Assessment Committee has also responded to the concern of potential CV adverse outcomes associated with the use of T, and they have concluded in their October meeting of this year that the use of T in men who do not produce enough T raises the risk of heart diseases. In our review, we highlighted the association between exogenous T and major adverse CV outcomes. Additionally, we focused on the interplay between exogenous T and some endocrine abnormalities such as diabetes mellitus type 2, metabolic syndrome, dyslipidemia, and obesity. Copyright © 2015 Wolters Kluwer Health, Inc.


Status EMBASE

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Publisher Lippincott Williams and Wilkins (E-mail: kathiest.clai@apta.org)

Date Created 20161222

Year of Publication 2016

299.

Exercise improves the effects of testosterone replacement therapy and the durability of response after cessation of treatment: A pilot randomized controlled trial.

The effects of the combination of exercise and TRT on symptoms of late-onset hypogonadism (LOH) and the durability of response after cessation of TRT were investigated. A total of fifty patients with erectile dysfunction (ED) who had a sedentary lifestyle and low serum total testosterone (T) levels were enrolled and followed for 20 weeks. Patients were randomly divided into two groups; all of them received T gel for 12 weeks and it was discontinued for 8 weeks. Patients assigned to Group II were offered a supervised exercise program for 20 weeks. Measurement of serological testing was performed and self-assessment questionnaires and Global Assessment Question (GAQ) were asked. Baseline characteristics and the initial symptom scores showed no significant difference between the two groups. Serum total T levels and the symptom scores were increased at 12 weeks in both groups, and Group II showed better results with statistical significance. There was a decrease in T levels and worsening of symptom scores at week 20 compared to week 12 in both groups, and Group II showed better results with statistical significance. On the GAQ, Group II showed higher ratio of "yes" at week 12 and the same tendency was sustained at week 20 with significant difference between two groups. The combination of exercise and TRT showed significant improvements in serum T levels and LOH symptoms compared to TRT alone. In addition, these improvements were maintained in the combination group with continuous exercise, even after cessation of TRT.
Effect of oral methadone on ECG characteristics and endocrine hormonal changes and their inter-relationship.

Bonakdaran S., Daloe M.H.Z., Manteghi A.A., Akbarirad M., Firoozi A., Akbarirad F.

Endocrine, Metabolic and Immune Disorders - Drug Targets. 16 (3) (pp 168-173), 2016. Date of Publication: 2016.

Introduction: Methadone is the most common opioid in use for opioid substitution therapy. The relation of methadone and electrocardiographic findings is nearly well known while the relationship between its electrocardiographic indexes and hormonal changes is not well recognized. Objective: To evaluate the hormonal changes in patients who are taking methadone maintenance treatment (MMT) and its effects on electrocardiographic indexes, in comparison with healthy control groups. Patients and Methods: 40 patients receiving MMT therapy for at least last six months and 40 healthy subjects were enrolled in the study. Serum estradiol, testosterone, luteinizing hormone, follicle stimulating hormone and thyroid function tests were measured. Mean QT Interval, P-R Interval (PRI) and QRS duration were also documented in maximum. Results: There were no significant differences in hormonal parameters between MMT and control groups. No significant relation was found between hormonal parameters, dose and duration of methadone usage in patients group. QTc was significantly higher in methadone users than control groups. QTc had a significant negative correlation with Testosterone level ($r=-0.581$, $P=0.007$) in males. Significant difference was found between PRI in patients and control groups ($P=0.007$).

Conclusion: Electrocardiographic changes are an important complication of methadone that seems to be related to low testosterone level in men. Copyright © 2016 Bentham Science Publishers.

Status

EMBASE

Institution
Enclomiphene citrate for the treatment of secondary male hypogonadism.
Rodriguez K.M., Pastuszak A.W., Lipshultz L.I.

[Article]
AN: 611100168

ABSTRACT: Introduction: Hypogonadism is a growing concern in an aging male population. Historically treated using exogenous testosterone, concerns about possible adverse effects of testosterone have led physicians to seek alternative treatment approaches. Areas covered: Enclomiphene citrate is the trans isomer of clomiphene citrate, a non-steroidal estrogen receptor antagonist that is FDA-approved for the treatment of ovarian dysfunction in women. Clomiphene citrate has also been used off-label for many years to treat secondary male hypogonadism, particularly in the setting of male infertility. Here we review the literature examining the efficacy and safety of enclomiphene citrate in the setting of androgen deficiency. Expert opinion: Initial results support the conclusion that enclomiphene citrate increases serum testosterone levels by raising luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, without negatively
impacting semen parameters. The ability to treat testosterone deficiency in men while maintaining fertility supports a role for enclomiphene citrate in the treatment of men in whom testosterone therapy is not a suitable option. Copyright © 2016 Informa UK Limited, trading as Taylor & Francis Group.

PMID

Status
EMBASE

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Publisher
Taylor and Francis Ltd (E-mail: healthcare.enquiries@informa.com)

Date Created
20160708

Year of Publication
2016

302.
Efficacy of crizotinib in first-line treatment of adults with ALK-positive advanced NSCLC.
Zhang Y.-C., Zhou Q., Wu Y.-L.

Embase
[Article]
AN: 611286648

ABSTRACT: Introduction: The treatment of advanced non-small cell lung cancer (NSCLC) has evolved from palliative cytotoxic chemotherapy to precise medicine based on genetic alternations over the last decade. Anaplastic lymphoma kinase (ALK) rearrangement characterizes a molecular subset of NSCLC with an impressive response to crizotinib. Areas covered: To analyze the efficacy of crizotinib in first-line treatment of adults with advanced ALK-positive NSCLC,
updated data on development and recent advances of first-line crizotinib in this subset population are reviewed. Expert opinion: To date, crizotinib should be established as a standard of care in previously untreated advanced NSCLC with ALK-rearrangement. However, the efficacy of first-line crizotinib is limited by acquired resistance. Second generation ALK inhibitors have demonstrated clinical activity in both crizotinib-refractory and crizotinib naive setting. How to maximize first-line benefit for advanced ALK-positive NSCLC remains challenging. Combinational strategy, advances in companion diagnostics and optimization of ALK inhibitors might contribute to improve outcome in this subset of patients in future. Copyright © 2016 Informa UK Limited, trading as Taylor & Francis Group.


Status EMBASE

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Publisher Taylor and Francis Ltd (E-mail: healthcare.enquiries@informa.com)

Date Created 20160722

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303.
The current management of Turner Syndrome.
Kriksciuniene R., Zilaitiene B., Verkauskiene R.

Embase
Minerva Endocrinologica. 41 (1) (pp 105-121), 2016. Date of Publication: March 2016.
[Review]
AN: 612962650

Turner Syndrome (TS) is a rare disease, with the incidence of 1 of 2500 life born females. Characteristic features are: growth retardation, gonadal dysgenesis and impairment, congenital
and acquired cardiovascular disorders. New management possibilities in Turner Syndrome are coming along with the new scientific evidence on the pathogenesis of TS developmental, metabolic, cardiovascular and reproductive issues. Attitude to the growth retardation treatment and hormone replacement therapy is changing. The effectiveness of additional androgen doses for growth improvement and low estrogen doses in the early childhood for better puberty induction and metabolic outcomes has been demonstrated recently. There are some new concerns about pregnancy induced progression of cardiovascular pathology in TS. Inadequate follow-up despite strict and clear guidelines of TS patients is still an issue in the health care system in many countries. This rare disorder requires multidiscipline approach of experienced professionals. The aim of this review is to overview recent studies evaluating TS, to focus on the possibilities to avoid crucial outcomes of this disorder and to improve management and follow-up.

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Second Malignant Neoplasms and Cause of Death in Patients With Germ Cell Cancer: A Danish Nationwide Cohort Study.


Embase
Importance: Patients given systemic treatment for testicular germ cell cancer (GCC) are at increased risk for a second malignant neoplasm (SMN). Previous studies on SMN and causes of death lacked information on the exact treatment applied or were based on patients receiving former treatment options. Objective: To evaluate the treatment-specific risks for SMN and death in a nationwide population-based cohort of patients with GCC treated with current standard regimens.

Design, Setting, and Participants: This study examined a Danish nationwide cohort of 5190 men with GCC who entered the Danish Testicular Cancer database between January 1, 1984, and December 31, 2007. Treatment results were compared with a randomly sampled, age-stratified, population-based control group. Cases of gonadal and extragonadal primary were included in the nationwide cohort. The treatments were surveillance only; retroperitoneal radiotherapy (RT); bleomycin, etoposide, and cisplatin (BEP); or more than 1 line of treatment (MTOL).

Main Outcomes and Measures: Cumulative incidence and hazard ratios (HRs) for SMN and death calculated by the Cox proportional hazards model were compared with those of age-matched controls.

Results: The study population comprised 2804 patients with seminoma and 2386 with nonseminoma. The median follow-up was 14.4 years (interquartile range, 8.6-20.5 years). The 20-year cumulative incidence of SMN with death as a competing risk was 7.8% (surveillance), 7.6% (BEP), 13.5% (RT), 9.2% (MTOL), and 7.0% (controls). We found no increased risk for SMN after surveillance, while the HRs were 1.7 (95% CI, 1.4-2.0), 1.8 (95% CI, 1.5-2.3), and 3.7 (95% CI, 2.5-5.5), respectively, after BEP, RT, and MTOL. Mortality owing to non-GCC causes was decreased after surveillance, but increased by 1.3 times after BEP and RT and by 2.6 times after MTOL. Excess mortality due to SMN was found after BEP (HR, 1.6; 95% CI, 1.2-2.2), RT (HR, 2.1; 95% CI, 1.5-2.9), and MTOL (HR, 5.8; 95% CI, 3.6-9.6).

Conclusions and Relevance: We found no increased risk for SMN or death among patients undergoing surveillance only. The risks for SMN and death due to SMN were increased after BEP alone, RT alone, and MTOL. Approaches to define patients who might benefit from less intensive treatment are needed.

Hypogonadotropic Hypogonadism in Non-Functioning Pituitary Adenomas: Impact of Intervention.
Monteiro D.M., Freitas P., Vieira R., Carvalho D.
Embase
[Article In Press]
AN: 614484451
Purpose To determine the prevalence of hypogonadotropic hypogonadism (HH) among patients with non-functioning pituitary adenomas (NFPA) and the post-surgery outcome on pituitary gonadotropins secretion (PGS); to determine the prevalence of erectile dysfunction (ED) on male patients with NFPA, to evaluate the impact of testosterone replacement therapy (TRT) in those with HH. Methods Retrospective evaluation of gonadal function in 109 NFPA patients (45 males), with a mean age of 51.8 years, diagnosed on the last 10 years. ED questionnaire applied to 34 male patients. Results Male patients with NFPA were significantly older (males 58.1+/−15.8 vs. females 47.4+/−16.94; p=0.001). Most patients had macroadenomas (67%; p=0.001) and only a minority were incidentalomas (19%; p<0.001). Prevalence of HH was 40% (60% on males, 25% on females; p<0.001). Surgery was performed in 54% of all patients (71% of males, 42% of females; p<0.003). After intervention, 14% became HH, 69% maintained previous function and 17% improved. On the questionnaire, 76% reported having ED, 54% of which had HH and 21% were under TRT. Of the patients under TRT, 79% still had ED. Median age of patients with ED was significantly higher [with ED 65 vs. without 49 years; p=0.012]. There was no BMI difference between patients with or without TRT (28.0 vs. 27.4 Kg/m2). Conclusions NFPA was more frequent in older rather than younger patients. Males were older, had more HH and surgery. There was no significant improvement of pituitary function with surgery (17%) and 13% became iatrogenic HH. TRT had a low efficacy to improve ED in these patients. Copyright © 2016, Georg Thieme Verlag KG. All rights reserved.

Status
ARTICLE IN PRESS

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Publisher
Georg Thieme Verlag (E-mail: kunden.service@thieme.de)

Date Created
20170222

Year of Publication
2016
A subset of men with age-related decline in testosterone have gonadotroph autoantibodies.


Embase
[Article]
AN: 614272744

Context: Age-related decline in serum testosterone (T) is being increasingly diagnosed. In most men, it associates with low or inappropriately normal gonadotropin levels, which suggests a hypothalamic-pituitary etiology. Autoantibodies against adenohypophyseal cells have been associated with pituitary dysfunction; however, the prevalence of pituitary autoimmunity in this age-related T decline has not been assessed.

Objectives: This is a proof-of-concept study with the objective of determining the prevalence of antibodies to gonadotrophs in older men with age-related low T and compare it with healthy young and older eugonadal men.

Study Design: This is a cross-sectional case-control study of 182 men. Cases included 100 older men (>=65 years) with age-related low T levels; the control groups were composed of 50 young and 32 older healthy eugonadal men. Serum antibodies against the anterior pituitary gland were measured using a two-step approach: 1) single indirect immunofluorescence (ie, participant serum only) to determine the pattern of cytosolic staining; and 2) double indirect immunofluorescence (ie, participant serum plus a commercial adenohypophyseal hormone antibody) to identify the anterior pituitary cell type recognized by the patient's antibodies.

Results: In participants with positive antipituitary antibodies, the granular cytosolic pattern (highly predictive of pituitary autoimmunity) was only seen in older men with age-related low T (4%) and none in control groups (0%, P = .001). Double indirect immunofluorescence confirmed that pituitary antibodies were exclusively directed against the gonadotrophs.

Conclusion: A subset of older men with age-related low T levels have specific antibodies against the gonadotrophs. Whether these antibodies are pathogenic and contributory to the age-related decline in T remains to be established. Copyright © 2016 by the Endocrine Society.
307.
Effects of testosterone therapy on cognitive function in aging: A systematic review.
Hua J.T., Hildreth K.L., Pelak V.S.
Embase
Cognitive and Behavioral Neurology. 29 (3) (pp 122-138), 2016. Date of Publication: 01 Sep 2016.
[Review]
AN: 612590300
Endogenous testosterone in the aging man has been scrutinized extensively in regard to its effects on performance in many cognitive domains, especially verbal fluency, visuospatial and visuoperceptual abilities, memory, and executive function. Studies of testosterone supplementation have sought to identify potential cognitive improvements in men with and without baseline cognitive impairment, and have had a wide range of results. The variability in outcomes is likely related, in part, to the lack of consensus on methods for testosterone measurement and supplementation and, in part, to the disparate measures of cognitive function used in randomized controlled studies. Despite the limitations imposed by such inconsistent methods, promising associations have been found between cognition and testosterone supplementation in both
eugonadal men and men with low testosterone levels, with and without baseline cognitive dysfunction. This systematic review highlights the cognitive measures used in and the outcomes of existing studies of testosterone and cognition in aging men. The review suggests that larger studies and a more standardized approach to assessment will be needed before we can fully understand and realize sustained benefits from testosterone supplementation in the elderly male population, particularly given the substantial increase in testosterone supplementation in clinical practice. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.


Status EMBASE

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Publisher Lippincott Williams and Wilkins (E-mail: kathiest.clai@apta.org)

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Year of Publication 2016

308.
Hypogonadism in patients with chronic obstructive pulmonary disease: relationship with airflow limitation, muscle weakness and systemic inflammation.
Embase
Alexandria Journal of Medicine. 52 (1) (pp 27-33), 2016. Date of Publication: 01 Mar 2016.
[Article]
AN: 602518990
Objectives To determine the prevalence of hypogonadism in male patients with Chronic obstructive pulmonary diseases (COPD), and to study its impact on skeletal muscle dysfunction and assess the effect of systemic markers of inflammation on testosterone level and muscle function. The study included 50 stable male COPD patients and 30 controls. Methods Both groups were subjected to the following measurements; inflammatory markers levels (high-sensitivity C-reactive protein (hs-CRP) and interleukin - 6 (IL-6)), sex hormones including; serum total (T) and free testosterone (FT), sex hormone binding globulins (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and 17beta estradiol levels (E2), the exercise capacity (6-minute walk distance (6MWT)) and quadriceps muscle force (One repetition maximum (1RM) and EMG). COPD patients underwent spirometry. Results There was a higher prevalence of hypogonadism in COPD patients than the controls (62% versus 17%). There was a significant negative correlation between serum testosterone levels (T and FT) and the severity of airway obstruction. Quadriceps muscle force and the exercise capacity were significantly lower in COPD patients than controls but they showed no correlation with the testosterone level. Inflammatory markers were significantly higher in COPD patients compared to controls and showed a significant correlation with the severity of airflow obstruction. The higher inflammatory markers levels were related to more muscle weakness as hs-CRP was inversely correlated with the quadriceps strength and exercise capacity, while IL-6 was inversely correlated to quadriceps strength only. Conclusion Hypogonadism is highly prevalent in clinically stable COPD patients and is particularly related to the severity of the airway obstruction. Systemic inflammation is present in stable COPD patients and its intensity is related to the severity of the underlying disease and it predisposes to skeletal muscle weakness and exercise intolerance. However, we failed to find a significant association between hypogonadism and muscle weakness or systemic inflammation. Copyright © 2015 The Authors
Effects of dutasteride on serum free-testosterone and clinical significance of testosterone changes.
Enatsu N., Miyake H., Haraguchi T., Chiba K., Fujisawa M.
Embase
Andrologia. 48 (10) (pp 1195-1201), 2016. Date of Publication: 01 Dec 2016.
[Article]
AN: 609432888
Sixty-two patients with benign prostate hyperplasia (BPH) who were being treated with dutasteride participated in this study. Prostate volume, uroflowmetry, blood tests, the International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF-5) were determined before and 1, 3 and 12 months after the treatment with dutasteride. Patients were divided into two groups based on changes in serum testosterone after 1 month: Group A (>20% increase; n = 33) or Group B (<20% increase; n = 29). Serum free-testosterone levels were 20.4% higher after 1 month and remained constant thereafter. When Groups A and B were compared, baseline free-testosterone levels were significantly lower in Group A, IPSS QOL was significantly better in Group A at 3 and 12 months, and no significant differences were observed in uroflowmetry, prostate volume, IPSS or IIEF-5. A univariate analysis identified serum free-testosterone levels and the IPSS storage symptom subscore as significant factors influencing IPSS QOL at 12 months, and only the IPSS storage symptom subscore appeared to be independently related to IPSS QOL. These results indicate that dutasteride increases serum free-testosterone levels in BPH patients, particularly with low baseline free-testosterone levels, and the increase in free-testosterone may have further add-on impacts on their urinary tract symptoms.

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PMID
Status
EMBASE
Institution
Hormonal and echocardiographic abnormalities in adult patients with sickle-cell anemia in Bahrain.
Garadah T.S., Jaradat A.A., Alalawi M.E., Hassan A.B.
Embase
[Article]
AN: 614218126
Background: Adrenal, thyroid, and parathyroid gland hormonal changes are recognized in children with homozygous (HbSS) sickle-cell anemia (SCA), but are not clear in adult patients with SCA. Aim: To assess the metabolic and endocrine abnormalities in adult patients with SCA and evaluate left ventricular (LV) systolic and diastolic functions compared with patients with no SCA and further study the relationship between serum levels of cortisol, free thyroxine (T4), and testosterone with serum ferritin. Materials and methods: The study was conducted on 82 patients with adult HbSS SCA compared with a sex- and age-matched control group. The serum levels of cortisol, parathyroid hormone (PTH), testosterone, thyroid-stimulating hormone (TSH), and free T4 were compared. Blood levels of hemoglobin, reticulocyte count, lactate dehydrogenase (LDH), calcium, alkaline phosphatase (ALP), vitamin D3, and ferritin were also compared. Pulsed Doppler echo was performed to evaluate the LV mass, wall thickness, and cavity dimensions with diastolic filling velocities of early (E) and atrial (A) waves. Biometric data were analyzed as mean +/- standard deviation between the two groups. Multiple regression analysis was performed between serum levels of ferritin as independent variable and testosterone, cortisol, and thyroid hormones. Results: A total of 82 adult patients with HbSS SCA were enrolled who had a mean age of 21+/-5.7 years, with 51 males (62%). Patients with SCA compared with the control group
had significantly lower hemoglobin, body mass index, cortisol, vitamin D3, testosterone, and T4. Furthermore, there were significantly high levels of reticulocyte count, PTH, TSH, ferritin, LDH, ALP, and uric acid. The incidence of subclinical hypothyroidism and adrenal insufficiency was 7% and 4.8%, respectively, with hypogonadism 9.8% and vitamin D3 deficiency 61%. There were inverse relationships between ferritin as independent variable and serum levels of testosterone, T4, and cortisol, with regression coefficients of -0.49 (P<0.001), -0.33 (P<0.001), and -0.11 (P<0.92), respectively. Conclusion: Patients with adult SCA had a high prevalence of in vivo hypoadrenalism (4.8%), hypogonadism (9.8%), and hypothyroidism (7%). There were significant inverse relationships between serum ferritin as independent variable and cortisol, testosterone, and T4. Pulsed Doppler echocardiography showed increased LV mass, with a restrictive LV diastolic pattern suggestive of diastolic dysfunction. Copyright © 2016 Garadah et al.

Lower insulin sensitivity is related to lower relative muscle cross-sectional area, lower muscle density and lower handgrip force in young and middle aged non-diabetic men.

Objectives: This study investigated whether an association between insulin resistance (IR) and muscle parameters is appreciable in young healthy men, independent of obesity. Furthermore, markers of muscle metabolism and hormones/possible determinants, were explored.

Methods: 358 healthy young men were divided into a less and more insulin sensitive (LIS [age=33.2+/−5.4, BMI=23.4+/−2.3] and MIS [age=35.5+/−5.3, BMI=28.1+/−3.7]) group based on upper and lower quartile of HOMA-IR. Muscle cross-sectional area (CSA), density, handgrip force, serum testosterone, estradiol, SHBG, Vitamin 25(OH)D, creatinine, IGF-1, IGFBP-3 and leptin levels were compared between these groups, correcting for differences in age, physical activity and fat mass. Correlations between HOMA-IR and these parameters, and between muscle measures and biochemical parameters, were calculated.

Results: LIS is related to lower relative muscle CSA, muscle density, muscle/ fat CSA ratio, relative handgrip force and level of physical activity. Furthermore, lower levels in SHBG, testosterone, Vitamin 25(OH)D and higher leptin, IGF-1 & IGFBP-3 levels were observed in LIS. Bio available T, FT, TE2, FE2, bioavailable E2, serum and urinary creatinine levels did not differ between groups.

Conclusion: Differences in muscle performance are already present in healthy men with lower insulin sensitivity and could be possibly modifiable risk factors for the development of type 2 diabetes.

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Prevalence and Etiology of Hypogonadism in Young Men With Chronic Spinal Cord Injury: A Cross-Sectional Analysis From Two University-Based Rehabilitation Centers.
Sullivan S.D., Nash M.S., Tefera E., Tinsley E., Blackman M.R., Groah S.

Embase PM and R. (no pagination), 2016. Date of Publication: April 21, 2016.
[Article In Press]
AN: 614103027

Background: Spinal cord injury (SCI) triggers an accelerated aging process that may include development of hypogonadism, even among younger men with SCI; however, few studies have investigated the prevalence or etiology of hypogonadism in men with SCI. Young men with SCI also are at increased risk for developing metabolic dysfunction after injury, which may be exacerbated by concomitant testosterone (T) deficiency, thus identifying the prevalence and risk factors for T deficiency in men with SCI is important for their long-term health.

Objective: To investigate the prevalence, risk factors, and etiology of T deficiency (hypogonadism) in otherwise-healthy men with chronic, motor complete SCI.

Design: Secondary cross-sectional analysis.

Setting: Rehabilitation research centers in Washington, DC, and Miami, Florida.

Participants: Men (n = 58) aged 18-45 years with chronic (>=1 year), motor complete SCI without comorbidities or use of testosterone therapy.

Methods: Plasma concentrations of hormones were measured with standardized assays. Body composition was assessed with dual-energy x-ray absorptiometry scan.

Main Outcome Measurements: Serum total T and calculated free T.

Results: T deficiency was more common in men after SCI than in a matched cohort of similarly-aged men without SCI (25%, SCI versus 6.7%, non-SCI, . P < .001). The risk of hypogonadism appeared to be increased in men with more extensive injury and with higher percent body fat. The majority of men with SCI with low T had low serum LH levels, suggesting that central suppression of the hypothalamic-pituitary-gonadal axis may be the most common etiology of hypogonadism after SCI.

Conclusions: Hypogonadism is more common in young men with SCI than in similarly aged men without SCI, suggesting that SCI should be identified as a risk factor for T deficiency and that routine screening for hypogonadism should be performed in the SCI population.

Level of Evidence: To be determined. Copyright © 2016 American Academy of Physical Medicine and Rehabilitation.
Systemic lupus erythematosus and prolactin.

Tanev D., Robeva R., Kumanov Ph., Rashkov R., Kolarov Zl.

Embase

Revmatologija (Bulgaria). 24 (2) (pp 25-34), 2016. Date of Publication: 2016.

[Review]

AN: 614043816

Systemic lupus erythematosus (SLE) is a rare autoimmune disease of the connective tissue that affects seven to ten times more often women in comparison to men. The reasons for the overt sex dimorphism are still obscure. Prolactin is a hormone that directly influences gonadal functions and sex steroids production. However, it could also play a significant role as an immune system
modulator. In the present review, the interrelations between the prolactin concentrations, immune system and SLE as well as the potential role of the dopamine agonists in the treatment of SLE have been discussed. Lymphocytes could produce prolactin and prolactin receptors have been found on T-lymphocytes, B-lymphocytes and macrophages. Prolactin could stimulate the cell-mediated and the humoral immune responses. In SLE animals the hormone aggravates the signs of the disease. In humans hyperprolactinemia is more frequent in patients with lupus than in healthy persons, but the studies are still insufficient to draw any conclusions. Dopamine agonists like bromocriptine decrease the prolactin concentrations. Some but not all authors have shown positive effect of this drug on the clinical signs of SLE. Larger studies are necessary to reveal the role of prolactin on the lupus onset, clinical signs and complications. These findings could help in the development of new therapeutic strategies especially in some specific patient groups.

Status
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Publisher
Medical Information Center

Date Created
20170119

Year of Publication
2016

314.
Poor Sleep Quality Predicts Hypogonadal Symptoms and Sexual Dysfunction in Male Nonstandard Shift Workers.
Pastuszak A.W., Moon Y.M., Scovell J., Badal J., Lamb D.J., Link R.E., Lipshultz L.I.
Embase
Urology. (no pagination), 2016. Date of Publication: July 24, 2016.
[Article In Press]
AN: 614092797
Objective: To investigate the impact of sleep quality in hypogonadal symptoms and sexual function in men working nonstandard shifts. Materials and Methods: Men treated at a single andrology clinic between July and October 2014 completed questionnaires assessing sleep quality, hypogonadal symptoms (Androgen Deficiency in the Aging Male [ADAM/qADAM]), and sexual function (International Index of Erectile Function [IIEF]). Serum hormone levels were assessed at the time of survey completion. Results: One hundred eighty-two men were identified as working nonstandard shifts (work that starts before 7 a.m. or after 2 p.m., rotates, or regularly includes hours outside of the standard 7 a.m. to 6 p.m. workday) with a mean +/- SD age of 41.1 +/- 10.8 years. Of men working nonstandard shifts, those with better sleep quality had fewer hypogonadal symptoms and better sexual function. Multivariate regression analysis revealed significant linear associations between sleep quality and qADAM score (P = .008), positive ADAM responses (P = .003), and IIEF score (P = .0004). When comparing individual groups, men who were very satisfied (n = 60) with sleep quality had higher qADAM scores than men who were somewhat dissatisfied (P = .02), and men who were very dissatisfied had significantly lower IIEF scores than men who were very satisfied (P = .001) and somewhat satisfied (P = .005). No associations between sleep quality and mean serum testosterone, free testosterone, estrogen, dehydroepiandrosterone, follicle-stimulating hormone, and luteinizing hormone levels were observed. Conclusion: Men who work nonstandard shifts and have poor sleep quality are at increased risk for hypogonadal symptoms and sexual dysfunction. Copyright © 2016 Elsevier Inc.

Status
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20170119

Year of Publication
2016
Adenomyosis is a benign gynecological disorder associated with abnormal uterine bleeding, dysmenorrhea, dyspareunia and infertility, requiring a life-long management plan through medical or surgical treatment. The choice depends on woman's age, reproductive status and clinical symptoms. However, until now no drug labelled for adenomyosis is available; thus, the present review will focus on medical treatments currently used for adenomyosis and those in development. Adenomyosis may be considered a sex steroid hormone-related disorder associated with an intense inflammatory process. The use of gonadotropin-releasing hormone agonists (GnRH-a) for treating adenomyosis is described blocking the hypothalamic-pituitary-gonadal axis; however, it has long been associated with frequent and intolerable hypoestrogenic side effects. An antiproliferative effect of progestins suggests their use for treating adenomyosis, reducing bleeding and pain. Continuous oral norethisterone acetate or medroxyprogesterone acetate may help to inducing regression of adenomyosis, relief pain and reduce bleeding. The use of vaginal danazol has therapeutic effect on adenomyosis combining progestogenic and anti-inflammatory activity. The intrauterine device releasing levonorgestrel (Lng-IUD) is widely assessed in menorrhagia, and has been shown to be extremely effective in resolving pain and bleeding symptoms associated with adenomyosis. Recent data show a therapeutic effect of dienogest on adenomyosis symptoms. New drugs are under development for the treatment of adenomyosis, such as aromatase inhibitors (AIs) and selective estrogen receptor modulators (SERMs), that produce a hypoestrogenic environment reducing pain, but are correlated with some adverse effects and a recurrence of symptoms after discontinuation of treatment. Selective progesterone receptor modulators (SPRMs) may reduce adenomyosis-associated pelvic pain, by inhibiting endometrial proliferation and suppressing adenomyotic lesion growth, as shown in animal models; however, the long-term effect with SPRMs needs further determination.
316.
Association of Aryl hydrocarbon receptor-related gene variants with the severity of autism spectrum disorders.
Embase
[Article]
AN: 613703629
Exposure to environmental chemicals, such as dioxin, is known to have adverse effects on the homeostasis of gonadal steroids, thereby potentially altering the sexual differentiation of the brain to express autistic traits. Dioxin-like chemicals act on the aryl hydrocarbon receptor (AhR), polymorphisms, and mutations of AhR-related gene may exert pathological influences on sexual differentiation of the brain, causing autistic traits. To ascertain the relationship between AhR-related gene polymorphisms and autism susceptibility, we identified genotypes of them in patients and controls and determined whether there are different gene and genotype distributions between both groups. In addition, to clarify the relationships between the polymorphisms and the severity of autism, we compared the two genotypes of AhR-related genes (rs2066853, rs2228099) with the severity of autistic symptoms. Although no statistically significant difference was found between autism spectrum disorder (ASD) patients and control individuals for the genotypic distribution of any of the polymorphisms studied herein, a significant difference in the total score of severity was observed in rs2228099 polymorphism, suggesting that the polymorphism modifies the severity of ASD symptoms but not ASD susceptibility. Moreover, we found that a significant
difference in the social communication score of severity was observed. These results suggest that the rs2228099 polymorphism is possibly associated with the severity of social communication impairment among the diverse ASD symptoms. Copyright © 2016 Fujisawa, Nishitani, Iwanaga, Matsuzaki, Kawasaki, Tochigi, Sasaki, Kato and Shinohara.

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2016

317.

Embase
[Article In Press]
AN: 613997782
Introduction: There has been renewed interest in the use of subcutaneous testosterone pellets for the treatment of hypogonadism since the introduction of Testopel in 2008 by Slate Pharmaceuticals (Durham, NC, USA). Manufacturer guidelines recommend using two to six pellets; however, in the clinical setting, this is deemed insufficient. This has produced a wide variety of testosterone pellet usage that is not fully understood. Aim: To better understand subcutaneous testosterone pellet implantation practices among members of the Sexual Medicine Society of North America (SMSNA). Methods: A 19-item questionnaire was emailed to the 687 members of the SMSNA. Of the 19 questions, 17 were multiple choice and two required write-in responses. Usage patterns, satisfaction rates, and complication rates were investigated. Main Outcome Measures: Data regarding indications for initiating treatment with Testopel, initial dosage, follow-up of testosterone levels and dose titration, patient tolerance and satisfaction, technique of implantation, and procedural complications were collected. Results: Eighty-seven survey responses were received (12.9%). At initiation of Testopel therapy, 80.5% of respondents would implant at least 10 pellets, whereas only 4.6% would place six to seven pellets and 3.4% would implant fewer than six pellets. Many respondents would determine the starting dose based on some combination of baseline testosterone level and weight, although 24.1% described using a standard starting dose for all patients. All respondents would check testosterone levels within 3 months of initiating therapy, with the vast majority (72.4%) doing so at 1 month. Subsequent dosing of Testopel was not changed in most patients, with 41.4% and 26.4% of respondents reporting that 60% to 80% and 80% to 100% of patients, respectively, remained on their initial dose. Most respondents would re-implant pellets at a 3-month (21.8%) or 4-month (43.7%) interval. High patient satisfaction was described by respondents, with 56.3% finding patients to be satisfied "most times" and 34.5% "almost always.". Conclusion: This study provides insight into the usage of Testopel among members of the SMSNA. We found that the vast majority of specialists use at least 10 pellets at initial implantation, with limited need for subsequent dose adjustments, good durability of response, and high patient satisfaction and tolerability. Copyright © 2016 International Society for Sexual Medicine.
Clinical Characteristics, Health Care Utilization and Costs Among Men with Primary or Secondary Hypogonadism in a US Commercially Insured Population.
Grabner M., Bodhani A., Khandelwal N., Palli S., Bonine N., Khera M.
Embase
[Article In Press]
AN: 613967098
Introduction: Hypogonadism is broadly associated with increases in chronic comorbid conditions and health care costs. Little is known about the specific impact of primary and secondary hypogonadism on health care costs. Aim: To characterize the health care cost and utilization burden of primary and secondary hypogonadism in a population of US men with commercial insurance. Methods: Newly diagnosed patients with . International Classification of Diseases, Ninth Revision, Clinical Modification codes associated with specific medical conditions known to have a high prevalence of testosterone deficiency (ie, relating to primary or secondary hypogonadism) or who had fills for testosterone replacement therapy from January 1, 2007 through April 30, 2013 were identified in administrative claims data from the HealthCore Integrated Research Database. A cohort of patients without hypogonadism was matched on demographics and comorbidities. The matched hypogonadism and non-hypogonadism cohorts (n = 5,777 in each cohort) were compared during a 12-month follow-up period. Main Outcome Measures: Direct health care expenditures and utilization were assessed for all causes and for hypogonadism-related claims. Costs included out-of-pocket patient expenditures and those paid by the insurer. Results: Hypogonadism and matched non-hypogonadism cohorts were similar in demographics (mean age = 50 years) and diagnosed comorbid conditions in the 12 months preceding the index date. In the year after the index date, mean all-cause expenditures for patients with hypogonadism increased by 62% (from $5,425 to $8,813) compared with 25% for the matched controls (from $4,786 to $5,992; . P < .01 for follow-up difference between groups). Approximately 16% of total mean costs ($1,377), primarily outpatient and pharmacy costs, were identifiable as related to hypogonadism. Conclusion: These data from a population of US men
with commercial insurance coverage showed a greater resource use burden for patients with primary and secondary hypogonadism compared with similar patients without hypogonadism. Additional management might be required to address unmet need and decrease the cost burden for patients with hypogonadism. Copyright © 2016 The Authors.

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319.
The reproductive health indices and sex hormone levels in middle-aged and elderly Chinese men.

Embase
Aging Male. 19 (3) (pp 143-147), 2016. Date of Publication: 02 Jul 2016.
[Article]
AN: 610651188

Objective: The aim of this study was to analyze the age-related recession trajectory of reproductive health indices in middle-aged and elderly Chinese men. Methods: A population-based cross-sectional study was conducted in Jiashan County, Zhejiang in 2012. Healthy men between 40 and 80 years of age were considered eligible for the study. Physical examination and the sex hormones were measured. The subjects were assessed based on the 5-item version of the International Index of Erectile Function (IIEF-5) for Erectile Dysfunction (ED), and Aging
Males’ Symptoms (AMS) scale for Symptomatic Late-Onset Hypogonadism (SLOH). Results: TG showed a decrease at age 60 years. Testis volume and TT did not show significant difference among the four age groups; cFT began to decrease at age 50 years and Bio-T decreased faster at age 50 years. SHBG and LH increased faster at age 50 and 70 years, respectively. IIEF5 score decrease faster at age 60 years. AMS scores increased faster at age 70 years. With the increase in age, the symptoms of ED and SLOH became severer. Conclusion: Different indices on reproductive health of men showed turning points at different ages. At first, androgenic sex hormones decreased faster, and then erectile dysfunction got severer, and the last overall male syndromes declined. Copyright © 2016 Informa UK Limited, trading as Taylor & Francis Group.

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320.
Effects of tadalafil treatment combined with physical activity in patients with low onset hypogonadism: results from a not-randomized single arm phase 2 study.
Embase
Aging Male. 19 (3) (pp 155-160), 2016. Date of Publication: 02 Jul 2016.
[Article]
AN: 610258606
Purpose: To investigate a possible relation between penile Doppler ultrasound examination (PDUE) parameters and efficacy of chronic therapy with tadalafil (TAD) combined with a protocol
of aerobic physical activity (PA) in patients with late onset hypogonadism (LOH). Methods: The study evaluated 30 patients consecutively enrolled with LOH and erectile dysfunction which present contraindication to hormonal replacement therapy for concomitant prostate disease. These patients were subjected to a combined protocol with phosphodiesterase V selective inhibitors (TAD 5 mg daily) and aerobic PA. Results: After three months, we observed significant improvements in erectile function [IIEF-5, median (IQR) = 13.0 (7.0-18.0) versus 6.0 (5.0-6.75); p < 0.01] and of the main metabolic [homeostatic model assessment index, median (IQR) = 2.5 (1.62-3.37) versus 3.0 (2.0-3.75); p < 0.01; body mass index, median (IQR) = 27.0 (24.0-28.75) versus 27.5 (24.0-29.5)] and vascular parameters [peak systolic velocity, median (IQR) = 29.5 (24.25-31.0) versus 28.0 (23.0-24.25); acceleration time, median (IQR) = 114 (105.25-134.0) versus 115.0 (106.5-134.0)], assessed by PDUE. Conclusion: PA in association with phosphodiesterase V inhibitors could compensate the effects of hypogonadism on erectile function and facilitate the clinical response to these drugs even in the absence of adequate serum concentrations of total testosterone. Copyright © 2016 Informa UK Limited, trading as Taylor & Francis Group.

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321.
Genetic and epigenetic effects in sex determination.
Gunes S.O., Metin Mahmutoglu A., Agarwal A.
Sex determination is a complex and dynamic process with multiple genetic and environmental causes, in which germ and somatic cells receive various sex-specific features. During the fifth week of fetal life, the bipotential embryonic gonad starts to develop in humans. In the bipotential gonadal tissue, certain cell groups start to differentiate to form the ovaries or testes. Despite considerable efforts and advances in identifying the mechanisms playing a role in sex determination and differentiation, the underlying mechanisms of the exact functions of many genes, gene-gene interactions, and epigenetic modifications that are involved in different stages of this cascade are not completely understood. This review aims at discussing current data on the genetic effects via genes and epigenetic mechanisms that affect the regulation of sex determination.
Preliminary evidence that acute stress moderates basal testosterone's association with retaliatory behavior.


Embase
Hormones and Behavior. (no pagination), 2016. Date of Publication: January 16, 2016.
[Article In Press]
AN: 613877316

A contribution to a special issue on hormones and human competition: Testosterone is theorized to increase retaliation after social provocation. However, empirical evidence in support of these theories is mixed. The present research investigated whether acute stress causally suppresses testosterone's association with retaliation. We also explored sex differences in behavioral responses to acute stress. Thirty-nine participants (51.28% male) were randomly assigned to a high- or low-stress condition. Then participants engaged in 20 one-shot rounds of the ultimatum game, which was used to assess retaliatory behavioral responses to unfair treatment.

Participants provided two saliva samples to measure testosterone and cortisol concentrations - one sample before the stress manipulation, and the second after the ultimatum game (20. minutes post-stressor). Results revealed a positive association between basal testosterone and retaliation in the low-stress condition, but not in the high-stress condition. Further, cortisol concentrations increased in the high- compared to the low-stress condition, and these cortisol changes moderated the association between basal testosterone and retaliation. The associations between basal testosterone and retaliation under varying levels of stress were similar in men and women. However, there was a sex difference in behavioral responses to the stress manipulation that was independent of testosterone. In women, the high-stress condition reduced retaliation compared to the low-stress condition, whereas in men the opposite pattern emerged. Collectively, this study (i) provides preliminary evidence that experimentally manipulated stress blocks basal testosterone's association with retaliation, and (ii) reveals a sex difference in retaliation under varying levels of stress. Discussion focuses on mechanisms, limitations, and the need for follow-up studies with larger sample sizes. Copyright © 2016 Elsevier Inc.

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323.

Standards for Clinical Trials in Male and Female Sexual Dysfunction: I. Phase I to Phase IV Clinical Trial Design.


Embase


[Article]

AN: 613503405

This series of articles outlines standards for clinical trials of treatments for male and female sexual dysfunctions, with a focus on research design and patient-reported outcome assessment. These articles consist of revision, updating, and integration of articles on standards for clinical trials in male and female sexual dysfunction from the 2010 International Consultation on Sexual Medicine developed by the authors as part of the 2015 International Consultation on Sexual Medicine. We are guided in this effort by several principles. In contrast to previous versions of these guidelines, we merge discussion of standards for clinical trials in male and female sexual dysfunction in an integrated approach that emphasizes the common foundational practices that underlie clinical trials in the two settings. We present a common expected standard for clinical trial design in male and female sexual dysfunction, a common rationale for the design of phase I to IV clinical trials, and common considerations for selection of study population and study duration in male and female sexual dysfunction. We present a focused discussion of fundamental principles in patient- (and partner-) reported outcome assessment and complete this series of
articles with specific discussions of selected aspects of clinical trials that are unique to male and to female sexual dysfunction. Our consideration of standards for clinical trials in male and female sexual dysfunction attempts to embody sensitivity to existing and new regulatory guidance and to address implications of the evolution of the diagnosis of sexual dysfunction that have been brought forward in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. The first article in this series focuses on phase I to phase IV clinical trial design considerations. Subsequent articles in this series focus on the measurement of patient-reported outcomes, unique aspects of clinical trial design for men, and unique aspects of clinical trial design for women.

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Introduction

Testosterone deficiency (TD), also known as hypogonadism, is a condition affecting a substantial proportion of men as they age. The diagnosis and management of TD can be challenging and clinicians should be aware of the current literature on this condition. Aim

To review the available literature concerning the diagnosis and management of TD and to provide clinically relevant recommendations from the Fourth International Consultation for Sexual Medicine (ICSM) meeting.

Methods

A literature search was performed using the PubMed database for English-language original and review articles published or e-published up to January 2016. Main Outcome Measures

Levels of evidence (LoEs) and grades of recommendations are provided based on a thorough analysis of the literature and committee consensus.

Results

Recommendations were given for 12 categories of TD: definition, clinical diagnosis, routine measurement, screening questionnaires, laboratory diagnosis, threshold levels for the biochemical diagnosis of TD, prostate cancer, cardiovascular disease, fertility, testosterone (T) formulations, alternatives to T therapy, and adverse events and monitoring. A total of 42 recommendations were made: of these, 16 were unchanged from the Third ICSM and 26 new recommendations were made during this Fourth ICSM. Most of these recommendations were supported by LoEs 2 and 3. Several key new recommendations include the following: (i) the clinical manifestations of TD occur as a result of decreased serum androgen concentrations or activity, regardless of whether there is an identified underlying etiology [LoE = 1, Grade = A]; (ii) symptomatic men with total T levels lower than 12 nmol/L or 350 ng/dL should be treated with T therapy [LoE = 1, Grade = C]; (iii) a trial of T therapy in symptomatic men with total T levels higher than 12 nmol/L or 350 ng/dL can be considered based on clinical presentation [LoE = 3, Grade = C]; (iv) there is no compelling evidence that T treatment increases the risk of developing prostate cancer or that its use is associated with prostate cancer progression [LoE = 1, Grade = C]; and (v) the weight of evidence indicates that T therapy is not associated with increased cardiovascular risk [LoE = 2, Grade = B].

Conclusion

TD is an important condition that can profoundly affect the sexual health of men. We provide guidance regarding its diagnosis and management. Men with TD who receive treatment often experience resolution or improvement in their sexual symptoms and non-sexual health benefits.
Testosterone replacement therapy and voiding dysfunction.
Baas W., Kohler T.S.
Embase
Translational Andrology and Urology. 5 (6) (pp 890-897), 2016. Date of Publication: 2016.
[Review]
AN: 613769226
Testosterone replacement therapy (TRT) represents an increasing popular treatment option for men with late-onset hypogonadism (LOH). Because of unsubstantiated beliefs of testosterone's effect on the prostate, the FDA has recently placed a warning on testosterone products, stating
that TRT may worsen benign prostatic hyperplasia (BPH). Within this review article we have demonstrated the current understanding of the physiology of testosterone and its relationship with prostatic and lower urinary tract physiology. The current evidence suggests that not only does TRT not worsen lower urinary tract symptoms (LUTS), but that hypogonadism itself is an important risk factor for LUTS/BPH. Copyright © Translational Andrology and Urology. All rights reserved.

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326.
Effects of varicocelectomy on serum testosterone.
Whelan P., Levine L.
Embase
Translational Andrology and Urology. 5 (6) (pp 866-876), 2016. Date of Publication: 2016.
[Review]
AN: 613769211
Varicocele is most often surgically repaired due to male infertility, however, has recently been linked to low serum testosterone. This paper serves to review the current literature regarding varicocele and its subsequent repair on serum testosterone. Twenty-eight human studies were identified with fifteen showing improved serum testosterone after repair. The majority of the studies that demonstrated improvement had preoperative testosterone levels that were low or below normal. Additionally, multiple well-designed studies with control groups not undergoing surgical repair demonstrated significant difference between groups. This improvement was less observed in studies with normal preoperative serum testosterone. A majority of these patients
studied were presenting for infertility. It remains to be determined if these findings can be reproduced in men without infertility. The findings suggest that microsurgical varicocele repair can improve serum testosterone in men with low levels preoperatively in appropriately counseled men. It remains to be seen whether varicocele repair can help prevent the development of low testosterone in the future or which patients are at risk of developing low testosterone due to varicocele. Copyright © Translational Andrology and Urology. All rights reserved.

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327.
Testosterone replacement in the infertile man.
Majzoub A., Sabanegh E.

Embase

Translational Andrology and Urology. 5 (6) (pp 859-865), 2016. Date of Publication: 2016.

[Review]

AN: 613769206

Hypogonadism is a common clinical condition affecting men of different age groups. In addition to its sexual consequences, it has several implications posing significant concerns for a man's health and well-being. Recent advances in testosterone (T) supplementation have facilitated hypogonadism treatment. Despite that, patients complaining of infertility or seeking conception are still hindered by the unfavorable effects supplemental T has on testicular function. Consequently, alternative approaches that can stimulate endogenous T production are favored. Selective estrogen receptor modulators, gonadotropins and aromatase inhibitors (AIs) can be
successful in restoring serum T levels, preserving fertility, and providing symptomatic relief.

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328.
Off label therapies for testosterone replacement.
DiGiorgio L., Sadeghi-Nejad H.
Embase
Translational Andrology and Urology. 5 (6) (pp 844-849), 2016. Date of Publication: 2016.
[Review]
AN: 613769191
The incidence of hypogonadism has been steadily increasing over the last few years. Exogenous testosterone has been the standard treatment for hypogonadal men, but is associated with suppression of spermatogenesis as well as other possible adverse effects. There are other medications, currently considered "off label" for androgen replenishment, that exert their effect through modulation of the hypothalamicgonadal axis. These medications increase endogenous testosterone levels and offer a different therapeutic approach. This review will focus on these alternative (off-label) therapies for androgen replacement in men. Copyright © Translational Andrology and Urology. All rights reserved.
Status
EMBASE
Institution
329.
Pharmacology of testosterone replacement therapy preparations.
Embase
Translational Andrology and Urology. 5 (6) (pp 834-843), 2016. Date of Publication: 2016.
[Review]
AN: 613769182
The goal of testosterone replacement therapy (TRT) is to return serum testosterone levels to within physiologic range and improve symptoms in hypogonadal men. Some of the symptoms aimed to improve upon include decreased libido, erectile dysfunction, infertility, hot flashes, depressed mood, and loss of muscle mass or hair. Clinical use of testosterone for replacement therapy began approximately 70 years ago. Over the decades, numerous preparations and formulations have been developed primarily focusing on different routes of delivery and thus pharmacokinetics (PKs). Currently the routes of delivery approved for use by the United States Food and Drug Administration encompasses buccal, nasal, subdermal, transdermal, and intramuscular (IM). Many factors must be considered when a clinician is choosing the most correct formulation for a patient. As this decision depends highly on the patient, active patient participation is important for effective selection. The aim of this review is to describe and compare all testosterone preparations currently available and approved by the United States Food and Drug Administration. Areas of focus will include pharmacology, PKs, adverse effects, and specifics related to individual delivery routes.
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Testosterone deficiency (TD) has become a growing concern in the field of men's sexual health, with an increasing number of men presenting for evaluation of this condition. Given the increasing demand for testosterone replacement therapy (TRT), a panel of experts met in August of 2015 to discuss the treatment of men who present for evaluation in the setting of low or normal gonadotropin levels and the associated signs and symptoms of hypogonadism. This constellation of factors can be associated with elements of both primary and secondary hypogonadism. Because this syndrome commonly occurs in men who are middle-aged and older, it was termed adult-onset hypogonadism (AOH). AOH can be defined by the following elements: low levels of testosterone, associated signs and symptoms of hypogonadism, and low or normal gonadotropin levels. Although there are significant benefits of TRT for patients with AOH, candidates also need to understand the potential risks. Patients undergoing TRT will need to be monitored regularly because there are potential complications that can develop with long-term use. This review is aimed at providing a deeper understanding of AOH, discussing the benefits and risks of TRT, and outlining each modality of TRT in use for AOH. Copyright © Translational Andrology and Urology. All rights reserved.
331.

Special considerations in the evaluation and management of breast cancer in men.
Massarweh S.A., Choi G.L.

Embase
[Review]
AN: 613011763

Breast cancer in men is relatively uncommon but its incidence has been rising. Traditionally, the management of breast cancer in men is based on extrapolation from clinical trials of breast cancer in women, due to the much more extensive data available in women with this disease. There are, however, unique characteristics that distinguish breast cancer in men and these should be taken into consideration when managing this patient population. Breast cancer in men is more frequently estrogen receptor (ER) and progesterone receptor (PgR) positive, and less frequently HER2 amplified. Lobular carcinoma, which accounts for 10-15% of breast cancers in women, is exceptionally rare in men. Genetic risk factors, particularly BRCA2 mutations, are increasingly recognized as a key risk factor for breast cancer in men and genetic testing is now routinely recommended for all men diagnosed with breast cancer. Tamoxifen remains the gold standard endocrine therapy for breast cancer in men, but other endocrine agents such as the aromatase inhibitors (AI) and fulvestrant are increasingly being used. While superior to tamoxifen in postmenopausal women, the use of AIs for adjuvant therapy in men with breast cancer may not be optimal since the physiology of hormonal regulation in men resembles that of premenopausal rather than postmenopausal women. Emerging areas of investigation include the role of genomic
risk stratification to gain further insight into the biology of breast cancer in men, the study of the androgen receptor (AR) as a therapeutic target, and the role of gonadal suppression in the management of the disease. There is clearly a more concerted effort to study breast cancer in men as a unique disease in order to have a better understanding of its biology and we are likely to witness further advances that will help us better manage this unique disease situation.

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332.
Relationship between waist circumference and insulin resistance and its impact on sperm parameters. <Relacion circunferencia abdominal e insulinorresistencia y su impacto en parametros seminales.>
Aguilar-Roa P., Echavarria-Sanchez M.
Embase
Perinatologia y Reproduccion Humana. 30 (2) (pp 75-81), 2016. Date of Publication: 2016.
[Short Survey]
AN: 613516293
Infertility affects between 8-15% of general population of reproductive age. The term refers to the inability of couples to achieve pregnancy after one year of unprotected sexual activity. The male factor is solely responsible in 20%, and 30-40% with the couple. The initial evaluation of the male reproductive situation is the seminogram, which is considered as a key assessment tool. Several conditions may be associated with infertility in men, such as endocrine-metabolic diseases such
as hypogonadism, hyperprolactinaemia, dysthyroidism, dyslipidaemia, alterations glucose and insulin alteration, central obesity, or to the group of parameters called metabolic syndrome (MS). Obesity contributes to development of hypertension, dyslipidaemia and insulin resistance. The aim of our review was to find documents that showed the impact of the association between waist circumference and insulin resistance in semen parameters as a possible origin of male infertility. The search for information was conducted in Medline, ScienceDirect, and Scopus. The terms used for the basic search were: obesity, abdominal circumference, insulin resistance, male infertility, semen, semen parameters. There are studies documenting the deleterious effect of obesity and insulin resistance in female fertility. Some performed in men suggest harmful effects on their reproductive potential. Semen anomalies are found in obese men with insulin resistance, but still require further studied to assess the association between them. The literature reports semen anomalies associated with obesity that are still to be elucidated. Copyright © 2016 Instituto Nacional de Perinatologia Isidro Espinosa de los Reyes Status EMBASE Institution (Aguilar-Roa, Echavarria-Sanchez) Departamento de Andrologia, Instituto Nacional de Perinatologia, Ciudad de Mexico, Mexico Publisher Elsevier Doyma (E-mail: editorial@elsevier.com) Date Created 20161226 Year of Publication 2016

The effects of androgens on hematopoiesis are well documented. These drugs have been major pharmacological agents for stimulation of erythropoiesis before the recombinant hematopoietic growth factors were available. Their effects on red blood cells are best studied. They stimulate erythropoiesis and increase levels of red blood cells, hemoglobin and hematocrit. There are conflicting data on the effects of androgens on leucopoiesis and platelets. The stimulatory effect of androgens on erythropoiesis is a problem in patients with hypogonadism undergoing testosterone replacement. Increased blood viscosity in these patients is associated with increased risk of cardiovascular thrombotic events. Three major mechanisms for the effects of testosterone on erythropoiesis are proposed: increased erythropoietin set point, increased iron utilization and conversion of androgens in estrogens. Testosterone-induced increase in hematocrit and hemoglobin is probably associated with elevated erythropoietin levels, but the available data on the relationship between testosterone and erythropoietin are too contradictory. The effects of testosterone on erythropoiesis are accompanied by other mechanisms, such as reduced hepcidin probably by direct inhibition of its transcription. The direct erythropoietic effect of testosterone is likely mediated by inducing the synthesis of IGF-1 through a receptor-mediated mechanism although this mechanism can not completely explain the effects of testosterone on erythropoiesis. Interaction of androgens with some cytokines and growth factors may also influence hemopoiesis. It is contradictory if the effect of testosterone on erythropoiesis requires its conversion into estrogens or not. More experimental and clinical trials are needed to investigate the exact mechanism of stimulatory effect of androgens on erythropoiesis.

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Fertility in disorders of sex development: A review.
Van Batavia J.P., Kolon T.F.

Embase

Introduction Disorders of sex development (DSD) are a heterogeneous group of complex conditions that can affect chromosomal, gonadal, and/or phenotypical sex. In addition to impacts on internal and external genitalia, these conditions can affect fertility potential to various degrees. In this review we discuss fertility issues including gonadal preservation and reproductive outcomes based on specific DSD conditions.

Methods and Materials A systematic literature review was performed on EmbaseTM, PubMed, and Google ScholarTM for disorders of sex development and infertility. Original research articles and relevant reviews were examined and a synopsis of these data was generated for a comprehensive review of fertility potential in disorders of sex development. Results While patients with some DSDs may have functioning gonads with viable germ cells but an inability to achieve natural fertility secondary to incongruent internal or external genitalia, other patients may have phenotypically normal genitalia but infertility due to abnormal gonad development. Fertility rates in females with congenital adrenal hyperplasia (CAH) depend on phenotype and are inversely proportional to the severity of the disease. Men with classic CAH have reduced fertility and due to the presence of testicular adrenal rest tumors and to suppression of the hypothalamic-pituitary-gonadal axis by high systemic levels of androgens. Infertility is seen in complete androgen insensitivity and subfertility is common in partial cases. Fertility is rare in pure or mixed gonadal dysgenesis, ovotesticular disorder, Klinefelter syndrome, and XX males. Conclusion Fertility potential appears to be the highest in patients with XX or XY CAH, especially non-classic forms. Advancements in assisted reproduction techniques has in rare cases produced offspring in some diagnoses thought to be universally infertile. Discussion of fertility issues with the patient and family is essential to the optimal treatment of each patient and an important part of the multi-disciplinary approach to evaluating and counseling these families.

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Winners, losers, and posers: The effect of power poses on testosterone and risk-taking following competition.

Smith K.M., Apicella C.L.

Hormones and Behavior. (no pagination), 2016. Date of Publication: January 13, 2016. [Article In Press]

AN: 613819877

A contribution to a special issue on Hormones and Human Competition. The effect of postural power displays (i.e. power poses) on hormone levels and decision-making has recently been challenged. While Carney et al. (2010) found that holding brief postural displays of power leads to increased testosterone, decreased cortisol and greater economic risk taking, this failed to replicate in a recent high-powered study (Ranehill et al. 2015). It has been put forward that subtle differences in social context may account for the differences in results. Power displays naturally occur within the context of competitions, as do changes in hormones, and researchers have yet to examine the effects of poses within this ecologically relevant context. Using a large sample of 247 male participants, natural winners and losers of a physical competition were randomly assigned to hold a low, neutral or high-power postural display. We found no main effect of pose type on testosterone, cortisol, risk or feelings of power. Winners assigned to a high-power pose had a relative, albeit small, rise in testosterone compared to winners who held neutral or low-power poses. For losers, we found little evidence that high-power poses lead to increased testosterone relative to those holding neutral or low-powered poses. If anything, the reverse was observed - losers had a reduction in testosterone after holding high-power poses. To the extent that changes in testosterone modulate social behaviors adaptively, it is possible that the relative reduction in testosterone observed in losers taking high-powered poses is designed to inhibit further winner-like behavior that could result in continued defeat and harm. Still, effects were
small, multiple comparisons were made, and the results ran counter to our predictions. We thus treat these conclusions as preliminary. Copyright © 2016 Elsevier Inc.

336.
Unilateral Gynaecomastia in a Young Man with Chronic Myeloid Leukemia.
Jain A., Varma S., Garg R., Malhotra P.
Embase
[Article In Press]
AN: 613789777
Male reproductive issues are frequently overlooked in patients of chronic myeloid leukemia (CML) on imatinib therapy. Current article describes a young man with CML on imatinib mesylate since 13 years who presented to us with painful left sided breast swelling. Mammography and fine needle aspiration cytology confirmed the diagnosis of gynaeomastia and hormone profile revealed low testosterone levels. Gynaeomastia was attributed to imatinib related hypogonadism. Gynaeomastia improved after hormone replacement therapy. Need for long term monitoring of reproductive hormones in patients of CML on imatinib therapy is emphasized in this report. Copyright © 2016 Indian Society of Haematology & Transfusion Medicine

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ARTICLE IN PRESS
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2016
Effects of 8-Year Treatment of Long-Acting Testosterone Undecanoate on Metabolic Parameters, Urinary Symptoms, Bone Mineral Density, and Sexual Function in Men With Late-Onset Hypogonadism.

Permpongkosol S., Khupulsup K., Leelaphiwat S., Pavavattananusorn S., Thongpradit S., Petchthong T.

Embase

[Article]
AN: 613175992

Introduction The long-term effects of long-acting testosterone undecanoate (TU) and androgen receptor CAG repeat lengths in Thai men with late-onset hypogonadism (LOH) have not been reported. Aim To analyze the 8-year follow-up effects of intramuscular TU therapy on metabolic parameters, urinary symptoms, bone mineral density, and sexual function and investigate CAG repeat lengths in men with LOH. Methods We reviewed the medical records of 428 men with LOH who had been treated with TU and 5 patients were diagnosed with prostate cancer during TU therapy. There were 120 patients (mean age = 65.6 +/- 8.9 years) who had 5 to 8 years of continuous TU supplementation and sufficiently completed records for analysis. Genomic DNA was extracted from peripheral blood and the CAG repeat region was amplified by polymerase chain reaction. Fragment analysis, sequencing, electropherography, and chromatography were performed. Main Outcome Measures The main outcome measure was dynamic parameter changes during testosterone supplementation. Results TU did not improve all obesity parameters. A statistically significant decrease was found in waist circumference, percentage of body fat, glycated hemoglobin, cholesterol, low-density lipoprotein, and International Prostate Symptom
Score (P < .05). TU did not produce differences in body mass index, high-density lipoprotein, triglyceride, or the Aging Male Symptoms score from baseline. However, a statistically significant increase was found in the level of testosterone, prostate-specific antigen, hematocrit, International Index of Erectile Function score, and vertebral and femoral bone mineral density (P < .05). No major adverse cardiovascular events or prostate cancer occurred during this study. The CAG repeat length was 14 to 28 and the median CAG length was 22. There was no association between CAG repeat length and any of the anthropometric measurements.

Conclusion Long-term TU treatment in men with LOH for up to 8 years appears to be safe, tolerable, and effective in correcting obesity parameters.

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338.
Re: Testosterone Treatment and Sexual Function in Older Men with Low Testosterone Levels.
Seftel A.D.

Embase
[Article In Press]
Possible influence of vitamin D on male reproduction.
Boisen I.M., Bollehuus Hansen L., Mortensen L.J., Lanske B., Juul A., Blomberg Jensen M.
Embase
[Article In Press]
AN: 613545146
Vitamin D is a versatile signaling molecule with an established role in the regulation of calcium homeostasis and bone health. In recent years the spectrum of vitamin D target organs has expanded and a reproductive role is supported by the presence of the vitamin D receptor (VDR) and the vitamin D metabolizing enzymes in the gonads, reproductive tract, and human spermatozoa. Interestingly, expression levels of VDR and the vitamin D inactivating enzyme CYP24A1 in human spermatozoa serve as positive predictive markers of semen quality and are higher expressed in spermatozoa from normal than infertile men. VDR mediates a non-genomic increase in intracellular calcium concentration, sperm motility, and induces the acrosome reaction. Furthermore, functional animal model studies have shown that vitamin D is important for sex steroid production, estrogen signaling, and semen quality. Cross-sectional clinical studies have supported the notion of a positive association between serum 25-hydroxyvitamin D (25-OHD) level and semen quality in both fertile and infertile men. However, it remains to be determined whether this association reflects a causal effect. The VDR is ubiquitously expressed and activated vitamin D is a regulator of insulin, aromatase, and osteocalcin. Hence, it is plausible that the influence of vitamin D on gonadal function may be mediated indirectly through other
vitamin D regulated endocrine factors. Recent studies have indicated that vitamin D supplementation may be beneficial for couples in need of assisted reproductive techniques as high serum vitamin D levels were found to be associated with a higher chance of achieving pregnancy. Randomized clinical trials are needed to determine whether systemic changes in vitamin D metabolites can influence semen quality, fertility, and sex steroid production in infertile men. In this review known and possible future implications of vitamin D in human male reproduction function will be discussed. Copyright © 2016.

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340.

Sexual dysfunction in Klinefelter's syndrome patients.
El Bardisi H., Majzoub A., Al Said S., Alnawasra H., Dabbous Z., Arafay M.

Embase
Andrologia. (no pagination), 2016. Date of Publication: 2016.
[Article In Press]
AN: 613139385

Klinefelter's syndrome (KS) is the most common chromosomal abnormality in men with infertility and hypogonadism. Although its influence on fertility has been extensively investigated, very few studies assessed the sexual function of patients with KS. Our aim was to assess the prevalence
of sexual dysfunction in patients with KS and investigate possible aetiological factors for reported findings. Medical records of 53 patients with KS were retrospectively reviewed and compared to 75 age-matched control subjects who were prospectively recruited. Sexual history was evaluated through utilisation of international index of erectile function-5 and Arabic index for premature ejaculation questionnaires. Sexual desire was reported subjectively by patients or controls. The incidence of erectile dysfunction and premature ejaculation in patients with KS was 18.9% and 22.6% respectively. Compared to age-matched controls, patients with KS had significantly lower incidence of PE. However, there was no statistically significant difference between both groups regarding erectile function. Libido was significantly lower in patients with KS than normal controls (54.7% vs. 17.3%, p = 0.001). Klinefelter's syndrome is a condition that has a variable presentation. Despite having a higher likelihood of reduced sexual desire, patients may have normal erectile function comparable to age-matched individuals. They tend to have a lower incidence of premature ejaculation. Copyright © 2016 Blackwell Verlag GmbH.

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341. Comparing calculated free testosterone with total testosterone for screening and diagnosing late-onset hypogonadism in aged males: A cross-sectional study.

Embase
Objective: The aim of this study is to compare calculated free testosterone (cFT) and total testosterone (T) in predicting late-onset hypogonadism (LOH) in middle-aged and elderly males.

Methods: We surveyed a random sample of 608 males between the ages of 45 and 87 years from Shanghai, China. The Aging Male Symptoms (AMS) questionnaire and the Androgen Deficiency in Aging Male (ADAM) questionnaire were completed by the subjects. Testosterone (T), sex hormone-binding globulin (SHBG), albumin, and other blood biochemical indexes were measured in 332 males. The corresponding cFT was obtained using the Vermeulen formula and the correlations between T and cFT were analyzed by SPSS statistical software. Results: Among the 332 males who underwent biochemical evaluation, 289 males (87.0%) was positively screened by the ADAM questionnaire and 232 males (69.9%) by the AMS questionnaire. As suggested by linear regression, cFT exhibited a negative correlation with age in both ADAM+ and AMS+ group, whereas T did not appear to have significant correlation with age. Besides, there were statistically significant differences in cFT (P<.001) in the AMS questionnaire. Conclusions: Calculated free testosterone levels are more reliable than T levels for diagnosing LOH in middle-aged and elderly males. Copyright © 2016 Wiley Periodicals, Inc.

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342.
Effects of melatonin and gonadal androgens on cell proliferation in the pituitary of viscachas (Lagostomus maximus maximus).
Rosales G.J., Busolini F.I., Mohamed F.H., Filippa V.P.

Embase
Cell Proliferation. (no pagination), 2016. Date of Publication: 2016.
[Article In Press]
AN: 611543999

Objectives: Melatonin and androgens are involved in the regulation of cell proliferation. However, effects of these hormones on pituitary pars distalis (PD) of male viscachas is not fully understood.

In the present study, we analysed melatonin and gonadal androgens’ effects on proliferating cell nuclear antigen (PCNA) expression. Materials and methods: Pituitary glands from foetuses, immature individuals, prepubertal individuals and adult viscachas during their reproductive cycle, after melatonin administration and after castration, were used. PCNA-ir cells were detected by immunocytochemistry and morphometrically quantified using image analysis.

Results: Total percentage of PCNA-ir cells varied seasonally in the adult pituitary, with maximum values during the reproductive period and minima during gonadal regression periods. Percentages of PCNA-ir cells increased after melatonin administration, whereas it decreased after castration. Caudal end and ventral regions were the PD zones which were most affected by seasonal variations and castration. PCNA expression was highest in foetal pituitary from midpregnancy. Numbers of PCNA-ir cells decreased during sexual maturity.

Conclusions: Our results demonstrate the effect of gonadal androgens on cell proliferation during the reproductive period and sexual maturity of these animals. Exogenous melatonin increased PD cell proliferation in adults. Thus, these hormones seem to be involved in different mechanisms that regulate cell renewal of PD in this seasonally breeding rodent.

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Introduction: Evidence from well-designed studies documenting the benefit of testosterone replacement therapy as a function of patient demographic and clinical characteristics is lacking.

Aim: To determine demographic and clinical predictors of treatment outcomes in hypogonadal men with low sex drive, low energy, and/or erectile dysfunction. Methods: Post hoc analysis of a randomized, multicenter, double-blinded, placebo-controlled, 16-week study of 715 hypogonadal men (mean age = 55.3 years, age range = 19-92 years) presenting with low sex drive and/or low energy who received placebo or testosterone solution 2% for 12 weeks. Main Outcomes and Measures: Two levels defined patient-reported improvement (PRI) in sex drive or energy: level 1 was at least "a little better" and level 2 was at least "much better" in energy or sex drive on the Patient Global Impression of Improvement at study end point. PRI in erectile function was stratified by erectile dysfunction severity at baseline as measured by the erectile function domain of the International Index for Erectile Function: mild at baseline (change of 2), moderate at baseline (change of 5), and severe at baseline (change of 7). Associations of demographic and clinical characteristics with PRI were calculated with stepwise forward multiple logistic regression analysis. Odds ratios represented the likelihood of PRI in symptoms among variable categories.

Results: Higher levels of end-point testosterone were associated with higher rates of PRI (at levels 1 and 2) in sex drive and energy (P < .001 for the two comparisons). Lower baseline testosterone levels were associated with higher rates of level 1 PRI in sex drive (P = .028); and classic hypogonadism (vs non-classic hypogonadism) was associated with higher rates of level 2 PRI in sex drive (P = .005) and energy (P = .006). Conclusion: When assessing the potential for improvements in men with testosterone deficiency using patient-reported outcome questionnaires, possible predictors of treatment outcomes to consider include the etiology of hypogonadism and testosterone levels (baseline and end point).
Effects of liver transplantation on endocrine function: A systematic review.
Gariani K., Toso C., Philippe J., Orci L.A.
Embase
[Article In Press]
AN: 611093850
Patients with chronic liver disease (CLD) often experience secondary endocrine dysfunction. Therefore, because the liver plays a major role in endocrine function, liver transplantation (LT) may also be beneficial for the restoration of hormonal regulation. This systematic review collects and interprets the available literature on the effect of LT on endocrine and sexual function in adult patients. A systematic review was conducted by searching Pubmed (including Medline) and EMBASE for studies published from database inception until November 2015. We collected all relevant studies that discussed changes in hormonal and sexual function after LT. Studies were included if they assessed the effect of LT on sexual function or one of the following components of the hormone/endocrine axis: the hypothalamus-pituitary-gonadal axis, growth hormone (GH), insulin-like growth factor-1 (IGF-1) or thyroid function. The results are reported according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. Twenty-one studies with a total of 1274 patients were included. The results collected from the included studies suggested that LT improves the hormonal perturbation associated with CLD by restoring
physiological levels of circulating GH, IGF-1, testosterone, estradiol, prolactin, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Thyroid function was not affected by LT, and sexual function was partially improved after LT. This systematic review suggests that LT is associated with an improvement in endocrine and sexual function in patients with CLD. This information should encourage clinicians who treat CLD patients to identify endocrine disturbances in this population, inform their patients of the effects of LT and assess post-transplantation improvements. Copyright © 2016 John Wiley & Sons A/S.

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345.
Cancer in adolescents and young adults in France: Epidemiology and pathways of care. <Les cancers des adolescents et des jeunes patients: vision epidemiologique et organisations des soins en France.>
Desandes E., Lacour B., Clavel J.

Embase
[Article]
AN: 613663457
In adolescents and young adults (AYA), cancers are rare but represent the third significant cause of death. The aim of this paper was to investigate epidemiological data and pathways of care of AYA in France. During the 2000-2008 period, overall age-standardized incidence rates (ASR) were 254.1/106 in 15-24-year-olds. The most frequently diagnosed cancers in male AYA were malignant gonadal germ-cell tumors and Hodgkin's lymphoma, and were melanoma, thyroid carcinoma and Hodgkin's disease in females. The ASR appeared stable over time. During the 2000-2004 period, the 5-year overall survival for all cancers was 81.8%, with differences between genders and age groups: 78.8% for males and 85.2% for females; 78.5% in 15-19-year-olds and 84.3% in 20-24-year-olds. Survival has significantly improved over time. During the 2006-2007 period, the pathways of care for French adolescent patients with cancer were heterogeneous: 82% were treated in an adult environment, 27% were included in clinical studies, and in 54% of cases the management decisions were taken in the context of a multidisciplinary team. Studies looking at management of AYA with cancer have shown a wide disparity and a lack of collaboration between adult oncologists and pediatric oncologist. An AYA cancer multidisciplinary interest group has been created to determine priorities and coordinate efforts to improve AYA cancer services and care.

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Effect of Testosterone Solution 2% on Testosterone Concentration, Sex Drive and Energy in Hypogonadal Men: Results of a Placebo Controlled Study.

Embase
[Article]
AN: 608302564

Purpose We determined the effect of testosterone solution 2% on total testosterone level and the 2 symptoms of hypogonadism, sex drive and energy level. Materials and Methods This was a randomized, multicenter, double-blind, placebo controlled, 16-week study to compare the effect of testosterone and placebo on the proportion of men with a testosterone level within the normal range (300 to 1,050 ng/dl) upon treatment completion. We also assessed the impact of testosterone on sex drive and energy level measured using SAID (Sexual Arousal, Interest and Drive scale) and HED (Hypogonadism Energy Diary), respectively. A total of 715 males 18 years old or older with total testosterone less than 300 ng/dl and at least 1 symptom of testosterone deficiency (decreased energy and/or decreased sexual drive) were randomized to 60 mg topical testosterone solution 2% or placebo once daily. Results Of study completers 73% in the testosterone vs 15% in the placebo group had a testosterone level within the normal range at study end point (p <0.001). Participants assigned to testosterone showed greater baseline to end point improvement in SAID scores (low sex drive subset p <0.001 vs placebo) and HED scores (low energy subset p = 0.02 vs placebo, not significant at prespecified p <0.01). No major adverse cardiovascular or venous thrombotic events were reported in the testosterone group. The incidence of increased hematocrit was higher with testosterone vs placebo (p = 0.04). Conclusions Once daily testosterone solution 2% for 12 weeks was efficacious in restoring normal testosterone levels and improving sexual drive in hypogonadal men. Improvement was also seen in energy levels on HED though not at the prespecified p <0.01. No new safety signals were identified. Copyright © 2016 American Urological Association Education and Research, Inc.


Status
EMBASE
Institution
347.
Mok C.C.
Embase
Nephrology Dialysis Transplantation. 31 (10) (pp 1561-1566), 2016. Date of Publication: 01 Oct 2016.
[Article]
AN: 613233334
Renal disease in systemic lupus erythematosus (SLE) carries significant morbidity and mortality. Cyclophosphamide (CYC)- and mycophenolate mofetil (MMF)-based induction regimens are not ideal in terms of efficacy and toxicity. The adverse effects of CYC, such as infection risk, infertility, urotoxicity and oncogenicity, limit its use in lupus nephritis. Although MMF is non-inferior to CYC as induction therapy and has reduced gonadal toxicity and oncogenic potential, meta-analyses of clinical trials do not show a lower rate of infective and gastrointestinal complications. Tacrolimus (TAC) has recently been shown to have equal efficacy to either MMF or CYC for inducing remission of lupus nephritis. A low-dose combination of MMF and TAC appears to be more
effective than intravenous CYC pulses in Chinese patients, and has potential to replace the more
toxic CYC regimens in high-risk subgroups. TAC may be considered as another non-CYC
alternative for induction therapy of lupus nephritis and in those with refractory disease or
intolerance to CYC or MMF. TAC has no negative effect on fertility in younger women, and unlike
MMF and CYC, it is safe in pregnancy. However, TAC has a narrow therapeutic window and drug
level monitoring is required to ensure drug exposure and minimize acute toxicities. Current
evidence for the efficacy of TAC in lupus nephritis is limited to 6 months and the incidence of
renal flare after discontinuation of therapy or switching to azathioprine appears to be higher than
other induction agents. Long-term data and the incidence of chronic nephrotoxicity of TAC as
maintenance therapy in lupus nephritis are currently lacking and further prospective trials are
needed to address these issues. Copyright © 2016 The Author 2016. Published by Oxford
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348.
Testosterone therapy in men with testosterone deficiency: Are we beyond the point of no return?.
Traish A.
Embase
Investigative and Clinical Urology. 57 (6) (pp 384-400), 2016. Date of Publication: November
2016.
[Article]
AN: 613238821
Although testosterone therapy in men with testosterone deficiency was introduced in the early
1940s, utilization of this effective treatment approach in hypogonadal men is met with
considerable skepticism and resistance. Indeed, for decades, the fear that testosterone may cause prostate cancer has hampered clinical progress in this field. Nevertheless, even after considerable knowledge was acquired that this fear is unsubstantiated, many in the medical community remain hesitant to utilize this therapeutic approach to treat men with hypogonadism. As the fears concerning prostate cancer have subsided, a new controversy regarding use of testosterone therapy and increase in cardiovascular disease was introduced. Although the new controversy was based on one ill-fated clinical trial, one meta-analysis with studies that utilized unapproved formulation in men with liver cirrhosis, and two retrospective studies with suspect or nonvalidated statistical methodologies and database contaminations, the flames of such controversy were fanned by the lay press and academics alike. In this review we discuss the adverse effect of testosterone deficiency and highlight the numerous proven benefits of testosterone therapy on men's health and debunk the myth that testosterone therapy increases cardiovascular risk. Ultimately, we believe that there is considerable scientific and clinical evidence to suggest that testosterone therapy is safe and effective with restoration of physiological levels in men with testosterone deficiency, irrespective of its etiology. Copyright © The Korean Urological Association, 2016.

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349.
Erectile dysfunction and low sex drive in men with type 2 DM: The potential role of diabetic pharmacotherapy.
Al-Kuraishy H.M., Al-Gareeb A.I.
Embase
Introduction: Diabetic men with erectile dysfunction have not been widely studied. They have low testosterone levels, causing low sex drive and erectile dysfunction. Aim: To assess the erectile dysfunction and sex drive in relation to testosterone serum levels in type 2 Diabetes Mellitus (DM) patients. Materials and Methods: A total of 64 patients with type 2DM were enrolled in this cross-sectional study, according to the treatment types they were divided into three groups, group (A): 34 patients treated with metformin, group (B): 30 patients treated with sulfonylurea and group (C): 27 healthy normal non-diabetic men are taken as control. Total testosterone (TT), Free Testosterone (FT), Free Androgenic Index (FAI), Sex Hormone Binding Globulin (SHBG), lipid profile and anthropometric parameters in metformin and sulfonylurea treated patients were compared to normal healthy men along with Sexual Health Inventory for Men (SHIM). Results: Total testosterone serum levels were high in sulfonylurea treated patients as compared to metformin treated patients' p < 0.0001. Similarly, SHBG levels were significantly higher in sulfonylurea treated patients compared to metformin treated patients p < 0.0001. FT was also significantly higher in sulfonylurea treated patients compared to metformin treated patients p =0.014 and significantly low compared to the control p =0.0002. FAI was also significantly higher in sulfonylurea treated patients compared to metformin treated patients p < 0.0001. On other hand Bioavailable testosterone (BT) was low in metformin treated patients (2.75+/-1.12 nmol/L) compared to the control p< 0.0001. SHIM was low in metformin treated patients 10.61+/-3.22 which significantly differed from control and sulfonylurea treated patients p< 0.0001, intergroup differences was significant p=0.001. Conclusion: Metformin leads to significant reduction in testosterone levels, sex drive and induction of low testosterone-induced erectile dysfunction, whereas; sulfonylurea leads to significant elevation in testosterone levels, sex drive and erectile function. Copyright © 2016, Journal of Clinical and Diagnostic Research. All rights reserved.
Opioids commonly used for pain relief may lead to hypogonadism, which is characterised by suppression of production of the gonadotropin-releasing hormone (GnRH) resulting in inadequate production of sex hormones. The aim of this narrative review was to highlight the effects of opioids on the endocrine system and the development of hypogonadism. MEDLINE, EMBASE and Cochrane Library were searched for relevant articles investigating hypogonadism in patients undertaking opioid therapy by using a combination of both indexing and free-text terms. The suppression of GnRH leading to a decrease in sex hormones has been described as the principal mechanism of opioid-induced hypogonadism. However, there is no consensus on the threshold for the clinical diagnosis of hypogonadism. Evidence indicates that chronic opioid use can lead to hypogonadism. Clinicians should be aware of symptomatology associated with hypogonadism and should regularly monitor patients with appropriate laboratory investigations. Copyright © 2016, BMJ Publishing Group. All rights reserved.
Impact of Baseline Total Testosterone Level on Successful Treatment of Sexual Dysfunction in Men Taking Once-Daily Tadalafil 5 mg for Lower Urinary Tract Symptoms and Benign Prostatic Hyperplasia: An Integrated Analysis of Three Randomized Controlled Trials.
Mulhall J.P., Brock G.B., Glina S., Baygani S., Donatucci C.F., Maggi M.


Introduction
Controversy exists as to whether erectile response to phosphodiesterase type 5 inhibitors is compromised in men with low total testosterone (TT) levels. This is amplified by reports of improved response to phosphodiesterase type 5 inhibitor therapy after coadministration of testosterone replacement therapy in hypogonadal men unresponsive to phosphodiesterase type 5 inhibitors. Aim To determine whether TT and luteinizing hormone levels influence efficacy of tadalafil for erectile dysfunction in men with concomitant lower urinary tract symptoms and benign prostatic hyperplasia. Methods This integrated analysis included 1,075 men randomized to once-daily tadalafil 5 mg (n = 540) or placebo (n = 535) for 12 weeks in three prospective clinical trials who had not received concomitant testosterone replacement therapy. Subjects were categorized at baseline by low vs normal TT levels (n = 1,049; <300 vs >=300 ng/dL) and normal vs high luteinizing hormone levels (n = 1,058; <=9.4 vs >9.4 mIU/mL). Treatment-group differences in International Index of Erectile Function (IIEF) by hormone subgroups were assessed using analysis of covariance. Main Outcome Measures Changes in IIEF erectile function domain and other domain scores. Results The overall study population was comprised primarily of white men (>86%) with a mean age range of 64 to 70 years. Median baseline TT level in the integrated population was 355 ng/dL; levels were lower than 300 ng/dL (cutoff for normal) in 32.4% of men. Men with low TT levels reported diabetes (21.8%), cardiovascular disease (54.1%), and hypertension (49.1%) numerically more often than men with normal TT levels.
(10.6%, 43.2%, and 36.7%, respectively). Low TT and high luteinizing hormone levels were associated with numerically, but not statistically significantly, lower 12-week IIEF domain scores compared with those with normal levels. Changes in most 12-week IIEF domain scores showed that tadalaafil was significantly more effective than placebo (P < .02). Conclusion Low TT levels at baseline did not negatively influence response to tadalaafil in men of advancing age with concomitant lower urinary tract symptoms and benign prostatic hyperplasia and erectile dysfunction. Copyright © 2016 International Society for Sexual Medicine
(total testosterone < 300 ng/dL) were randomized to receive testosterone or placebo for 12 weeks. Main Outcome Measures Effects of testosterone on primary outcomes were evaluated using the International Index of Erectile Function (IIEF) and the Men's Sexual Health Questionnaire, Ejaculatory Dysfunction, Short Form (MSHQ-EjD-SF) questionnaires. Treatment differences were calculated using analysis of covariance. Results In total, 715 men (mean age = 55 years) were randomized to placebo (n = 357) or testosterone (n = 358). Most sexually active men who reported IIEF scores had some degree of erectile dysfunction (IIEF erectile function score < 26). Although ejaculatory function score (MSHQ-EjD-SF) improved in the testosterone group compared with placebo (P < .001), improvement on the "bother" item did not reach statistical significance. Treatment-related adverse events in the testosterone group affecting at least 1% of patients were increased hematocrit, upper respiratory tract infection, arthralgia, burning sensation, fatigue, increased prostate-specific antigen, erythema, and cough. Few patients in either treatment group developed at least one adverse event leading to discontinuation (testosterone = 1.98% vs placebo = 3.09%; P = .475). Conclusion Hypogonadal men receiving testosterone solution 2% therapy experience significantly greater improvement in ejaculatory function, compared with placebo, as assessed by the MSHQ-EjD-SF. However, improvement in "bother" was not statistically different between the two groups. Testosterone therapy was generally well tolerated. Copyright © 2016 International Society for Sexual Medicine

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The scope of palliative care includes goal setting, symptom management, and care of the caregiver. Palliative care is essential for patient-centered care of the older cancer patients. The diversity of this population in terms of life expectancy, treatment tolerance, function, disability, and social support mandates personalized treatment plans. The assessment of physiologic age is currently based on a comprehensive geriatric assessment (CGA). A number of biologic markers of aging including the inflammatory index, the genomic clock, the expression of p16INKa4, and the circulating levels of vitamin D may complement the CGA and fine-tune the determination of physiologic age. Goal setting in older patients may be complicated by communication difficulties related to hearing, cognition, expectation, and culture. Cancer-related pain is a major hindrance to the maintenance of functional independence and fatigue is harbinger of disability and death. The article explores the assessment and the management of the most common and debilitating symptoms in older cancer patients. Copyright © 2016, Springer Science+Business Media New York.
Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: A randomised controlled trial.
Sinclair M., Grossmann M., Hoermann R., Angus P.W., Gow P.J.
Embase
[Article]
AN: 613260845

Background & Aims Low testosterone and sarcopenia are common in men with cirrhosis and both are associated with increased mortality. Whether testosterone therapy in cirrhosis improves muscle mass and other outcomes is unknown. Methods We conducted a 12-month, double-blinded, placebo-controlled trial of intramuscular testosterone undecanoate in 101 men with established cirrhosis and low serum testosterone (total testosterone <12 nmol/L or free testosterone <230 pmol/L) in a single tertiary centre. Body composition was assessed using dual-energy X-ray absorptiometry at baseline, 6 and 12 months. Results At study completion, appendicular lean mass was significant higher in testosterone-treated subjects, with a mean adjusted difference (MAD) of +1.69 kg, (CI +0.40; +2.97 kg, p = 0.021). Secondary outcomes included a substantially higher total lean mass in the active group (MAD +4.74 kg, CI +1.75; +7.74 kg, p = 0.008), matched by reduced fat mass (MAD -4.34 kg, CI -6.65; -2.04, p <0.001). Total bone mass increased (MAD +0.08 kg, CI +0.01; +0.15 kg, p = 0.009) as did bone mineral density at the femoral neck (MAD +0.287 points, CI +0.140; +0.434, p <0.001). Haemoglobin was higher with testosterone therapy (MAD +10.2 g/L, CI +1.50; +18.9 g/L, p = 0.041) and percentage glycosylated haemoglobin (HbA1c) lower (MAD -0.35%, CI -0.05; -0.54, p = 0.028). Mortality was non-significantly lower in testosterone-treated patients (16% vs. 25.5%, p = 0.352). There was no increase in adverse events in testosterone-treated subjects. Conclusion Testosterone therapy in men with cirrhosis and low serum testosterone safely increases muscle mass, bone mass and haemoglobin, and reduces fat mass and HbA1c. This is the first evidence-based therapy for sarcopenia in cirrhosis and thus requires larger-scale investigation into its potential impact on mortality. Lay summary Both low testosterone and muscle wasting are associated with increased risk of death in men with severe liver disease. Administering testosterone to men with liver disease who have low testosterone levels significantly increases their muscle mass. In addition, testosterone has non-muscle beneficial effects which may be able to increase survival in this population. Clinical trial number Australian New Zealand Clinical Trials Registry trial number ACTRN 12614000526673. Copyright © 2016 European Association for the Study of the Liver
A novel morphological approach to gonads in disorders of sex development.

Lepais L., Morel Y., Mouriquand P., Gorduza D., Plotton I., Collardeau-Frachon S., Dijoud F.

Embase
Modern Pathology. 29 (11) (pp 1399-1414), 2016. Date of Publication: 01 Nov 2016.
[Article]
AN: 611533326

Disorders of sex development are defined as congenital conditions with discordance between the phenotype, the genotype, the karyotype, and the hormonal profile. The disorders of sex development consensus classification established in 2005 are mainly based on chromosomal and biological data. However, histological anomalies are not considered. The aims of this study were to define the specific pathological features of gonads in various groups of disorders of sex development in order to clarify the nosology of histological findings and to evaluate the tumor risk in case of a conservative approach. One hundred and seventy-five samples from 86 patients with disorders of sex development were analyzed following a strict histological reading protocol. The term 'gonadal dysgenesis' for the histological analysis was found confusing and therefore excluded. The concept of 'dysplasia' was subsequently introduced in order to describe the architectural disorganization of the gonad (various degrees of irregular seminiferous tubules, thin albuginea, fibrous interstitium). Five histological types were identified: normal gonad, hypoplastic testis, dysplastic testis, streak gonad, and ovotestis. The analysis showed an association between undifferentiated gonadal tissue, a potential precursor of gonadoblastoma, and dysplasia. Dysplasia and undifferentiated gonadal tissue were only encountered in cases of genetic or chromosomal abnormality ('dysgenesis' groups in the disorders of sex development consensus
'Dysgenetic testes', related to an embryonic malformation of the gonad, have variable histological presentations, from normal to streak. Conversely, gonads associated with hormonal deficiencies always display a normal architecture. A loss of expression of AMH and alpha-inhibin was identified in dysplastic areas. Foci of abnormal expression of the CD117 and OCT4 immature germ cells markers in dysplasia and undifferentiated gonadal tissue were associated with an increased risk of neoplasia. This morphological analysis aims at clarifying the histological classification and gives an indication of tumor risk of gonads in disorders of sex development. Copyright © 2016 USCAP, Inc All rights reserved.

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Low Testosterone in Men with Cardiovascular Disease or Risk Factors: To Treat or Not To Treat?.
Cassimatis D.C., Crim M.T., Wenger N.K.

Embase

Current Treatment Options in Cardiovascular Medicine. 18 (12) (no pagination), 2016. Article Number: 75. Date of Publication: 01 Dec 2016.

[Review]
Current evidence supports the use of testosterone replacement in men with the clinical-biochemical syndrome of hypogonadism, defined as low testosterone serum levels and symptoms such as fatigue, exercise intolerance, erectile dysfunction, low libido, or depression. Although the evidence consistently shows that hypogonadism is associated with elevated cardiovascular risk, evidence is mixed regarding whether testosterone (T) replacement provides cardiovascular (CV) benefit or harm. For a man with symptomatic hypogonadism in the setting of CV disease, clinical heart failure, and/or traditional CV risk factors (hypertension, diabetes, and hyperlipidemia), a balanced approach would be to counsel him that overall, the evidence should not dissuade him from utilizing T replacement for non-cardiac symptom relief but that more data are needed before a definitive recommendation can be made about T replacement for CV benefit. The preponderance of available evidence, reviewed in this article, suggests that T replacement, at appropriate doses and with monitored response, is likely to be safe for men with CV disease or CV risk factors and may even reduce major adverse cardiovascular events (MACE). The 2015 American Association of Clinical Endocrinologists and American College of Endocrinology position statement supports this stance and calls for improved prospective data. There is a clear need for a large, prospective randomized trial evaluating the impact of T replacement on MACE, for men both with and without CV disease or CV risk factors. Clinicians should be aware that all men who elect to take T replacement therapy require regular follow-up with the prescribing physician to include both clinical assessment and surveillance laboratory assessment of total T level, complete blood count, and prostate specific antigen. Copyright © 2016, Springer Science+Business Media New York.

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Development of the Hypogonadism Impact of Symptoms Questionnaire Short Form: Qualitative Research.


Embase

AN: 612934642

Introduction Hypogonadism in men is often associated with poor libido, erectile dysfunction, irritability, fatigue, and psychological and relationship problems. Many of these symptoms can be best assessed through patient report. The 28-item Hypogonadism Impact of Symptoms Questionnaire (HIS-Q) was developed to evaluate hypogonadism symptoms in men with low testosterone in the context of clinical trials. Aim To develop a briefer version of the HIS-Q that could be practical for use in treatment settings. Methods Participants with low testosterone levels and symptoms consistent with hypogonadism were recruited through clinical sites. Focus groups and interviews were conducted to elicit symptom concepts and identify those that were most relevant to patients, including changes as a consequence of treatment. Main Outcome Measures Systematic analysis of the qualitative data and expert clinician input were used to develop the HIS-Q short form (HIS-Q-SF). One-on-one cognitive interviews were conducted to confirm the content validity of the HIS-Q-SF. Results Thirty-five men participated in this qualitative research. Concept elicitation was conducted through focus group discussions (n = 18) and telephone interviews (n = 2); then, the draft HIS-Q-SF was evaluated through cognitive interviews (n = 15). The mean age of total sample was 53.2 +/- 6.8 years, and the mean serum total testosterone level was 184.9 +/- 55.2 ng/dL. Results suggest that the HIS-Q-SF has demonstrated content validity, including the content coverage, comprehensibility, and the appropriateness of the response options and recall period. The final version of the HIS-Q-SF includes 17 items and is aligned with the original longer version of the instrument. Conclusion The HIS-Q-SF is a comprehensive measurement of hypogonadism symptom severity in men. Content coverage and content validity were confirmed. The instrument will be evaluated further to establish the psychometric characteristics and to assess the utility of the measurement in clinical treatment settings. Copyright © 2016 The Authors

Status
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Psychometric Evaluation of the Hypogonadism Impact of Symptoms Questionnaire.


Embase


[Article]

AN: 612934638

Introduction The Hypogonadism Impact of Symptoms Questionnaire (HIS-Q) is a patient-reported outcome measurement designed to comprehensively evaluate the symptoms of hypogonadism and to detect changes in these symptoms in response to treatment. Aim To conduct item analysis and reduction, evaluate the psychometric properties of the HIS-Q, and provide guidance on interpreting the instrument score. Methods A 12-week observational, longitudinal study of hypogonadal men was conducted. Participants completed the HIS-Q every 2 weeks. Blood samples were collected to evaluate testosterone levels. Participants also completed the Aging Male's Symptoms Scale, the International Index of Erectile Function, the Short Form-12 Health Survey, and the Patient-Reported Outcomes Measurement Information System Sexual Activity, Satisfaction with Sex Life, Sleep Disturbance, and Applied Cognition Scales (at baseline and weeks 6 and 12). Clinicians completed the Clinical Global Impression of Severity and Change measurements and a clinical form. Main Outcome Measures Individual item performance was evaluated using descriptive statistics and Rasch analyses. Reliability (internal consistency and
test-retest), validity (concurrent and know groups), and responsiveness were assessed. Results
In total, 177 men participated in the study (mean age = 54.1 years, range = 23-83). The original
53-item draft HIS-Q was reduced to 28 items; the final instrument included five domains (sexual,
energy, sleep, cognition, and mood) with two sexual subdomains (libido and sexual function). For
all domains, test-retest reliability was acceptable (intraclass correlation coefficients > 0.70),
construct validity was good ( r > 0.30
for all comparisons). Known-groups validity was demonstrated for all HIS-Q domain scores,
subdomain scores, and the total score as measured by the Clinical Global Impression of Severity,
and total testosterone level at baseline (P < .05 for all comparisons). All domains and
subdomains were responsive to change based on patient-rated anchor questions (P < .05 for all
comparisons). Conclusion The final 28-item HIS-Q is reliable, valid, and responsive. The HIS-Q is
suitable for inclusion in future clinical trials to help characterize the effects of testosterone
replacement therapy.

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359.
Psychological and Interpersonal Dimensions of Sexual Function and Dysfunction.
Introduction Psychological, interpersonal, and sociocultural factors play a significant role in making one vulnerable to developing a sexual concern, in triggering the onset of a sexual difficulty, and in maintaining sexual dysfunction in the long term. Aim To focus on psychological and interpersonal aspects of sexual functioning in women and men after a critical review of the literature from 2010 to the present. Methods This report is part 1 of 2 of our collaborative work during the 2015 International Consultation on Sexual Medicine for Committee 2. Main Outcome Measures Systematic review of the literature with a focus on publications since 2010. Results Our work as sexual medicine clinicians is essentially transdisciplinary, which involves not only the collaboration of multidisciplinary professionals but also the integration and application of new knowledge and evaluation and subsequent revision of our practices to ensure the highest level of care provided. There is scant literature on gender non-conforming children and adolescents to clarify specific developmental factors that shape the development of gender identity, orientation, and sexuality. Conversely, studies consistently have demonstrated the interdependence of sexual function between partners, with dysfunction in one partner often contributing to problems in sexual functioning and/or sexual satisfaction for the other. We recommend that clinicians explore attachment styles of patients, childhood experiences (including sexual abuse), onset of sexual activity, personality, cognitive schemas, infertility concerns, and sexual expectations. Assessment of depression, anxiety, stress, substance use and post-traumatic stress (and their medical treatments) should be carried out as part of the initial evaluation. Clinicians should attempt to ascertain whether the anxiety and/or depression is a consequence or a cause of the sexual complaint, and treatment should be administered accordingly. Cognitive distraction is a significant contributor to sexual response problems in men and women and is observed more consistently for genital arousal than for subjective arousal. Assessment of physical and mental illnesses that commonly occur in later life should be included as part of the initial evaluation in middle-aged and older persons presenting with sexual complaints. Menopausal status has an independent effect on reported changes in sex life and difficulties with intercourse. There is strong support for the use of psychological treatment for sexual desire and orgasm difficulties in women (but not in men). Combination therapies should be provided to men, whenever possible. Conclusion Overall, research strongly supports the routine clinical investigation of psychological factors, partner-related factors, context, and life stressors. A biopsychosocial model to understand how these
factors predispose to sexual dysfunction is recommended. Copyright © 2016 International Society for Sexual Medicine

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360.
Treatment of Men for "Low testosterone": A systematic review.

Embase
Testosterone products are recommended by some prescribers in response to a diagnosis or presumption of "low testosterone" (low-T) for cardiovascular health, sexual function, muscle weakness or wasting, mood and behavior, and cognition. We performed a systematic review of 156 eligible randomized controlled trials in which testosterone was compared to placebo for one or more of these conditions. We included studies in bibliographic databases between January 1, 1950 and April 9, 2016, and excluded studies involving bodybuilding, contraceptive effectiveness, or treatment of any condition in women or children. Studies with multiple relevant endpoints were included in all relevant tables. Testosterone supplementation did not show consistent benefit for cardiovascular risk, sexual function, mood and behavior, or cognition. Studies that examined clinical cardiovascular endpoints have not favored testosterone therapy over placebo. Testosterone is ineffective in treating erectile dysfunction and controlled trials did not show a consistent effect on libido. Testosterone supplementation consistently increased muscle strength but did not have beneficial effects on physical function. Most studies on mood-related endpoints found no beneficial effect of testosterone treatment on personality, psychological well-being, or mood. The prescription of testosterone supplementation for low-T for cardiovascular health, sexual function, physical function, mood, or cognitive function is without support from randomized clinical trials. Copyright © 2016 Huo et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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Intramuscular depot formulations of leuprolide acetate suppress testosterone levels below a 20 ng/dL threshold: A retrospective analysis of two phase III studies.
Embase
Research and Reports in Urology. 8 (pp 159-164), 2016. Date of Publication: 23 Aug 2016.
[Article]
AN: 612915871

Introduction: Androgen deprivation therapy (ADT) with gonadotropin-releasing hormone (GnRH) analogs is a standard treatment for advanced prostate cancer. GnRH analog therapy can reduce testosterone to "castrate" levels, historically defined as <50 ng/dL. With the advent of newer assays, a lower threshold of <20 ng/dL has recently been proposed. We report the results of a retrospective analysis of two Phase III trials of 4- and 6-month depot microsphere formulations of leuprolide acetate (LA), a GnRH agonist that has previously demonstrated efficacy in testosterone suppression to <50 ng/dL in patients on ADT. This analysis investigates the ability of these LA formulations to suppress to <=20 ng/dL levels. Methods: In two of five AbbVie/Abbott clinical trials of microsphere formulations of LA for ADT, analytic technology permitting testosterone detection as low as 3 ng/dL was used and thus was selected for this analysis. Both trials were open-label, fixed-dose studies in prostate cancer patients, naive to ADT. Patients received either 30 mg (4-month formulation; n=49) or 45 mg (6-month formulation; n=151) depot injections of LA microspheres. Treatment duration was up to 32 weeks for the 4-month formulation and 48 weeks for the 6-month formulation. The proportion of patients achieving the 20 ng/dL threshold was determined every 4 weeks. Results: Pooled analysis showed that 152 of 193 (79%) of patients achieved serum testosterone levels of <=20 ng/dL at 4 weeks, and sustained the improvement at week 24 (169/189, 89%). Additionally, in the 6-month study, 127/135 (94.1%) patients were suppressed to <=20 ng/dL at 48 weeks. Conclusion: Both 4- and 6-month intramuscular depot formulations of LA achieved and maintained mean serum testosterone levels <=20 ng/dL in the vast majority of patients as early as 4 weeks following treatment initiation. Additional research on the clinical relevance of this lower testosterone threshold is warranted.
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362.
Neurotherapeutic Strategies for Multiple Sclerosis.
Embase
Neurologic Clinics. 34 (3) (pp 483-523), 2016. Date of Publication: 01 Aug 2016.
[Review]
AN: 612904089
Multiple sclerosis (MS) is the most common disabling neurologic disease of young adults. There are now 16 US Food and Drug Administration (FDA)-approved disease-modifying therapies for MS as well as a cohort of other agents commonly used in practice when conventional therapies prove inadequate. This article discusses approved FDA therapies as well as commonly used practice-based therapies for MS, as well as those therapies that can be used in patients attempting to become pregnant, or in patients with an established pregnancy, who require concomitant treatment secondary to recalcitrant disease activity. Copyright © 2016 Elsevier Inc.
Status

Although popular discussion of testosterone’s influence on males often centers on aggression and antisocial behavior, contemporary theorists have proposed that it instead enhances behaviors involved in obtaining and maintaining a high social status. Two central distinguishing but untested predictions of this theory are that testosterone selectively increases status-relevant aggressive behaviors, such as responses to provocation, but that it also promotes nonaggressive behaviors, such as generosity toward others, when they are appropriate for increasing status. Here, we tested these hypotheses in healthy young males by injecting testosterone enanthate or
a placebo in a double-blind, between-subjects, randomized design (n = 40). Participants played a version of the Ultimatum Game that was modified so that, having accepted or rejected an offer from the proposer, participants then had the opportunity to punish or reward the proposer at a proportionate cost to themselves. We found that participants treated with testosterone were more likely to punish the proposer and that higher testosterone levels were specifically associated with increased punishment of proposers who made unfair offers, indicating that testosterone indeed potentiates aggressive responses to provocation. Furthermore, when participants administered testosterone received large offers, they were more likely to reward the proposer and also chose rewards of greater magnitude. This increased generosity in the absence of provocation indicates that testosterone can also cause prosocial behaviors that are appropriate for increasing status. These findings are inconsistent with a simple relationship between testosterone and aggression and provide causal evidence for a more complex role for testosterone in driving status-enhancing behaviors in males.

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Spanish consensus on the risks and detection of antipsychotic drug-related hyperprolactinaemia.


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[Short Survey]
AN: 608646616

Introduction
Iatrogenic hyperprolactinaemia (IHPRL) has been more frequently related to some antipsychotic drugs that provoke an intense blockade of dopamine D2 receptors. There is a wide variation in clinical practice, and perhaps some more awareness between clinicians is needed. Due to the high frequency of chronic treatment in severe mental patients, careful attention is recommended on the physical risk. IHPRL symptoms could be underestimated without routine examination. Methodology
An intense scientific literature search was performed in order to draw up a multidisciplinary consensus, including different specialists of psychiatry, endocrinology, oncology and internal medicine, and looking for a consensus about clinical risk and detection of IHPRL following evidence-based medicine criteria levels (EBM I- IV). Results
Short-term symptoms include amenorrhea, galactorrhoea, and sexual dysfunction with decrease of libido and erectile difficulties related to hypogonadism. Medium and long-term symptoms related to oestrogens are observed, including a decrease bone mass density, hypogonadism, early menopause, some types of cancer risk increase (breast and endometrial), cardiovascular risk increase, immune system disorders, lipids, and cognitive dysfunction. Prolactin level, gonadal hormones and vitamin D should be checked in all patients receiving antipsychotics at baseline although early symptoms (amenorrhea-galactorrhoea) may not be observed due to the risk of underestimating other delayed symptoms that may appear in the medium term. Routine examination of sexual dysfunction is recommended due to possible poor patient tolerance and low compliance. Special care is required in children and adolescents, as well as patients with PRL levels >50 ng/ml (moderate hyperprolactinaemia). A possible prolactinoma should be investigated in patients with PRL levels >150 ng/ml, with special attention to patients with breast/endometrial cancer history. Densitometry should be prescribed for males >50 years old,
amenorrhea > 6 months, or early menopause to avoid fracture risk. Copyright © 2016 SEP y SEPB

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Publisher
"Is late-onset hypogonadotropic hypogonadism a specific age-dependent disease, or merely an epiphenomenon caused by accumulating disease-burden?.


Embase

Minerva Endocrinologica. 41 (2) (pp 196-210), 2016. Date of Publication: June 2016.

[Review]

AN: 612971385

BACKGROUND: The aim of this paper is to summarize the available evidence supporting the link between late onset hypogonadism (LOH) and associated common clinical illnesses, focusing on metabolic diseases. The possible benefits or risks related to testosterone replacement therapy (TRT) in these conditions will also be analyzed. METHODS: An extensive Medline search was performed. RESULTS: LOH is closely associated with a worse metabolic profile and a higher cardiovascular risk. The relationship between hypogonadism obesity and insulin resistance is complex and bidirectional. Emerging evidence suggests a positive role of TRT in improving body composition and metabolic outcomes in subjects with LOH. CONCLUSIONS: Despite the aforementioned data, it is not completely known whether reduced testosterone levels in elderly males might play a direct pathogenetic role in these conditions or whether low T and associated morbidities are concomitant conditions, both associated with the aging process. Further and longer studies are advisable to confirm the preliminary results.  

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366.
High circulating oestrone and low testosterone correlate with adverse clinical outcomes in men with advanced liver disease.

Sinclair M., Gow P.J., Angus P.W., Hoermann R., Handelsman D.J., Wittert G., Martin S., Grossmann M.

Embase
Liver International. 36 (11) (pp 1619-1627), 2016. Date of Publication: 01 Nov 2016.
[Article]
AN: 609945555

Background & Aims: Circulating testosterone is usually reduced in men with cirrhosis, but there has not been a comprehensive analysis of androgen status or circulating oestrogens. Little is known about associations between circulating sex steroids with aspects of health in this population. Methods: We report data from men with cirrhosis and low serum testosterone (<12 nmol/L or calculated free testosterone <230 pmol/L). Comprehensive circulating sex steroid profiles were measured by liquid chromatography-mass spectrometry and compared with age-matched controls. Relationships between sex hormone levels, severity of liver disease, biochemistry and clinical outcomes were assessed. Results: Serum oestrone and oestradiol were significantly elevated in men with cirrhosis compared with controls (median, 869.1 pmol/L vs. 133.8 pmol/L and 166.7 pmol/L vs. 84.6 pmol/L respectively). Serum oestrone correlated with
MELD score (correlation +0.306, P < 0.001) and inversely correlated with serum sodium (correlation -0.208, P = 0.004) and haemoglobin (correlation -0.177, P = 0.012). No such correlations were observed for oestradiol. Serum testosterone levels inversely correlated with MELD score (correlation -0.294, P < 0.001) and positively with handgrip strength (correlation +0.242, P < 0.001), physical activity (correlation +0.276, P = 0.012), haemoglobin (correlation +0.282, P < 0.001) and serum sodium (+0.344, P < 0.001). Dihydrotestosterone inversely correlated with MELD score (correlation -0.225, P = 0.002) and shared similar significant relationships to testosterone. Conclusion: Low serum androgens and elevated serum oestrone (but not oestradiol) are associated with higher MELD and individual adverse health outcomes in cirrhotic cohort of men selected for low testosterone. Serum oestrone may be a novel marker of ill health in this population. Whether low androgens are markers or mediators of ill health requires further investigation.
Despite a lack of evidence, there have been stated concerns that testosterone replacement therapy (TRT) can pose a risk to men suffering with lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH). TRT may improve components of the metabolic syndrome, which is associated with worsening LUTS. Furthermore, the evidence suggests that TRT may decrease prostatic inflammation, which is also associated with worsening LUTS. The data on the relationship between TRT and LUTS have never shown worsening of LUTS, often show no change in LUTS, and occasionally show improvement. Copyright © 2016 Elsevier Inc.
Methods: MEDLINE, PubMed, and ClinicalTrials.gov were searched for articles that referenced the evaluation of testosterone serum level and/or testosterone treatment on premenopausal women with low libido from 1995 to 2015. Additional references were obtained from the reference sections of other papers and from peer review. Studies that included only postmenopausal women were excluded. A total of 13 studies were reviewed in detail. Nine studies examined the relationship between testosterone serum levels and sexuality, an additional three studies examined the effect of testosterone treatment on premenopausal women with low libido, and one study examined both the topics. Results: Six of the ten testosterone serum evaluation studies failed to show a significant association between testosterone serum level and libido. Only one out of four studies examining testosterone treatment in premenopausal women was able to show any clear improvement in libido; however, the effect was limited to only the intermediate dose of testosterone, with the low and high doses of testosterone not producing any effect. Conclusion: The currently available evidence does not support testosterone serum evaluation or treatment in premenopausal women with low libido. Hence, further studies are warranted. Copyright © 2016 Reed et al.

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369.
Short-term estrogen withdrawal increases adiposity in healthy men.
Chao J., Rubinow K.B., Kratz M., Amory J.K., Matsumoto A.M., Page S.T.
Embase
Context: T deprivation increases risk of insulin resistance in men, but whether this risk is independent of changes in body composition is unknown. Further, the metabolic roles of T and its metabolite estradiol have not been clearly defined in men. Objective: This study sought to establish the effects of selective sex steroid withdrawal on insulin sensitivity in healthy men. Design, Setting, and Participants: This was a double-blinded, placebo-controlled, randomized trial at an academic medical center of 56 healthy men, 19-55 years of age. Interventions: Subjects received the GnRH antagonist acyline plus one of the following: placebo gel (Castrate), 1.25 g testosterone gel (Low T/E), 5 g testosterone gel (Normal T/E), or 5 g testosterone gel with letrozole (Normal T/Low E) daily for 4 weeks. Body composition and glucose tolerance were assessed at baseline and end of treatment. Main Outcome Measure: Insulin sensitivity was quantified by the Matsuda index. Results: Predicted circulating sex steroid concentrations were achieved in all treatment groups. The time-by-group interaction for Matsuda index did not achieve significance in overall repeated measures ANOVA (baseline vs week 4; P = .16). A significant time-by-group interaction was observed for fat mass (P = .003), with changes in fat mass attributable predominantly to estrogen exposure in linear regression analysis (P = .016). A time-by-group interaction also was observed for lean mass (P = .03) and influenced by androgen exposure (P = .003). Conclusions: Short-term sex steroid withdrawal in healthy men causes adverse changes in body composition. These findings support the role of estradiol as a determinant of adiposity in men. Copyright © 2016 by the Endocrine Society.
Personalized treatment in advanced ALK-positive non-small cell lung cancer: From bench to clinical practice.
Passaro A., Lazzari C., Karachaliou N., Spitaleri G., Pochesci A., Catania C., Rosell R., de Marinis F.

Embase
OncoTargets and Therapy. 9 (pp 6361-6376), 2016. Date of Publication: 17 Oct 2016.
[Review]
AN: 612738322

The discovery of anaplastic lymphoma kinase (ALK) gene rearrangements and the development of tyrosine kinase inhibitors (TKI) that target them have achieved unprecedented success in the management of patients with ALK-positive non-small cell lung cancer (NSCLC). Despite the high efficacy of crizotinib, the first oral ALK TKI approved for the treatment of ALK-positive NSCLC, almost all patients inevitably develop acquired resistance, showing disease progression in the brain or in other parenchymal sites. Second- or third-generation ALK TKIs have shown to be active in crizotinib-pretreated or crizotinib-naive ALK-positive patients, even in those with brain metastases. In this review, the current knowledge regarding ALK-positive NSCLC, focusing on the biology of the disease and the available therapeutic options are discussed. Copyright © 2016 Passaro et al.
9-Month Efficacy and Safety Study of Testosterone Solution 2% for Sex Drive and Energy in Hypogonadal Men.
Brock G., Heiselman D., Knorr J., Ni X., Kinchen K.
Embase
[Article]
AN: 612934766
Purpose We evaluated the continued safety and efficacy of testosterone solution 2% (T-sol) in a 6-month open label extension study following a 3-month, double-blind, placebo controlled study in which T-sol was safe and efficacious for sex drive in men with androgen deficiency. Materials and Methods A total of 558 hypogonadal participants with a mean (SD) age of 55 (11) years entered the open label treatment study. Of these patients 275 had previously received placebo (formerly placebo group) and 283 had received active treatment with T-sol (continuing active group) during the double-blind phase. Outcome measures were the proportion of men with total testosterone levels within the normal range; assessment of treatment induced change in sex drive measured using the Sexual Arousal, Interest, and Drive scale; and assessment of treatment induced change in energy measured using the Hypogonadism Energy Diary. Results At the completion of the open label phase 60% and 66% of the participants had total testosterone levels within the normal range in the formerly placebo and continuing active groups, respectively. Participants assigned to both groups showed baseline to end point improvement in Sexual Arousal, Interest, and Drive score (both p <0.001) and Hypogonadism Energy Diary score (both p <0.001) during the open label phase. No new safety concerns were reported. Conclusions Once daily T-sol administered for 6 months in an open label study did not indicate new safety concerns, and the outcomes of low sex drive and low energy showed further improvement after the double-blind phase.
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Status
EMBASE
Effect of testosterone on hepcidin, ferroportin, ferritin and iron binding capacity in patients with hypogonadotropic hypogonadism and type 2 diabetes.

Dhindsa S., Ghanim H., Batra M., Kuhadiya N.D., Abuaysheh S., Green K., Makdissi A., Chaudhuri A., Dandona P.

Embase
Clinical Endocrinology. 85 (5) (pp 772-780), 2016. Date of Publication: 01 Nov 2016.

[Article]
AN: 612751724

Context: As the syndrome of hypogonadotropic hypogonadism (HH) is associated with anaemia and the administration of testosterone restores haematocrit to normal, we investigated the potential underlying mechanisms. Design: Randomized, double-blind, placebo-controlled trial.

Methods: We measured basal serum concentrations of erythropoietin, iron, iron binding capacity, transferrin (saturated and unsaturated), ferritin and hepcidin and the expression of ferroportin and transferrin receptor (TR) in peripheral blood mononuclear cells (MNC) of 94 men with type 2 diabetes. Forty-four men had HH (defined as subnormal free testosterone along with low or normal LH concentrations) while 50 were eugonadal. Men with HH were randomized to testosterone or placebo treatment every 2 weeks for 15 weeks. Blood samples were collected at baseline, 3 and 15 weeks after starting treatment. Twenty men in testosterone group and 14 men in placebo group completed the study. Results: Haematocrit levels were lower in men with HH (41.1 +/- 3.9% vs 43.8 +/- 3.4%, P = 0.001). There were no differences in plasma concentrations of hepcidin, ferritin, erythropoietin, transferrin or iron, or in the expression of ferroportin or TR in MNC among HH and eugonadal men. Haematocrit increased to 45.3 +/- 4.5%, hepcidin
decreased by 28 +/- 7% and erythropoietin increased by 21 +/- 7% after testosterone therapy (P < 0.05). There was no significant change in ferritin concentrations, but transferrin concentration increased while transferrin saturation and iron concentrations decreased (P < 0.05). Ferroportin and TR mRNA expression in MNC increased by 70 +/- 13% and 43 +/- 10%, respectively (P < 0.01), after testosterone therapy. Conclusions: The increase in haematocrit following testosterone therapy is associated with an increase in erythropoietin, the suppression of hepcidin, and an increase in the expression of ferroportin and TR. Copyright © 2016 John Wiley & Sons Ltd


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2016
Objective. Obesity is a risk factor for hypogonadotropic hypogonadism in men. Weight loss has been shown to improve hypogonadism in obese men. This study evaluated the early changes in sex hormones profile after bariatric surgery. Methods. This is a prospective study including 29 morbidly obese men. Main outcomes were changes in serum levels of total testosterone (TT), free testosterone (cFT), SHBG, estradiol, adiponectin, and leptin at 1 and 6 months after surgery. Results. The mean age of patients was 31 +/- 8 years and the mean BMI was 56.8 +/- 11.7 kg/m2. Fifteen patients underwent Roux-en-Y gastric bypass and 14 patients underwent sleeve gastrectomy. At baseline, 22 patients (75.9%) had either low TT levels (<10.4 nmol/L) or low cFT levels (<225 pmol/L). Total testosterone and SHBG levels increased significantly at 1 month after surgery (p <= 0.001). At 6 months after surgery, TT and cFT increased significantly (p <= 0.001) and 22 patients (75.9%) had normalized TT and cFT levels. There were no changes in estradiol levels at either 1 month or 6 months after surgery. Conclusions. Increases in TT and SHBG levels occurred early at 1 month after bariatric surgery while improvements in cFT levels were observed at 6 months after bariatric surgery. Copyright © 2016 Patchaya Boonchaya-anant et al.

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[Article]
AN: 612507532
Purpose: To provide evidence-based guidance on the optimum management of chronic pain in adult cancer survivors. Methods: An ASCO-convened expert panel conducted a systematic literature search of studies investigating chronic pain management in cancer survivors. Outcomes of interest included symptom relief, pain intensity, quality of life, functional outcomes, adverse events, misuse or diversion, and risk assessment or mitigation. Results: A total of 63 studies met eligibility criteria and compose the evidentiary basis for the recommendations. Studies tended to be heterogeneous in terms of quality, size, and populations. Primary outcomes also varied across the studies, and in most cases, were not directly comparable because of different outcomes, measurements, and instruments used at different time points. Because of a paucity of high-quality evidence, many recommendations are based on expert consensus. Recommendations: Clinicians should screen for pain at each encounter. Recurrent disease, second malignancy, or late-onset treatment effects in any patient who reports new-onset pain should be evaluated, treated, and monitored. Clinicians should determine the need for other health professionals to provide comprehensive pain management care in patients with complex needs. Systemic nonopioid analgesics and adjuvant analgesics may be prescribed to relieve chronic pain and/or to improve function. Clinicians may prescribe a trial of opioids in carefully selected patients with cancer who do not respond to more conservative management and who continue to experience distress or functional impairment. Risks of adverse effects of opioids should be assessed. Clinicians should clearly understand terminology such as tolerance, dependence, abuse, and addiction as it relates to the use of opioids and should incorporate universal precautions to minimize abuse, addiction, and adverse consequences. Additional information is available at www.asco.org/chronic-pain-

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American Society of Clinical Oncology (E-mail: jcoservice@asco.org)

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2016

375.
Have the Testosterone Trials demonstrated the effectiveness of testosterone therapy in older men without classical hypogonadism?.
Gan E.H., Quinton R.

Embase
The 'Testosterone Trials' (TTT) are an interlinked and coordinated series of seven US National Institutes of Health (NIH)-sponsored, double-blinded, placebo controlled studies examining the potential benefits of testosterone therapy in a hyper-selected cohort of older men. TTT aimed to evaluate the impact of testosterone therapy on symptoms commonly associated with male ageing and also postulated to relate to testosterone deficiency, but were not powered to detect adverse outcomes. Findings from the three lead studies, focusing on vitality, sexual and physical function, were recently published. These three lead studies comprised 790 men (having screened 51,085 applicants) aged 65 years and older, with an average serum total testosterone concentration less than 275 ng/dl (9.5 nmol/l), from morning venepuncture on two separate days. Participants received either testosterone or placebo gel for 1 year. Each man could participate in one or more of the three trials, depending on their reported symptoms in relation to impairment of sexual function, physical function and/or vitality. In order to evaluate efficacy, assessments were made every three months from baseline to end-of-study at 12 months. Testogel (Androgel 1%) was initiated at 5 g daily and the dose titrated so as to achieve serum total testosterone concentrations in what would be the mid normal range for men aged between 19 and 40. A statistically significant improvement in sexual activity from baseline was observed in the treatment arm, as ascertained by the Psychosexual Daily Questionnaire score; this emerged from the Sexual Function Trial itself and also when data from all three trials were combined: OR 0.58 (p < 0.001) and 0.62 (p < 0.001), respectively. A better response was associated with a greater increase in testosterone level. Sexual desire and erectile function also improved with a treatment effect of 2.93 (p < 0.001) and 2.64 (p < 0.001), respectively. However, the magnitude of these responses began to decline in a linear manner from 9 months until observations ceased at the study end-point of 12 months. The Physical Function Trial examined the percentage of men whose 6-min walking distance increased by at least 50 m over the course of the study, and failed to identify any benefit from testosterone therapy, although a small but significant improvement was noted when data from all three studies were pooled (20.5% in T arm vs 12.6% receiving placebo: OR 1.75; p = 0.003). The Vitality Trial likewise failed to identify any significant improvements in this domain for the testosterone arm, although there was a statistically significant difference in PANAS (positive and negative affect schedule) scores compared with the placebo arm when data from all three studies were pooled, suggesting slightly better mood and lower severity of depressive symptoms with testosterone treatment. Overall, testosterone therapy increased levels of free testosterone, estradiol and dihydrotestosterone, but unsurprisingly did not increase levels of sex hormone binding globulin. No significant adverse effects were observed in
the treatment arms and no significant between-group differences were observed in cardiac adverse events in the 12-month study period. However, the study was a priori underpowered for evaluation of safety. Copyright © 2016 Royal College of Physicians of Edinburgh.

Background The effects of testosterone on cognitive function in older men are incompletely understood. We aimed to establish the effects of long-term testosterone administration on multiple domains of cognitive function in older men with low or low-to-normal testosterone concentrations. Methods We did the randomised, double-blind, placebo-controlled, parallel-group TEAAM trial at three medical centres in Boston, Phoenix, and Los Angeles, USA. Men aged 60 years and older with low or low-to-normal testosterone concentrations (3.47-13.9 nmol/L, or free testosterone (nmol/L) 10.4-37.5).
testosterone <173 pmol/L) were randomly assigned (1:1), via computer-generated randomisation, to receive either 7.5 g of 1% testosterone gel or placebo gel daily for 3 years. Randomisation was stratified by age (60-75 years vs >75 years) and study site. The testosterone dose was adjusted to achieve concentrations of 17.3-31.2 nmol/L. Participants and all study personnel were masked to treatment allocation. Multiple domains of cognitive function were assessed as prespecified secondary outcomes by use of standardised tests at baseline and months 6, 18, and 36. We did analyses by intention to treat (in men who had baseline assessments of cognitive function) and per protocol (restricted to participants who completed the study drug and had both baseline and 36 month assessments of cognitive function). The TEAAM trial is registered with ClinicalTrials.gov, number NCT00287586. Findings Between Sept 1, 2004, and Feb 12, 2009, we randomly assigned 308 participants to receive either testosterone (n=156) or placebo (n=152). 280 men had baseline cognitive assessments (n=140 per group). Mean follow-up time was 29.0 months (SD 11.5) in the testosterone group and 31.1 months (9.5) in the placebo group. The last participant completed the study on May 11, 2012. In the testosterone group, mean concentrations of serum total testosterone increased from 10.6 nmol/L (SD 2.2) to 19.7 nmol/L (9.2) and free testosterone concentrations increased from 222 pmol/L (62) to 364 pmol/L (222). In the placebo group, mean concentrations of serum total testosterone were 10.7 nmol/L (SD 2.3) at baseline and 11.1 nmol/L (3.2) post-intervention and free testosterone concentrations were 210 pmol/L (61) and 172 pmol/L (49), respectively. We recorded no between-group differences in changes in visuospatial ability (mean difference: Complex Figure Test -0.51, 95% CI -2.0 to 1.0), phonemic or category verbal fluency (phonemic fluency test 0.90, -1.3 to 3.1; categorical fluency test 1.1, -0.3 to 2.6), verbal memory (paragraph recall test 0.29, -1.2 to 1.8), manual dexterity (Grooved Pegboard Test 4.2, -1.3 to 9.7), and attention or executive function (Stroop Interference Test -2.6, -7.4 to 2.3) after adjustment for age, education, and baseline cognitive function. In both the intention-to-treat and per-protocol (n=86 per group) populations, changes in cognitive function scores were not related significantly to changes in total or free testosterone, or oestradiol concentrations. Interpretation Testosterone administration for 36 months in older men with low or low-to-normal testosterone concentrations did not improve cognitive function. Future long-term trials are needed to investigate the efficacy of testosterone replacement in patients with impaired cognition, such as people with Alzheimer's disease. Funding AbbVie Pharmaceuticals, Aurora Foundation, Boston Claude D Pepper Older Americans Independence Center, and Boston University's Clinical and Translational Science Institute. Copyright © 2016 Elsevier Ltd
377.
Effects of testosterone and estradiol deficiency on vasomotor symptoms in hypogonadal men.
Embase
Journal of Clinical Endocrinology and Metabolism. 101 (9) (pp 3479-3486), 2016. Date of
Publication: September 2016.
[Article]
AN: 612434710
Context: The hormonal basis of vasomotor symptoms (VMS) in hypogonadal men is incompletely
understood. Objective: To determine the contributions of testosterone and estradiol deficiency to
VMS in hypogonadal men. Design: Two randomized trials were conducted sequentially between
September 2004 and April 2011. Controls were recruited separately. Setting: A single-site
academic medical center. Participants: Healthy men ages 20-50, with normal serum testosterone
levels. Intervention: Cohort 1 (n = 198, 81% completion) received goserelin acetate every 4
weeks to suppress gonadal steroids and were randomized to placebo or 1.25, 2.5, 5, or 10 g of testosterone gel daily for 16 weeks. Cohort 2 (n = 202, 78% completion) received the same regimen as cohort 1 plus anastrozole to block aromatization of testosterone. Controls (n = 37, 89% completion) received placebos for goserelin acetate and testosterone. Main Outcome Measures: Incidence of visits with VMS. This was a preplanned secondary analysis. Results: VMS were reported at 26% of visits in cohort 1, and 35% of visits in cohort 2 (P = .02), demonstrating an effect of estradiol deficiency. When adjacent estradiol level groups in cohort 1 were compared, the largest difference in VMS incidence was observed between the 5-9.9 and 10-14.9 pg/mL groups (38% vs 16%, P < .001). In cohort 2, the 10-g testosterone group differed significantly from placebo (16% vs 43%, P = .048) after adjustment for small differences in estradiol levels, indicating that high testosterone levels may suppress VMS. Conclusions: Estradiol deficiency is the key mediator of VMS in hypogonadal men. At high levels, testosterone may have a suppressive effect.

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Prediction model for live birth in ICSI using testicular extracted sperm.
Meijerink A.M., Cissen M., Mochtar M.H., Fleischer K., Thoonen I., De Melker A.A., Meissner A.,
Repping S., Braat D.D.M., VanWely M., Ramos L.
Embase
[Article]
AN: 612436199
Study question: Which parameters have a predictive value for live birth in couples undergoing
ICSI after successful testicular sperm extraction (TESE-ICSI)? summaryanswer: Female age, a
first or subsequent started TESE-ICSI cycle, male LH, male testosterone, motility of the
spermatozoa during the ICSI procedure and the initial male diagnosis before performing TESE
were identified as relevant and independent parameters for live birth after TESE-ICSI. what is
known already: In reproductive medicine prediction models are used frequently to predict
treatment success, but no prediction model currently exists for live birth after TESE-ICSI. study
design, size, duration: Aretrospective cohort studybetween 2007 and 2015 in two academic
hospitals including 1559 TESEICSI cycles. The prediction model was developed using data from
one centre and validation was performed with data from the second centre. participants/materials,
setting, methods: We included couples undergoing ICSI treatment with surgically retrieved sperm
from the testis for the first time. In the development set we included 526 couples undergoing 1006
TESE-ICSI cycles. In the validation set we included 289 couples undergoing 553 TESE-ICSI
cycles. Multivariable logistic regression models were constructed in a stepwise fashion (P < 0.2
for entry). The external validation was based on discrimination and calibration. main results and
the role of chance: We included 224 couples (22.3%) with a live birth in the development set. The
occurrence of a live birthwas associated with lower female age, first TESE-ICSI cycle, lower male
LH, higher male testosterone, the use of motile spermatozoa for ICSI and having obstructive
azoospermia as an initial suspected diagnosis. The area under the receiver operating
characteristic (ROC) curve was 0.62. From validation data, the model had moderate
discriminative capacity (c-statistic 0.67, 95% confidence interval: 0.62-0.72) but calibrated well,
with a range from 0.06 to 0.56 in calculated probabilities. limitations, reasons for caution: We had
a lack of data about the motility of spermatozoa during TESE, therefore, we used motility of the
spermatozoa used for ICSI after freeze-thawing, information which is only available during
treatment. We had to exclude data on paternal BMI in the model because too many missing
values in the validation data hindered testing. We did not include a histologic diagnosis, which would have made our data set less heterogeneous and, finally, our model may not be applicable in centres which have a different policy for the indication for performing sperm extraction. The prognostic value of the model is limited because of a low ‘area under the curve’. wider implications of the findings: This model enables the differentiation between couples with a lower high chance to reach a live birth using TESE-ICSI. As such it can aid in the counselling of patients and in clinical decision-making. study funding/competing interest(s): This study was partly supported by an unconditional grant from Merck Serono (to D.D.M.B. and K.F.) and by the Department of Obstetrics and Gynaecology of Radboud University Medical Center, Nijmegen, The Netherlands, The Department of Obstetrics and Gynaecology, Jeroen Bosch Hospital, Den Bosch, The Netherlands, and the Department of Obstetrics and Gynaecology, Academic Medical Center, Amsterdam, The Netherlands. Merck Serono had no influence in concept, design, nor elaboration of this study. trial registration number: Not applicable. Copyright © The Author 2016.
Study question: Can an externally validated model, based on biological variables, be developed to predict successful sperm retrieval with testicular sperm extraction (TESE) in men with non-obstructive azoospermia (NOA) using a large nationwide cohort? Summary answer: Our prediction model including six variables was able to make a good distinction between men with a good chance and men with a poor chance of obtaining spermatozoa with TESE. What is known already: Using ICSI in combination with TESE even men suffering from NOA are able to father their own biological child. Only in approximately half of the patients with NOA can testicular sperm be retrieved successfully. The few models that have been developed to predict the chance of obtaining spermatozoa with TESE were based on small datasets and none of them have been validated externally. Study design, size, duration: We performed a retrospective nationwide cohort study. Data from 1371 TESE procedures were collected between June 2007 and June 2015 in the two fertility centres. Participants/materials, setting, methods: All men with NOA undergoing their first TESE procedure as part of a fertility treatment were included. The primary endpoint was the presence of one or more spermatozoa (regardless of their motility) in the testicular biopsies. We constructed a model for the prediction of successful sperm retrieval, using univariable and multivariable binary logistic regression analysis and the dataset from one centre. This model was then validated using the dataset from the other centre. The area under the receiver-operating characteristic curve (AUC) was calculated and model calibration was assessed. Main results and the role of chance: There were 599 (43.7%) successful sperm retrievals after a first TESE procedure. The prediction model, built after multivariable logistic regression analysis, demonstrated that higher male age, higher levels of serum testosterone and lower levels of FSH and LH were predictive for successful sperm retrieval. Diagnosis of idiopathic NOA and the presence of an azoospermia factor c gene deletion were predictive for unsuccessful sperm retrieval. The AUC was 0.69 (95% confidence interval (CI): 0.66-0.72). The difference between the mean observed chance and the mean predicted chance was <2.0% in all groups, indicating good calibration. In validation, the model had moderate discriminative capacity (AUC 0.65, 95% CI: 0.62-0.72) and moderate calibration: the predicted probability never differed by more than 9.2% of the mean observed probability. Limitations, reasons for caution: The percentage of men with Klinefelter syndrome among men diagnosed with NOA is expected to be higher than in our study.
population, which is a potential selection bias. The ability of the sperm retrieved to fertilize an oocyte and produce a live birth was not tested. wider implications of the findings: This model can help in clinical decision-making in men with NOA by reliably predicting the chance of obtaining spermatozoa with TESE. study funding/competing interest: This study was partly supported by an unconditional grant from Merck Serono (to D.D.M.B. and K.F.) and by the Department of Obstetrics and Gynaecology of Radboud University Medical Center, Nijmegen, The Netherlands, the Department of Obstetrics and Gynaecology, Jeroen Bosch Hospital, Den Bosch, The Netherlands, and the Department of Obstetrics and Gynaecology, Academic Medical Center, Amsterdam, The Netherlands. Merck Serono had no influence in concept, design nor elaboration of this study. trial registration number: Not applicable. Copyright © The Author 2016.

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380.
Perfluoroalkyl and polyfluoroalkyl substances and measures of human fertility: a systematic review.
Bach C.C., Vested A., Jorgensen K.T., Bonde J.P.E., Henriksen T.B., Toft G.
Embase
Critical Reviews in Toxicology. 46 (9) (pp 735-755), 2016. Date of Publication: 20 Oct 2016.
[Review]
AN: 612377894

Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are found widespread in the environment and humans. The relation of PFASs to fertility has now been examined in a relatively large number of epidemiologic studies and a synthesis is in order. The aim of this study was to assess the current human epidemiologic evidence on the association between exposure to PFASs and measures of human fertility, with particular emphasis on perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA). Systematic literature searches were initially conducted in MEDLINE and EMBASE and subsequently in references and citations of included papers. Studies were included if they assessed exposure to PFASs in biological samples in relation to reproductive hormones, semen characteristics, or time to pregnancy (TTP). Study characteristics and results were abstracted to predefined forms, and the studies were assessed for the risk of bias and confounding. Sixteen studies investigated the association between PFAS exposure in men and semen parameters, reproductive hormone levels, or TTP. There was a lack of consistent results among the numerous investigated exposure-outcome combinations. However, subtle associations between higher PFOS and lower testosterone or abnormal semen morphology cannot be excluded. Eleven studies assessed the association between PFAS exposure in women and TTP or reproductive hormones levels. Four of eight studies found prolonged TTP with higher PFOS or PFOA, but only one study found an association when restricting to nulliparous women. In men, there is little evidence of an association between PFAS exposure and semen quality or levels of reproductive hormones. For PFOS and PFOA, the literature indicates an association with female fecundability in parous women, which is most likely not causal. Copyright © 2016 Informa UK Limited, trading as Taylor & Francis Group.

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Guidelines: Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline for Pretreatment Endocrine Evaluation of Patients with Nonfunctioning Pituitary Adenomas.

Fleseriu M., Bodach M.E., Tumialan L.M., Bonert V., Oyesiku N.M., Patil C.G., Litvack Z., Aghi M.K., Zada G.

Embase Neurosurgery. 79 (4) (pp E527-E529), 2016. Date of Publication: 01 Oct 2016.

BACKGROUND: Nonfunctioning pituitary adenomas (NFPAs) are among the most common pituitary lesions and may present with hypopituitarism and/or hyperprolactinemia. OBJECTIVE: To review the existing literature as it pertains to preoperative endocrine assessment in the workup for NFPAs. METHODS: A systematic review methodology was utilized to identify and screen articles assessing the role and results of preoperative laboratory assessment in patients with NFPAs. The prevalence of individual pituitary hormonal axis deficiencies was reviewed. RESULTS: Twenty-nine studies met inclusion criteria for analysis. No class I evidence was available, and all studies met criteria for class II evidence. Baseline serum laboratory assessment showed a prevalence of overall hypopituitarism in 37% to 85% of patients. The most common hormonal axis deficiency was growth hormone deficiency, prevalent in 61% to 100% of patients. The next most common deficit was hypogonadism, seen in 36% to 95% of patients. Adrenal insufficiency was diagnosed in 17% to 62% of patients. Finally, hypothyroidism was seen in 8% to
81% of patients. Hyperprolactinemia was seen in 25% to 65% of patients, with a mean level of 39 ng/mL and with a minority of patients exceeding a serum prolactin level of 200 ng/mL. No evidence supporting routine biomarker testing (eg, alpha-subunit or chromogranin A) or genetic testing in patients with sporadic NFPAs was available. CONCLUSION: Despite a paucity of class I evidence, multiple retrospective studies have demonstrated a high prevalence of hypopituitarism in patients with NFPAs. Routine endocrine analysis of all anterior pituitary axes to assess for hypopituitarism is recommended, with prolactin and insulin-like growth factor 1 evaluation also valuable to assess for hypersecretion states that might not be clinically suspected. The full guidelines document for this chapter can be located at https://www.cns.org/guidelines/guidelines-management-patients-non-functioning-pituitary-adenomas/Chapter-3. Copyright © 2016 by the Congress of Neurological Surgeons.

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Low bone mineral density (BMD) and osteoporosis are common in patients with schizophrenia and detrimental to illness prognosis and life quality. Although the pathogenesis is not fully clear, series of studies have revealed factors related to low BMD such as lifestyle, psychotic symptoms, medication use and the activity of bone absorption markers. It has been known that antipsychotic-induced hyperprolactinemia plays a critical role on decreased BMD. However, it remains uncertain whether the risk factors differ between men and women. According to the effect on prolactin, antipsychotics can be classified into two groups: prolactin-sparing (PS) and prolactin-raising (PR). Our previous study has demonstrated that clozapine which is among the PS antipsychotics is beneficial for BMD when compared with PR antipsychotics in women with chronic schizophrenia. We have also found that risks factors associated with low BMD are different between men and women, suggesting that gender-specific risk factors should be considered for intervention of bone loss in patients with schizophrenia. This article reviews the effects of antipsychotics use on BMD with particular discussion for the differences on gender and age, which implicate the alterations of sex and other related hormones. In addition, currently reported protective and risk factors, as well as the effects of medication use on BMD including the combination of antipsychotics and other psychotropic agents and other potential medications are also reviewed.

Copyright © 2016, Korean College of Neuropsychopharmacology.
Aims: To evaluate the effect of testosterone replacement therapy (TRT) on body composition, insulin sensitivity, oxidative metabolism and glycaemic control in aging men with lowered bioavailable testosterone (BioT) levels and type 2 diabetes mellitus (T2D) controlled on metformin monotherapy. Materials and methods: We conducted a randomized, double-blind, placebo-controlled study in 39 men aged 50-70 years with BioT levels <7.3 nmol/L and T2D treated with metformin monotherapy. Patients were randomized to testosterone gel (TRT, n = 20) or placebo (n = 19) for 24 weeks. Lean body mass (LBM), total and regional fat mass were measured using whole-body dual-energy X-ray absorptiometry scans. Whole-body peripheral insulin sensitivity, endogenous glucose production (EGP) and substrate oxidation were assessed by euglycaemic-hyperinsulinaemic clamp with glucose tracer and combined with indirect calorimetry. Coefficients (beta) represent the placebo-controlled mean effect of intervention. Results: LBM (beta = 1.9 kg, p = 0.001) increased after TRT, while total fat mass (beta = -1.3 kg, p = 0.009), fat mass trunk (beta = -0.7 kg, p = 0.043), fat mass legs (beta = -0.7 kg, p = 0.025), fat mass arms (beta = -0.3 kg, p = 0.001), and HDL cholesterol (beta = -0.11 mmol/L, p = 0.009) decreased after TRT compared with placebo. Insulin-stimulated glucose disposal rates did not change in response to TRT compared with placebo (p = 0.18). Moreover, glycated haemoglobin, and basal and insulin-stimulated rates of EGP, lipid- and glucose-oxidation were unaltered after TRT. Conclusion: TRT in aging men with lowered BioT levels and T2D controlled on metformin monotherapy improved
body composition; however, glycaemic control, peripheral insulin sensitivity, EGP and substrate metabolism were unchanged. Copyright © 2016 John Wiley & Sons Ltd

384.
Testosterone therapy in men with testosterone deficiency: Are the benefits and cardiovascular risks real or imagined?

Traish A.M.

American Journal of Physiology - Regulatory Integrative and Comparative Physiology. 311 (3) (pp R566-R573), 2016. Date of Publication: 2016.

[Review]

AN: 612132117

In the adult male, testosterone (T) deficiency (TD) also known as male hypogonadism, is a well-established medical condition, which has been recognized for more than a century. T therapy in men with TD was introduced as early as 1940s and was reported to improve overall health with no concomitant serious adverse effects. A wealth of recent studies demonstrated that T therapy in men with TD is associated with increased lean body mass, reduced fat mass and waist circumference, improvement in glycemic control, and reduced obesity. T therapy is also associated with improvements in lipid profiles, amelioration of metabolic syndrome (Met S)
components, reduced inflammatory biomarkers, reduced systolic and diastolic blood pressure, and improvements in sexual function. More importantly, T therapy is associated with amelioration of diabetes and reduced mortality. However, few studies, marred with serious methodological and analytical flaws reported between 2010 and 2014, suggested that T therapy is associated with increased cardiovascular (CV) risk. As summarized in this review, a thorough and critical analysis of these studies showed that the risks purported are unsubstantiated and such studies lacked credible scientific and clinical evidence. Moreover, recent observational, registry studies, clinical trials, and meta-analyses, all revealed no increase in CV risks in men receiving T therapy. In this review, the benefits of T therapy in adult men with TD and the lack of credible evidence suggesting that T therapy is linked to increased CV risks are discussed. It should be noted that the literature is replete with studies demonstrating beneficial effects of T therapy on CV and overall health. Copyright © 2016 the American Physiological Society.

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385.
Effects of liver transplantation on endocrine function: a systematic review.
Gariani K., Toso C., Philippe J., Orci L.A.
Embase
Liver International. 36 (10) (pp 1401-1411), 2016. Date of Publication: 01 Oct 2016.
[Review]
AN: 612111357
Patients with chronic liver disease (CLD) often experience secondary endocrine dysfunction. Therefore, because the liver plays a major role in endocrine function, liver transplantation (LT)
may also be beneficial for the restoration of hormonal regulation. This systematic review collects and interprets the available literature on the effect of LT on endocrine and sexual function in adult patients. A systematic review was conducted by searching Pubmed (including Medline) and EMBASE for studies published from database inception until November 2015. We collected all relevant studies that discussed changes in hormonal and sexual function after LT. Studies were included if they assessed the effect of LT on sexual function or one of the following components of the hormone/endocrine axis: the hypothalamus-pituitary-gonadal axis, growth hormone (GH), insulin-like growth factor-1 (IGF-1) or thyroid function. The results are reported according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. Twenty-one studies with a total of 1274 patients were included. The results collected from the included studies suggested that LT improves the hormonal perturbation associated with CLD by restoring physiological levels of circulating GH, IGF-1, testosterone, estradiol, prolactin, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Thyroid function was not affected by LT, and sexual function was partially improved after LT. This systematic review suggests that LT is associated with an improvement in endocrine and sexual function in patients with CLD. This information should encourage clinicians who treat CLD patients to identify endocrine disturbances in this population, inform their patients of the effects of LT and assess post-transplantation improvements. Copyright © 2016 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd


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Emerging medication for the treatment of male hypogonadism.
Aydogdu A., Swerdloff R.S.

Expert Opinion on Emerging Drugs. 21 (3) (pp 255-266), 2016. Date of Publication: 02 Jul 2016.

Introduction: Male hypogonadism is characterized by inadequate production of Testosterone (T) (hypoandrogenism) and deficiencies in spermatogenesis. The main treatment of male hypogonadism is T replacement therapy (TRT), but for some of the patients, alternative drugs may be more suitable. Areas covered: The available literature of T and alternative treatments for male hypogonadism are discussed. Expert opinion: Transdermal application of T gels are the most commonly used route of T administration. Some oral T formulations are either associated with hepatic toxicity (i.e. methyltestosterone) or short half-lives that require multiple doses per day (i.e. oral testosterone undecanoate). Short acting, injectable T formulations are also available. If the patient prefers not to use daily drugs or short acting injectable formulations, depot formulations such as injectable testosterone undecanoate (TU) may be a good alternative. If the patient has hypogonadotropic hypogonadism and desires fertility or if he is adolescent, instead of TRT, gonadotropins can be started to stimulate testicular growth and spermatogenesis. In obese patients or for the patients having high risks for TRT, off label aromatase inhibitors (AI) and clomiphene citrate (CC), may be considered to stimulate LH, FSH and T levels. In patients with high prostate disease risk, selective androgen receptor modulators may be an alternative treatment but these latter treatments have not had high level evidence. Copyright © 2016 Informa UK Limited, trading as Taylor & Francis Group.
Bone health and vitamin D status in alcoholic liver disease.
Kizilgül M., Ozcelik O., Delibasi T.
Embase
Indian Journal of Gastroenterology. 35 (4) (pp 253-259), 2016. Date of Publication: 01 Jul 2016.
[Review]
AN: 611081002
Alcohol consumption is harmful to many organs and tissues, including bones, and it leads to osteoporosis. Hepatic osteodystrophy is abnormal bone metabolism that has been defined in patients with chronic liver disease (CLD), including osteopenia, osteoporosis, and osteomalacia. Decreased bone density in patients with CLD results from decreased bone formation or increased bone resorption. The prevalence of osteopenia in alcoholic liver disease (ALD) patients is between 34% and 48%, and the prevalence of osteoporosis is between 11% and 36%. Cirrhosis is also a risk factor for osteoporosis. The liver has an important role in vitamin D metabolism. Ninety percent of patients with alcoholic liver cirrhosis have vitamin D inadequacy (<80 nmol/L). The lowest serum vitamin D levels were observed in patients with Child-Pugh class C. Bone densitometry is used for the definitive diagnosis of osteoporosis in ALD. There are no specific controlled clinical studies on the treatment of osteoporosis in patients with ALD. Alcohol cessation and abstinence are principal for the prevention and treatment of osteoporosis in ALD patients, and the progression of osteopenia can be stopped in this way. Calcium and vitamin D supplementation is recommended, and associated nutritional deficiencies should also be corrected. The treatment recommendations of osteoporosis in CLD tend to be extended to ALD. Bisphosphonates have been proven to be effective in increasing bone mineral density (BMD) in chronic cholestatic disease and post-transplant patients, and they can be used in ALD patients. Randomized studies assessing the management of CLD-associated osteoporosis and the development of new drugs for osteoporosis may change the future. Here, we will discuss bone quality, vitamin D status, mechanism of bone effects, and diagnosis and treatment of osteoporosis in ALD. Copyright © 2016, Indian Society of Gastroenterology.
Collective hormonal profiles predict group performance.
Akinola M., Page-Gould E., Mehta P.H., Lu J.G.

Embase
[Conference Paper]
AN: 611894759

Prior research has shown that an individual's hormonal profile can influence the individual's social standing within a group. We introduce a different construct—a collective hormonal profile—which describes a group's hormonal make-up. We test whether a group's collective hormonal profile is related to its performance. Analysis of 370 individuals randomly assigned to work in 74 groups of three to six individuals revealed that group-level concentrations of testosterone and cortisol interact to predict a group's standing across groups. Groups with a collective hormonal profile characterized by high testosterone and low cortisol exhibited the highest performance. These collective hormonal level results remained reliable when controlling for personality traits and group-level variability in hormones. These findings support the hypothesis that groups with a biological propensity toward status pursuit (high testosterone) coupled with reduced stress-axis activity (low cortisol) engage in profit-maximizing decision-making. The current work extends the dual-hormone hypothesis to the collective level and provides a neurobiological perspective on the factors that determine who rises to the top across, not just within, social hierarchies.

Status
Testosterone treatment and sexual function in older men with low testosterone levels.

Embase
[Article]
AN: 611956626

Context: The Testosterone Trials are a coordinated set of seven trials to determine the efficacy of T in symptomatic men >=65 years old with unequivocally low T levels. Initial results of the Sexual Function Trial showed that T improved sexual activity, sexual desire, and erectile function.

Objective: To assess the responsiveness of specific sexual activities to T treatment; to relate hormone changes to changes in sexual function; and to determine predictive baseline characteristics and T threshold for sexual outcomes. Design: A placebo-controlled trial. Setting: Twelve academic medical centers in the United States. Participants: A total of 470 men >=65 years of age with low libido, average T <275 ng/dL, and a partner willing to have sexual intercourse at least twice a month. Methods: Men were assigned to take T gel or placebo for 1
year. Sexual function was assessed by three questionnaires every 3 months: the Psychosexual Daily Questionnaire, the Derogatis Interview for Sexual Function, and the International Index of Erectile Function. Results: Compared with placebo, T administration significantly improved 10 of 12 measures of sexual activity. Incremental increases in total and free T and estradiol levels were associated with improvements in sexual activity and desire, but not erectile function. No threshold T level was observed for any outcome, and none of the 27 baseline characteristics predicted responsiveness to T. Conclusions: In older men with low libido and low T levels, improvements in sexual desire and activity in response to T treatment were related to the magnitude of increases in T and estradiol levels, but there was no clear evidence of a threshold effect.

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390.
The drug treatment of delayed ejaculation.
Abdel-Hamid I.A., Elsaied M.A., Mostafa T.

Embase
Translational Andrology and Urology. 5 (4) (pp 576-591), 2016. Date of Publication: 01 Aug 2016.
[Review]
AN: 611873962
Delayed ejaculation (DE) is an uncommon and a challenging disorder to treat. It is often quite concerning to patients and it can affect psychosocial well-being. Here we reviewed how DE is treated pharmacologically. We also highlighted specific settings where drugs could be introduced to medical practice. Electronic databases were searched from 1966 to February 2016, including PubMed MEDLINE, EMBASE, EBCSO Academic Search Complete, Cochrane Systematic Reviews Database, and Google Scholar using key words; delayed ejaculation, retarded ejaculation, inhibited ejaculation, drugs, treatment, or pharmacology. To achieve the maximum sensitivity of the search strategy and to identify all studies, we combined "delayed ejaculation" as Medical Subject Headings (MeSH) terms or keywords with each of "testosterone" or "cabergoline" or "bupropion" or "amantadine" or "cyproheptadine" or "midodrine" or "imipramine" or "ephedrine" or "pseudoephedrine" or "yohimbine" or "buspirone" or "oxytocin" or "bethanechol" as MeSH terms or keywords. There are a number of drugs to treat patients with DE including: Testosterone, cabergoline, bupropion, amantadine, cyproheptadine, midodrine, imipramine, ephedrine, pseudoephedrine, yohimbine, buspirone, oxytocin, and bethanechol. Although there are many pharmacological treatment options, the evidence is still limited to small trials, case series or case reports. Review of literature showed that evidence level 1 (Double blind randomized clinical trial) studies were performed with testosterone, oxytocin, buspirone or bethanechol treatment. It is concluded that successful drug treatment of DE is still in its infancy. The clinicians need to be aware of the pathogenesis of DE and the pharmacological basis underlying the use of different drugs to extend better care for these patients. Various drugs are available to address such problem, however their evidence of efficacy is still limited and their choice needs to be individualized to each specific case. Copyright © Translational Andrology and Urology.

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Epidemiology of delayed ejaculation.

Di Sante S., Mollaioli D., Gravina G.L., Ciocca G., Limoncin E., Carosa E., Lenzi A., Jannini E.A.

Embase

Translational Andrology and Urology. 5 (4) (pp 541-548), 2016. Date of Publication: 01 Aug 2016.

[Review]

AN: 611873959

A large body of literature on diminished ejaculatory disorders has been generated without the use of a clear diagnostic definition. Many studies have not distinguished between the orgasm and ejaculation disorders leading to doubtful results. Delayed ejaculation (DE) is one of the diminished ejaculatory disorders, which range from varying delays in ejaculatory latency to a complete inability to ejaculate. The present review is aimed at providing a comprehensive overview of the current knowledge on the definition and epidemiology of diminished ejaculatory disorders. We focus on the acquired diseases, such as benign prostatic hyperplasia (BPH) and specific drug regimens that may cause an iatrogenic form of ejaculatory disorder. In addition, the impact of aging is discussed since the prevalence of DE appears to be moderately but positively related to age. Finally, we also focus on the importance of the hormonal milieu on male ejaculation. To date, evidence on the endocrine control of ejaculation is derived from small clinical trials, but the evidence suggests that hormones modulate the ejaculatory process by altering its overall latency.

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Former abusers of anabolic androgenic steroids exhibit decreased testosterone levels and hypogonadal symptoms years after cessation: A case-control study.
Rasmussen J.J., Selmer C., Ostergren P.B., Pedersen K.B., Schou M., Gustafsson F., Faber J., Juul A., Kistorp C.
Embase
[Article]
AN: 611884585
Aims: Abuse of anabolic androgenic steroids (AAS) is highly prevalent among male recreational athletes. The objective of this study was to investigate the impact of AAS abuse on reproductive hormone levels and symptoms suggestive of hypogonadism in current and former AAS abusers.
Methods: This study had a cross-sectional case-control design and involved 37 current AAS abusers, 33 former AAS abusers (mean (95%CI) elapsed duration since AAS cessation: 2.5 (1.7; 3.7) years) and 30 healthy control participants. All participants were aged 18-50 years and were involved in recreational strength training. Reproductive hormones (FSH, LH, testosterone, inhibin B and anti-Mullerian hormone (AMH)) were measured using morning blood samples. Symptoms of hypogonadism (depressive symptoms, fatigue, decreased libido and erectile dysfunction) were recorded systematically. Results: Former AAS abusers exhibited significantly lower median (25th-75th percentiles) total and free testosterone levels than control participants (total testosterone: 14.4 (11.9-17.7) nmol/l vs. 18.8 (16.6-22.0) nmol/l) (P < 0.01). Overall, 27.2%(13.3; 45.5) of former AAS abusers exhibited plasma total testosterone levels below the lower reference limit (12.1 nmol/l) whereas no control participants exhibited testosterone below this limit (P < 0.01). Gonadotropins were significantly suppressed, and inhibin B and AMH were significantly decreased in current AAS abusers compared with former AAS abusers and control participants (P < 0.01). The group of former AAS abusers had higher proportions of participants with depressive symptoms ((24.2%) (11.1; 42.2)), erectile dysfunction ((27.3%) (13.3; 45.6)) and decreased libido ((40.1%) (23.2; 57.0)) than the other two groups (trend analyses: P < 0.05). Conclusions: Former AAS abusers exhibited significantly lower plasma testosterone levels and higher frequencies of symptoms suggestive of hypogonadism than healthy control participants years after AAS cessation. Current AAS abusers exhibited severely decreased AMH and inhibin B indicative of
impaired spermatogenesis. Copyright © 2016 Rasmussen et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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393.
Vitamin D deficiency and low ionized calcium are linked with semen quality and sex steroid levels in infertile men.
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Human Reproduction. 31 (8) (pp 1875-1885), 2016. Date of Publication: 01 Aug 2016.
[Article]
AN: 611633716
STUDY QUESTION Are low vitamin D levels linked with semen quality and sex steroids in infertile men? SUMMARY ANSWER Infertile men with vitamin D deficiency had lower sperm motility, total numbers of motile sperm, Inhibin B, sex-hormone-binding-globulin (SHBG) and testosterone/estradiol ratio, but higher levels of free sex steroids, than infertile men with normal vitamin D levels. WHAT IS KNOWN ALREADY Low vitamin D levels have been associated with decreased sperm motility in healthy men, but a relationship between vitamin D and calcium with semen quality and especially sex steroids has not been sufficiently described in infertile men.

STUDY DESIGN, SIZE, DURATION This study comprises baseline characteristics of 1427 infertile men screened from 2011 to 2014 for inclusion in a randomized clinical trial, the Copenhagen-Bone-Gonadal Study. PARTICIPANTS/MATERIALS, SETTING, METHODS In total 1427 infertile men, consecutively referred to our tertiary andrological centre for fertility workup, underwent a physical examination and had semen quality assessed based on two samples and blood analysed for serum testosterone, SHBG, estradiol, inhibin B, luteinizing hormone, follicle-stimulating hormone (FSH), 25-hydroxyvitamin D (25-OHD), ionized calcium (Ca2+) and karyotype. There were 179 men excluded due to serious comorbidities or anabolic steroid usage, leaving 1248 patients for analyses. MAIN RESULTS AND THE ROLE OF CHANCE Men with 25-OHD >75 nmol/l had higher sperm motility and 66 and 111% higher total numbers of motile spermatozoa after 45 and 262 min, respectively, than men with 25-OHD <25 nmol/l (all P < 0.05). SHBG levels and testosterone/estradiol ratios were 15 and 14% lower, respectively, while free testosterone and estradiol ratios were 6 and 13% higher, respectively, in men with 25-OHD <25 nmol/l (all P < 0.05). Men with lower Ca2+ levels had higher progressive sperm motility and inhibin B/FSH ratio but lower testosterone/estradiol ratio (all P < 0.05). LIMITATIONS, REASONS FOR CAUTION All outcomes presented are predefined end-points but inferral of causality is compromised by the descriptive study design. It remains to be shown whether the links between vitamin D, calcium, semen quality and sex steroids in infertile men are causal. WIDER IMPLICATIONS OF THE FINDINGS The associations between vitamin D deficiency and low calcium with semen quality and sex steroids support the existence of a cross-link between regulators of calcium homeostasis and gonadal function in infertile men. STUDY FUNDING/COMPETING INTERESTS This study was supported by the Danish Agency for Science, Technology and Innovation, Horslev Fonden, Danish Cancer Society and Novo Nordisk Foundation. There are no conflicts of interest. Copyright © 2016 The Author.

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Testis ultrasound in Klinefelter syndrome infertile men: making the diagnosis and avoiding inappropriate management.

Rocher L., Moya L., Correas J.M., Mutuon P., Ferlicot S., Young J., Izard V., Benoit G., Brailly-Tabard S., Bellin M.F.

Embase

Abdominal Radiology. 41 (8) (pp 1596-1603), 2016. Date of Publication: 01 Aug 2016. [Article]

AN: 609366535

Objective: To compare the testicular Color Doppler ultrasound (US), hormone levels, and histological results from 67 infertile men with Klinefelter syndrome (KS), vs. 66 non-KS non-obstructive azoospermic men. Methods: Scrotal US images were collected from 67 infertile KS and 66 non-obstructive, non-KS azoospermic men. The testis volume, echotexture, vascularity, and microliths were evaluated and graded. We defined the following echo pattern alteration groups: normal, striated, coarse, and measurable nodules. The vascularization was classified as low, normal, moderate, or strong. Testosterone, follicle-stimulating hormone, luteinizing hormone, and inhibin B levels were determined. Large testicular nodules were removed. A testicular biopsy and sperm extraction was performed in 18 of the KS, and all of the 66 non-KS men. Results: The mean testis volume was low in the KS, compared to the non-KS patients: i.e., 2 vs. 8 mL (P <
0.0001). The distributions in the echotexture groups differed markedly, with coarse or nodular patterns in the KS men, and normal/striated patterns in the control patients (P < 0.0001). The vascularization and microlithiasis grades were higher in the KS patients than the control men (P < 0.0001 and P < 0.001, respectively). All of the nodules removed from the KS patients were benign Leydig cell tumors, and all of the biopsies showed marked Leydig cell hyperplasia, with spermatogenesis in only two patients. The non-KS biopsies were predominantly Sertoli cell-only syndrome. Conclusions: Small testes, with a coarse or nodular echotexture, hypervascularization, and microlithiasis are associated with KS. The KS nodules were benign Leydig cell tumors/hyperplasias. Copyright © 2016, Springer Science+Business Media New York.

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Recent studies have shown that ED is an early symptom of atherosclerosis. Fetuin-A, a glycoprotein secreted by the liver, kidneys and choroid plexus, has been linked to systemic fibrosis and calcification in human and rat studies. Deficiency of this compound may play a role in atherosclerosis and cardiovascular disease progression. The aim of the study was to examine whether serum fetuin-A level is related to erectile function or severity of ED. Sixty ED patients without cardiovascular disease were assigned to one of the three groups (mild, moderate or severe ED) depending on ED severity. Twenty healthy volunteers were included as the control group. The International Index of Erectile Function-5 questionnaire was used to measure erection quality in all four groups. Mean age, body mass index, total testosterone, low- and high-density lipoprotein cholesterol, and triglyceride levels did not significantly differ between the three erectile dysfunction and control groups (P > 0.05). The group with severe ED had a significantly lower mean fetuin-A level than the mild ED and control groups. For both mild and moderate ED groups, the mean serum fetuin-A level was significantly lower in comparison with the control group (P < 0.001). Serum fetuin-A level may be used as a supplemental biochemical parameter in preliminary evaluation of ED. Copyright © 2015 Blackwell Verlag GmbH

PMID
Testosterone therapy, association with age, initiation and mode of therapy with cardiovascular events: a systematic review.
Albert S.G., Morley J.E.
Embase
Clinical Endocrinology. 85 (3) (pp 436-443), 2016. Date of Publication: 01 Sep 2016.
[Article]
AN: 611711252

Background: Although male hypogonadism is associated with increased cardiovascular events (CVE), recent concerns are that testosterone supplementation may increase CVE. The purpose was to determine associations with age, initiation or mode of therapy to explain these discrepancies. Data synthesis: Meta-analyses were supplemented through Scopus and PubMed with search terms 'testosterone', 'random' and 'trial'. CVE, defined before data extraction, were death, myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, coronary bypass, syncope, arrhythmia, hospital admission for congestive heart failure or cerebrovascular event. Results: There were 45 trials with 5328 subjects evaluated, with a mean age of 63.3 (SD +/-7.9) years, followed for mean study duration of 10.6 (+/- 8.6) months. Overall, testosterone supplementation was not associated with increased CVE risk ratio (rr = 1.10 (95% CI 0.86; 1.41, P = 0.45)). However, there was an increase event rate during the first 12 months (rr = 1.79 (1.13;2.83, P = 0.012)), predominantly in those >=65 years, (rr = 2.90 (1.35:6.21, P = 0.006)). Within studies with lipid data, CVE were associated with fall in HDL, P = 0.002. Intramuscular testosterone appeared neutral for CVE (rr = 0.96 (0.462;1.98, P = 0.91)) compared with oral testosterone (rr = 2.28 (95% CI 2.28:8.59, P = 0.22)) and transdermal testosterone (rr = 2.80 (1.38;5.68, P = 0.004)). Intramuscular testosterone had the least effect of lowering HDL and non-HDL cholesterol (both P < 0.001). Conclusions: Testosterone supplementation may be associated with increased CVE in those >=65 years especially during the first year. Biological
actions may differ depending upon mode of testosterone administration with intramuscular
testosterone having less cardiovascular risk. Copyright © 2016 John Wiley & Sons Ltd
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397.
Metabolic syndrome in white European men presenting for primary couple's infertility:
investigation of the clinical and reproductive burden.
Ventimiglia E., Capogrosso P., Colicchia M., Boeri L., Serino A., Castagna G., Clementi M.C., La
Croce G., Regina C., Bianchi M., Mirone V., Damiano R., Montorsi F., Salonia A.
Embase
Andrology. 4 (5) (pp 944-951), 2016. Date of Publication: 01 Sep 2016.
[Article]
AN: 611710730
Despite complex interactions between obesity, dyslipidemia, hyperinsulinaemia, and the
reproductive axis, the impact of metabolic syndrome on human male reproductive function has
not been analysed comprehensively. Complete demographic, clinical, and laboratory data from
1337 consecutive primary infertile men were analysed. Health-significant comorbidities were
scored with the Charlson Comorbidity Index (categorised 0 vs. 1 vs. 2 or higher). NCEP-ATPIII
criteria were used to define metabolic syndrome. Semen analysis values were assessed based
on the 2010 World Health Organisation (WHO) reference criteria. Descriptive statistics and logistic regression models tested the association between semen parameters and clinical characteristics and metabolic syndrome. Metabolic syndrome was found in 128 (9.6%) of 1337 men. Patients with metabolic syndrome were older (p < 0.001) and had a greater Charlson Comorbidity Index of 1 or higher (chi-square: 15.6; p < 0.001) compared with those without metabolic syndrome. Metabolic syndrome patients had lower levels of total testosterone (p < 0.001), sex hormone-binding globulin (p = 0.004), inhibin B (p = 0.03), and anti-Mullerian hormone (p = 0.009), and they were hypogonadal at a higher rate (chi-square: 32.0; p < 0.001) than patients without metabolic syndrome. Conversely, the two groups did not differ significantly in further hormonal levels, semen parameters, and rate of either obstructive or non-obstructive azoospermia. At multivariate logistic regression analysis, testicular volume (OR: 0.90; p = 0.002) achieved independent predictor status for WHO pathological semen concentration; conversely, age, Charlson Comorbidity Index scores, metabolic syndrome, and inhibin B values did not. No parameters predicted normal sperm morphology and total progressive motility. Metabolic syndrome accounts for roughly 9% of men presenting for primary couple's infertility. Although metabolic syndrome patients have a lower general male health status, semen analysis values seem independent of the presence of metabolic syndrome. Copyright © 2016 American Society of Andrology and European Academy of Andrology

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Analysis of the correlation between lipotoxicity and pituitary-thyroid axis hormone levels in men and male rats.


Embase

Oncotarget. 7 (26) (pp 39332-39344), 2016. Date of Publication: 2016.

Lipotoxicity seriously harms human health, but it is unclear whether lipotoxicity is detrimental to the pituitary. We investigated the correlation between serum triglyceride and pituitary axis hormone levels in epidemiological and animal studies. In the epidemiological study, serum thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were greater in male patients with isolated hypertriglyceridemia than in controls, whereas adrenocorticotropic hormone (ACTH) levels were lower in the patients with hypertriglyceridemia. Pituitary hormone levels correlated with triglyceride levels, even after adjustment for potential confounders. In the animal study, male rats were fed a high-fat or control diet for 28 weeks. As the duration of high-fat feeding increased, the serum and pituitary triglyceride concentrations increased. At early times, the high-fat diet elevated serum TSH and triiodothyronine. At later times, much higher serum TSH levels coupled with reduced thyroxine were observed in the high-fat group. Serum levels of pituitary-gonadal and pituitary-adrenal axis hormones were not affected by the diet. The mRNA and protein expression of Tshbeta were greater in the high-fat group than in the control group, whereas expression of Fshbeta, Lhbeta and Acth had no difference between the groups. Overall, serum triglyceride levels were associated with pituitary-thyroid axis hormone levels.

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Anogenital distance as a marker of androgen exposure in humans.

Thankamony A., Pasterski V., Ong K.K., Acerini C.L., Hughes I.A.

Andrology. 4 (4) (pp 616-625), 2016. Date of Publication: 01 Jul 2016.

[Review]

AN: 611401518

Abnormal foetal testis development has been proposed to underlie common disorders of the male reproductive system such as cryptorchidism, hypospadias, reduced semen quality and testicular germ cell tumour, which are regarded as components of a ‘testicular dysgenesis syndrome’. The increasing trends and geographical variation in their incidence have been suggested to result from in utero exposure to environmental chemicals acting as endocrine disruptors. In rodents, the anogenital distance (AGD), measured from the anus to the base of genital tubercle, is a sensitive biomarker of androgen exposure during a critical embryonic window of testis development. In humans, several epidemiological studies have shown alterations in AGD associated with prenatal exposure to several chemicals with potential endocrine disrupting activity. However, the link between AGD and androgen exposure in humans is not well-defined. This review focuses on the current evidence for such a relationship. As in rodents, a clear gender difference is detected during foetal development of the AGD in humans which is maintained thereafter. Reduced AGD
in association with clinically relevant outcomes of potential environmental exposures, such as cryptorchidism or hypospadias, is in keeping with AGD as a marker of foetal testicular function. Furthermore, AGD may reflect variations in prenatal androgen exposure in healthy children as shorter AGD at birth is associated with reduced masculine play behaviour in preschool boys. Several studies provide evidence linking shorter AGD with lower fertility, semen quality and testosterone levels in selected groups of adults attending andrology clinics. Overall, the observational data in humans are consistent with experimental studies in animals and support the use of AGD as a biomarker of foetal androgen exposure. Future studies evaluating AGD in relation to reproductive hormones in both infants and adults, and to gene polymorphisms, will help to further delineate the effect of prenatal and postnatal androgen exposures on AGD. 

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400. Thalassemia and infertility. 
Castaldi M.A., Cobellis L. 
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Human Fertility. 19 (2) (pp 90-96), 2016. Date of Publication: 02 Apr 2016.

[Review]

AN: 611387068

Abstract: Beta-thalassemia (BTM) major is the most common haemoglobin disorder in the world, with high prevalence in people of Mediterranean, Arab or Asian origin. It has been estimated that about 1.5% of the global population (80-90 million people) are carriers of BTM. In patients with BTM, long-term transfusion therapy for the correction of anaemia leads to toxic iron overload, resulting in significant morbidity including liver damage, cardiac complications and endocrine dysfunction. The commonest abnormality is hypogonadotropic hypogonadism, which presents with primary amenorrhoea, delayed puberty or secondary amenorrhoea with consequent infertility. Nevertheless, current improvements in the management of thalassemia disorders offer patients the possibility of having a regularly functioning reproductive system and increased chances of achieving a pregnancy. The aim of the present review is to analyse all aspects of fertility management in BTM women, by examining the main causes of infertility, in order to give practical tools to ensure a complete diagnostic work-up and discuss intervention options to guarantee maximum reproductive health.

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401.

Variation of reproductive hormone profile in male patients with obstructive sleep apnea: A meta-analysis.

Zeng Z., Rao M., Liu G., Kong F., Liu S.

Embase
The pituitary-gonadal function in men with obstructive sleep apnea (OSA) has been investigated for several decades, however, the conclusions remain controversy. This meta-analysis was to investigate the reproductive hormone profile in male patients with OSA. We searched databases of Pubmed, Web of Science and China National Knowledge Infrastructure to identify studies that focused on the effect of OSA on male reproductive hormones. Standardized mean difference (SMD) was used to analyze the summary estimates for the variation of reproductive hormones between OSA patients and controls. Sensitivity analysis was performed by subgroup analysis and sequential omission of individual studies. At last, 16 eligible studies involving 681 OSA patients and 384 controls were included in the meta-analysis. The results showed that the overall SMD for total testosterone level in OSA patients was significantly lower than that in controls (SMD -0.47, 95 % CI -0.62, -0.31, P<0.001), other hormones in OSA patients were similar to those in controls, including FSH (P = 0.81), LH (P = 0.20), Estradiol (P = 0.85), prolactin (P = 0.36) and sex hormone binding globulin (P = 0.95). Subgroup analysis indicated that only patients with BMI >= 30 have a lower level of total testosterone than normal controls, whereas testosterone profiles in patients with BMI>=30 were not disrupted. We concluded that obese (BMI < 30) patients with OSA have a decreased level of total testosterone. Copyright © Japanese Society of Sleep Research 2015.

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Stable intraprostatic dihydrotestosterone in healthy medically castrate men treated with exogenous testosterone.


Embase


[Article]

AN: 611271915

Context: Concern exists that T replacement therapy (TRT) might increase the risk of prostate disease. There are limited data regarding the impact of TRT on prostate androgen concentrations. Objective: Determine the dose-dependent effects of exogenous T administration on intraprostatic androgen concentrations. Design: Twelve-week, double-blinded, randomized, placebo-controlled trial. Setting: Academic medical center. Participants: Sixty-two healthy eugonadal men, aged 25-55 years. Interventions: Subjects were randomly assigned to receive injections of acyline, a GnRH antagonist (used to achieve medical castration), every 2 weeks plus transdermal T gel (1.25 g, 2.5 g, 5.0 g, 10 g, or 15 g daily), or placebo injections and transdermal gel for 12 weeks. Main Outcomes: Serum T and dihydrotestosterone (DHT) were measured at baseline and every 2 weeks during treatment. Intraprostatic T and DHT concentrations were assessed from tissue obtained through ultrasound-guided prostate needle biopsies at week 12. Androgens were quantified by liquid chromatography-tandem mass spectrometry. Results: 51 men completed the study and were included in the analysis. There were no significant adverse events. Exogenous T resulted in a dose-dependent increase in serum T and DHT concentrations (190-770 and 60-180 ng/dL, respectively). Although intraprostatic T differed among dose groups (P <.01), intraprostatic DHT was comparable regardless of T dose (P <.11) and was 10-to 20-fold greater than intraprostatic T. Conclusions: In healthy, medically castrate men receiving exogenous T, the total intraprostatic androgen concentration (predominantly DHT) remained stable across serum T concentrations within the physiological range. These findings further our knowledge of the relationship between serum and intraprostatic androgens and suggest that physiological serum T achieved by TRT is unlikely to alter the prostate hormonal milieu.
Metabolic syndrome and infertility in women.
Al Awlaqi A., Alkhayat K., Hammadeh M.E.

Embase
International Journal of Women's Health and Reproduction Sciences. 4 (3) (pp 89-95), 2016.
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[Review]
AN: 611204462

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women and it affects approximately 5%-8% of premenopausal women. Metabolic syndrome has been reported in the reproductive literature to fall under a cluster of endocrine disturbances, including hypertension, obesity, dyslipidemia, and insulin resistance. Literature findings have demonstrated that conditions of negative energy balance and metabolic stress, such as diabetes mellitus type 1, acute inflammation, and chronic dietary restriction can affect fertility. These conditions cause
hypogonadism by suppressing the expression of the hypothalamic KiSS or kisspeptin. Diabetes affects reproductive function in women. The objective of the current review is to explore the correlation between metabolic syndrome and infertility in women. To achieve this, a review of literature studies between 2007 and 2015 was undertaken to evaluate current evidence-based practice on the topic. Keywords, such as metabolic disorders, women fertility, and reproduction were used to search for data from PubMed, MEDLINE, CINAHL, ERIC, and EMBASE databases. The inclusion and exclusion criteria was based on the appropriateness of the research design in reference of research objectives, risks of bias, statistical issues, quality reporting, choice of measures of outcome, quality of intervention, and studies conducted between 2007 and 2015. The results from the highest evidence available confirm that metabolic disorders have adverse impacts on the reproductive health of women, and specifically their fertility. Metabolic disorders like hyperlipidemia, obesity, and diabetes can directly or indirectly affect the fertility of women through the interruption of either the ovarian functions or the pituitary-hypothalamic functions. Furthermore, metabolic disorders increase the risks of cervical and endometrial cancers in women that hamper the reproductive health and fertility of women. Copyright © 2016 The Author(s).

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404.
DYSREGULATION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS INCREASES CENTRAL BODY FAT ACCUMULATION IN MALES AFFECTED BY DIABETES MELLITUS AND LATE-ONSET HYPOGONADISM.

Tirabassi G., Muscogiuri G., Colao A., Balercia G.
OBJECTIVE: Functional hypercortisolism (FH) is a condition which occurs in some clinical states, such as major depression, eating disorders, numerous psychiatric conditions, and diabetes mellitus (DM) and which exerts several negative systemic effects. No data exist on the potentially harmful role of FH on body composition. In this retrospective study, we evaluated the influence of hypothalamic-pituitary-adrenal (HPA) axis dysregulation on body composition in men affected by DM-associated late-onset hypogonadism (LOH).

METHODS: Fourteen subjects affected by FH (FH-LOH) and 18 subjects not affected (N-LOH) were studied. Clinical, hormonal, and body composition measures were considered.

RESULTS: The 2 groups had comparable age and weight. FH-LOH patients had lower levels of total (2 +/- 0.27 ng/mL versus 2.31 +/- 0.26 ng/mL; P = .003) and free (39.5 +/- 6.44 pg/mL versus 46.8 +/- 7.23 pg/mL; P = .005) (median, 38.7 [interquartile range, 36.1 to 41.3] pg/mL versus median, 46.1 [interquartile range, 40.4 to 52.7] pg/mL) testosterone compared to N-LOH patients. Abdominal fat amount was greater in FH-LOH than in N-LOH patients, even after adjustment for total testosterone. None of the bivariate correlations between body composition measures and hormonal variables were significant in N-LOH. Conversely, in FH-LOH, cortisol area under the curve (AUC) was found to be positively and significantly correlated with trunk (r = 0.933; P<.001) and abdominal fat (r = 0.852; P<.001) and negatively with lean leg (r = -0.607; P = .021). All of these associations were further confirmed upon linear regression analysis in FH-LOH (respectively, unstandardized beta = 10.988 [P<.001]; beta = 1.156 [P<.001]; beta = -7.675 [P = .021]). Multivariate regression analysis confirmed AUC cortisol as a predictor of trunk and abdominal fat in FH-LOH.

CONCLUSION: Dysregulation of the HPA axis in LOH-associated DM seems to be involved in abdominal fat accumulation.
Erectile Dysfunction and Sexual Hormone Levels in Men With Obstructive Sleep Apnea: Efficacy of Continuous Positive Airway Pressure.

Zhang X.-B., Lin Q.-C., Zeng H.-Q., Jiang X.-T., Chen B., Chen X.

Embase

Archives of sexual behavior. 45 (1) (pp 235-240), 2016. Date of Publication: 01 Jan 2016.

[Article]

AN: 611138942

In this study, the prevalence of erectile dysfunction (ED) and serum sexual hormone levels were evaluated in men with obstructive sleep apnea (OSA). In these patients, the efficacy of continuous positive airway pressure (CPAP) was determined. The 207 men (mean age 44.0 +/- 11.1 years) enrolled in the study were stratified within four groups based on their apnea-hypopnea index score: simple snoring (n = 32), mild OSA (n = 29), moderate OSA (n = 38), and severe OSA (n = 108). The International Index of Erectile Dysfunction-5 (IIEF-5) score was obtained from each patient, and blood samples for the analysis of sexual hormones (prolactin, luteotropin, follicle-stimulating hormone, estradiol, progestin, and testosterone) were drawn in the morning after polysomnography. The IIEF-5 test and serum sexual hormone measurements were repeated after 3 months of CPAP treatment in 53 men with severe OSA. The prevalence of ED was 60.6 % in OSA patients overall and 72.2 % in those with severe OSA. Compared with the simple snoring group, patients with severe OSA had significantly lower testosterone levels (14.06 +/- 5.62 vs. 17.02 +/- 4.68, p = .018) and lower IIEF-5 scores (16.33 +/- 6.50 vs. 24.09 +/- 1.94, p = .001). The differences in the other sexual hormones between groups were not significant. After 3 months of CPAP treatment, there were no significant changes in sexual hormone levels, but the IIEF-5 score had improved significantly (18.21 +/- 4.05 vs. 19.21 +/- 3.86, p = .001). Severe OSA patients have low testosterone concentration and high ED prevalence. IIEF-5 scores increased significantly after CPAP treatment, but there was no effect on serum testosterone levels.


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The reciprocal links between synaptophysin serum levels and the prevalence of metabolic syndrome according to selected low-grade inflammation indices and age-related androgen serum level changes in men.

Herman W.A., Wojcicka M., Kolodziejczak B., Losy J., Lacka K.

Embase

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[Article]

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UNLABELLED: The correlations between synaptophysin (SYP) plasma levels and the brain neurotransmission activity are still not strictly identified. However, the efficiency of neurotransmission depends, inter alia, on the age, hormonal status, and coexistence of a low-grade systemic inflammation (LGSI) which is regarded as a pathogenic link with obesity and insulin resistance, atherogenesis and aging per se. AIM: The aim of this study was to investigate the associations between synaptophysin serum levels and age, LGSI indices, homocysteine and
selected hormonal parameters (dehydroepiandrosterone and its sulfate, free-testosterone, SHBG) and the prevalence of metabolic syndrome (MS) in men over the age of 40.

MATERIALS AND METHODS: After randomization, 157 male volunteers aged 40-80 years were included in a retrospective study. MS was diagnosed according to the International Diabetes Federation criteria. For the diagnosis of late-onset hypogonadism (LOH) we adopted the criteria proposed by the European Male Aging Study (EMAS).

RESULTS: Synaptophysin plasma concentrations in respondents decreased with age, but only between the ages of 40 to 70 years. There were no differences in SYP plasma concentrations in men suffering from MS compared to healthy subjects (p=0.845). Men suffering from MS demonstrated while higher hs-CRP (high sensitive C - reactive protein) levels than healthy (p=0.019), contrary to the alpha1-antichymotrypsin and transferrin. A positive monotonic correlation between synaptophysin and hs-CRP was demonstrated (r=0.235; p=0.003). No statistically significant relationships between SYP and homocysteine plasma levels were presented (r=0.047; p=0.562), although in men diagnosed with MS higher homocysteine levels compared to healthy subjects were demonstrated. No correlations between synaptophysin and free testosterone (r=-0.036; p=0.651), DHEA (r=-0.122; p=0.128) and its sulphate (r=-0.024; p=0.764) as well as SHBG (r=-0.088; p=0.288) were demonstrated.

CONCLUSIONS: Although the correlations between synaptophysin plasma levels and age as well as strong LGSI indicator (hs-CRP) have been demonstrated, the usefulness of determining SYP serum concentration as a marker of age-related studied diseases (MS, LOH) seems to be significantly limited.

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Anonymous
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The proceedings contain 2623 papers. The topics discussed include: DREADDs reveal arcuate AgRP/NPY signaling controls both fasting-induced suppression of the hypothalamic-pituitary-thyroid axis and activation of hepatic thyroid hormone metabolism; thyroid function and type 2 diabetes risk: a population-based prospective cohort study; determining reference ranges and optimal thresholds for thyroid stimulating hormone and free thyroxine in older men; adipogenic differentiation of thyroid cancer cells through the pax8-pparg fusion protein is regulated by thyroid transcription factor 1 (TTF-1); thyroid hormone receptor alpha is important for maintenance of skeletal muscle satellite cell niche in vivo; metformin delays thyroid cancer progression and improves survival in a metastatic mouse model of thyroid cancer; closed-loop glucagon administration for the automated prevention and treatment of hypoglycemia in type 1 diabetes; diabetes management and outcomes of islet auto-transplant after total pancreatectomy: Dartmouth experience, using offsite and intra-operative islet isolation; effects of long-term therapy with testosterone undecanoate injections (TU) on glycaemic control in hypogonadal men: real-life data from a registry study; and evaluation of total daily dose and glycemic control for patients on U-500 insulin admitted to the hospital.
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Evaluation of Microdissection Testicular Sperm Extraction Results in Patients with Non-Obstructive Azoospermia: Independent Predictive Factors and Best Cutoff Values for Sperm Retrieval.

Cetinkaya M; Onem K; Zorba OU; Ozkara H; Alici B.
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PURPOSE: Testicular sperm extraction (TESE) for intracytoplasmic sperm injection (ICSI) was first introduced for the treatment of non-obstructive azoospermia. This study was conducted to detect predictive factors affecting the success of microTESE.

MATERIALS AND METHODS: We retrospectively evaluated the results of 191 cases who underwent microTESE. For each patient, the testicular volume, endocrine profile [follicle stimulating hormone (FSH), luteinizing hormone (LH), free testosterone (FT), total testosterone (TT)], serum inhibin B level, karyotype analysis, and Y chromosome microdeletions were recorded, and all data were analyzed to detect any predictors. The receiver operating characteristic curve, two-sample t-test and regression analysis were used for the statistical analysis.

RESULTS: The mean age of the patients was 34.4 +/- 5.6 years. Sperm retrieval was successful in 104 (54.5%) patients, and there was no sperm in 87 (45.5%). Seven factors including, testicular size, Johnson score, Y chromosome microdeletion, and serum FSH, LH, FT and TT levels were different between the successful and unsuccessful groups. Six patients had Klinefelter syndrome, and ten patients (5.2%) had a Y chromosome microdeletion (5 AZF-c, 1 AZF-b, 2 AZF-bc, 1 AZF-abc, and 1 AZF-ac). The Johnson score, TT level, family history and Y chromosome microdeletions were determined to be independent predictive factors for sperm found. According to the testicular histology, the sperm-found ratios were 36%, 48.6%, and 95.5% in the sertoli cell only syndrome, maturation arrest, and hypospermatogenesis groups, respectively.
CONCLUSION: According to our results, the Johnson score, TT level, family history-related infertility, and Y chromosome microdeletions were determined to be independent predictive factors for sperm found.

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Hypotestosteronaemia in the aging male: should we treat it?. [Review]
Christe N; Meier CA.
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The term male hypogonadism is defined as the failure to maintain physiological concentrations of testosterone, a physiological quantity of sperm or the combination of both. Aetiologically,
androgen deficiency can originate from the testes (primary hypogonadism) or from the hypothalamic-pituitary regulation of the testicular function (secondary hypogonadism). The causes of hypogonadism are very diverse and may be genetically determined (e.g. Klinefelter's syndrome) or acquired (tumours, infections, haemochromatosis). Classical hypogonadism linked to an underlying disease, such as a pituitary tumour, is a distinct indication for androgen substitution. But how about the aging male? It is known that there is a highly variable age-related decline in testosterone levels; whether this represents a variation of normality or has a true disease value requiring therapy has been disputed over more than a decade. The key questions surrounding this debate concern not only the age-dependent threshold for serum testosterone but, more importantly, the risks and benefits of testosterone replacement therapy in the aging male. We searched the literature for randomised controlled trials of testosterone administration in aging males with a size of at least 100 patients and a follow-up of at least 6 months, and identified eight studies. These studies mostly tried to evaluate the effect of testosterone on bone density, muscle strength and body composition, rather than clinically meaningful endpoints. Moreover, these trials have provided evidence for relevant cardiovascular adverse events in elderly men. This supports the need for further studies to define the treatment threshold for testosterone levels in the aging male, as well as with regard to the long-term risks and relevant benefits of testosterone therapy in this population. Until we have more solid data in aging males, testing for testosterone deficiency and testosterone replacement should remain reserved for patients with predisposing conditions, symptoms and signs of bona fide hypogonadism.

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Contribution of estradiol levels and hormonal contraceptives to sex differences within the fear network during fear conditioning and extinction.

Hwang MJ; Zsido RG; Song H; Pace-Schott EF; Miller KK; Lebron-Milad K; Marin MF; Milad MR.

BACKGROUND: Findings about sex differences in the field of fear conditioning and fear extinction have been mixed. At the psychophysiological level, sex differences emerge only when taking estradiol levels of women into consideration. This suggests that this hormone may also influence sex differences with regards to activations of brain regions involved in fear conditioning and its extinction. Importantly, the neurobiological correlates associated with the use of hormonal oral contraceptives in women have not been fully contrasted against men and against naturally cycling women with different levels of estradiol. In this study, we begin to fill these scientific gaps.

METHODS: We recruited 37 healthy men and 48 healthy women. Of these women, 16 were using oral contraceptives (OC) and 32 were naturally cycling. For these naturally cycling women, a median split was performed on their serum estradiol levels to create a high estradiol (HE) group (n = 16) and a low estradiol (LE) group (n = 16). All participants underwent a 2-day fear conditioning and extinction paradigm in a 3 T MR scanner. Using the 4 groups (men, HE women, LE women, and OC users) and controlling for age and coil type, one-way ANCOVAs were performed to look at significant activations within the nodes of the fear circuit. Using post-hoc analyses, beta-weights were extracted in brain regions showing significant effects in order to unveil the differences based on hormonal status (men, HE, LE, OC).

RESULTS: Significant main effect of hormonal status group was found across the different phases of the experiment and in different sub-regions of the insular and cingulate cortices, amygdala, hippocampus, and hypothalamus. During conditioning, extinction and recall, most of the observed differences suggested higher activations among HE women relative to men. During the unconditioned response, however, a different pattern was observed with men showing significantly higher brain activations.

CONCLUSIONS: Our data further support the important contribution of estradiol levels in the activation of brain regions underlying fear learning and extinction. The results highlight the need to document gonadal hormonal levels, menstrual cycle phase as well as oral contraceptive use in women in order to avoid overlooking sex differences when investigating the neurobiology of emotional regulation.
MEDLINE

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Adipokines in human reproduction. [Review]

Dupont J; Pollet-Villard X; Reverchon M; Mellouk N; Levy R.


[Journal Article. Review]

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Adipose tissue communicates with other central and peripheral organs by the synthesis and release of substances called adipokines. The most studied adipokine is leptin but others have been recently identified including resistin, adiponectin, chemerin, omentin and visfatin. These adipokines have a critical role in the development of obesity-related complications and inflammatory conditions. However, they are also involved in other functions in the organism including reproductive functions. Indeed, many groups have demonstrated that adipokine receptors, such as adiponectin and chemerin, but also adipokines themselves (adiponectin, chemerin, resistin, visfatin and omentin) are expressed in human peripheral reproductive tissues and that these adipokines are likely to exert direct effects on these tissues. After a brief description of these new adipokines, an overview of their actions in different human reproductive organs (hypothalamus, pituitary, ovary, testis, uterus and placenta) will be presented. Finally, comments will be made on the eventual alterations of these adipokines in reproductive disorders, with special attention to polycystic ovary syndrome, a disease characterized by dysfunction of gonadal axis and systemic nerve endocrine metabolic network with a prevalence of up to 10% in women of reproductive age.

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Authors Full Name
Dupont, Joelle; Pollet-Villard, Xavier; Reverchon, Maxime; Mellouk, Namya; Levy, Rachel.

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Is the protein expression window during testicular development affected in patients at risk for stem cell loss?

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[Journal Article. Research Support, Non-U.S. Gov't]

STUDY QUESTION: Is the protein expression window during testicular development affected in prepubertal patients at risk for stem cell loss?

SUMMARY ANSWER: Nuclear ubiquitin carboxyl-terminal esterase L1 (UCHL1) expression in Sertoli cells and interstitial expression of inhibin alpha (INHA), sex-determining region Y-box 9 (SOX9) and steroidogenic acute regulatory protein (STAR) was affected in patients with Klinefelter syndrome.

WHAT IS KNOWN ALREADY: Some patients undergoing testicular tissue banking have already been treated before the testis biopsy is taken. These treatments include chemotherapy or hydroxyurea, which can have an influence on the stem cell number and function. A germinal loss occurs in Klinefelter patients, but its cause is currently unknown.

STUDY DESIGN, SIZE, DURATION: Parrafin-embedded testicular tissue from 5 fetuses, 25 prepubertal patients and 5 adults was used to characterize the spatial and temporal distribution of different testicular marker proteins during testicular development. Expression of the markers was evaluated in germ cells, Sertoli cell and interstitial cells. The integrity of this time window was analyzed in patients at risk for germ cell loss: patients treated with hydroxyurea (n = 7), patients treated with chemotherapy (n = 6) and patients affected by Klinefelter syndrome (n = 5).

PARTICIPANTS/MATERIALS, SETTING, METHODS: Immunohistochemistry was performed in normal fetal, prepubertal and adult testicular tissue to set up a timeline for the expression of melanoma antigen family A4 (MAGE-A4), ubiquitin carboxyl-terminal esterase L1 (UCHL1), octamer-binding transcription factor 4 (OCT4), stage-specific embryonic antigen-4 (SSEA4), homeobox protein NANOG, INHA, anti-Mullerian hormone, androgen receptor (AR), SOX9 and STAR. The established timeline was used to evaluate whether the expression of these markers was altered in patients at risk for germ cell loss (patients treated for sickle cell disease (hydroxyurea) or cancer (chemotherapy) and patients with Klinefelter syndrome).

MAIN RESULTS AND THE ROLE OF CHANCE: A protein expression timeline was created using different markers expressed in different testicular cell types. Less positive tubules and less positive cells per tubule were observed for MAGE-A4 and UCHL1 expression in the KS compared
with the non-treated group (P < 0.01). Higher nuclear UCHL1 Sertoli cell expression was observed in the KS group compared with the non-treated group (P < 0.05). Higher interstitial expression of INHA (P < 0.05), SOX9 (P < 0.01) and STAR (P < 0.05) was observed in KS compared with the non-treated group.

LIMITATIONS, REASONS FOR CAUTION: Important age variations exist in the prepubertal groups. Therefore, data were represented in three age groups. However, owing to the limited access to prepubertal tissue, no statistical comparison was possible between these groups. For the Klinefelter group, tissue was only available from patients older than 12 years.

WIDER IMPLICATIONS OF THE FINDINGS: The expression timeline can add knowledge to the process of spermatogenesis and be used to evaluate altered protein patterns in patients undergoing potentially gonadotoxic treatments, to monitor spermatogenesis established in vitro and to unravel causes of germ cell loss in Klinefelter patients.

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Only a minority of sex chromosome abnormalities are detected by a national prenatal screening program for Down syndrome. Viuff MH; Stochholm K; Uldbjerg N; Nielsen BB; Danish Fetal Medicine Study Group; Gravholt CH.

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STUDY QUESTION: How does a national prenatal screening program for Down syndrome (DS) perform in detecting sex chromosome abnormalities (SCAs)-Turner syndrome (TS), Klinefelter syndrome, 47,XXX and 47,XYY syndromes.

SUMMARY ANSWER: The SCA detection rate resulting from DS screening was below 50% for all four groups of SCAs.

WHAT IS KNOWN ALREADY: The detection rates of SCAs are higher in countries with DS screening. TS is associated with greater nuchal translucency (NT) and lower pregnancy-associated plasma protein-A (PAPP-A). However, specific detection rates of SCAs using prenatal DS screening have not been determined. No clear trend in PAPP-A, free beta human chorionic gonadotropin (beta-hCG) and NT has been found in the remaining SCAs. Several lines of inquiry suggest that it would be advantageous for individuals with SCA to be detected early in life, leading to prevention or treatment of accompanying conditions. There is limited information about pre- and perinatal status that distinguishes SCA embryogenesis from normal fetal development.

STUDY DESIGN, SIZE, DURATION: A register-based case-control study from the Danish Central Cytogenetic Register (DCCR), cross-linked with the Danish Fetal Medicine Database (DFMD), was performed from 2008 to 2012. Groups of SCAs were compared with DS and then matched with non-SCA controls to assess differences between these groups in prenatal markers and birth outcomes.
PARTICIPANTS/MATERIALS, SETTING, METHODS: We included cases with prenatal and post-natal SCA karyotypes (n = 213), DS (n = 802) and 168 056 controls. We screened 275 037 individuals examined prenatally. We retrieved information regarding maternal age, NT, beta-hCG and PAPP-A, as well as details regarding maternal and newborn characteristics.

MAIN RESULTS AND THE ROLE OF CHANCE: The DS screening procedure detected 87 per 100 000 TS (42% of expected), 19 per 100 000 Klinefelter syndrome (13% of expected), 16 per 100 000 47,XXX (16% of cases) and 5 per 100 000 47,XYY (5% of expected) SCAs, with an overall detection rate of 27%. Compared with controls, all four SCA groups showed significantly higher NT and lower PAPP-A compared with controls (all P < 0.01) and similar to DS. The legal abortion rate was high for all four syndromes (47,XXX: 24%; 47,XYY: 29%; Klinefelter syndrome: 48%, TS: 84%). For SCA fetuses carried to term, only TS fetuses had consistently lower birthweights and placenta weights than non-SCA controls (both P = 0.0001). A few SCA cases localized in DCCR could not be found in DFMD (n = 16).

LIMITATIONS, REASON FOR CAUTION: Controls were matched on sex of the fetus of cases, meaning that all electively aborted fetuses (before week 12) were excluded, possibly reducing the diversity in the control group. We were not able to localize all diagnosed cases of SCA and DS in DFMD. Although these cases were present in DCCR, we were not able to account for the discrepancy. In addition, we suspect that several SCA children have not been diagnosed yet and future post-natal diagnosis of these cases would reduce the diagnostic yield reported here even further.

WIDER IMPLICATIONS OF THE FINDINGS: The prenatal detection rate is below 50% for all SCAs. The approach used for detecting DS cannot be extended to also include SCAs. In addition, all SCAs have low PAPP-A and increased NT, thus probably reflecting an abnormal embryogenesis. Growth retardation of TS fetuses is if anything more pronounced than previously reported, both when evaluating fetus and placenta.

STUDY FUNDING/COMPETING INTERESTS: This study received support from Aarhus University and the Novo Nordisk Foundation. The authors have no competing interests that may be relevant to the study.

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Effects of long-term testosterone replacement therapy, with a temporary intermission, on glycemic control of nine hypogonadal men with type 1 diabetes mellitus - a series of case reports.

Saad F; Yassin A; Almehmadi Y; Doros G; Gooren L.

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Type 2 diabetes mellitus (T2DM) is often associated with obesity and subnormal serum testosterone (T) levels. Until 5 years ago there was no indication that men with type 1 diabetes mellitus (T1DM) had subnormal serum T. But recent studies indicate that about 10% of men with T1DM suffer from hypogonadism, as a rule aged men and men with obesity. While hypogonadal men with T2DM benefit from normalization of their serum T, this has not been investigated in men with T1DM. Nine men with T1DM, erectile dysfunction and hypogonadism (total testosterone<=12nmol/L) received testosterone replacement therapy (TRT). In seven men TRT was intermitted: one man with prostate malignancy and six men because of problems of reimbursement. Incidentally, this provided an opportunity to monitor the effects of withdrawal and
of the reinstatement of TRT. In all men, glycemic control (serum glucose and HbA1c), weight, waist circumference, lipid profiles and erectile function improved upon TRT. The seven men whose TRT was intermitted showed a deterioration which improved again upon reinstatement of TRT. The data suggest that aging and obese men with T1DM might have subnormal T levels and that their glycemic control, lipid profiles and erectile function might benefit from TRT.

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415.
The effect of ezetimibe-statin combination on steroid hormone production in men with coronary artery disease and low cholesterol levels.
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[Clinical Trial. Journal Article. Research Support, Non-U.S. Gov't]
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BACKGROUND: Aggressive statin treatment was found to slightly reduce testosterone production. The aim of this study was to compare the effects of ezetimibe-statin combination and high-dose statin therapy on testicular and adrenal cortex function in men with LDL cholesterol levels below 70 mg/dL.

METHODS: The study included 26 adult men with coronary artery disease. Twelve of these patients did not tolerate high-dose statin therapy and were treated with lower doses of a statin plus ezetimibe. Fourteen patients tolerating high-dose simvastatin or rosuvastatin treatment continued high-dose statin therapy throughout the study period. Plasma lipids, glucose homeostasis markers and plasma levels of testosterone, cortisol, dehydroepiandrosterone sulphate, sex hormone-binding globulin, gonadotropins and ACTH, as well as urine free cortisol were assessed at baseline and after 16 weeks of treatment.

RESULTS: Replacing high-dose statin therapy with ezetimibe/statin combination therapy reduced plasma levels of LH by 32% (p=0.043), as well as increased plasma levels of testosterone by 20% (p=0.038). Ezetimibe/statin combination did not induce any significant changes in plasma levels or urine excretion of the remaining hormones. At the end of the study, plasma LH levels were higher, while plasma testosterone levels were lower in patients receiving the combination therapy than in those treated only with high-dose statin.

CONCLUSIONS: Our results indicate that ezetimibe combined with moderate statin dose exerts a less pronounced effect on testicular function in comparison with high-dose statin therapy.

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Infertility etiologies are genetically and clinically linked with other diseases in single meta-diseases.

Tarin J.J., Garcia-Perez M.A., Hamatani T., Cano A.

Embase

[Review]
AN: 615656446

The present review aims to ascertain whether different infertility etiologies share particular genes and/or molecular pathways with other pathologies and are associated with distinct and particular risks of later-life morbidity and mortality. In order to reach this aim, we use two different sources of information: (1) a public web server named DiseaseConnect (http://disease-connect.org) focused on the analysis of common genes and molecular mechanisms shared by diseases by integrating comprehensive omics and literature data; and (2) a literature search directed to find clinical comorbid relationships of infertility etiologies with only those diseases appearing after infertility is manifested. This literature search is performed because DiseaseConnect web server does not discriminate between pathologies emerging before, concomitantly or after infertility is manifested. Data show that different infertility etiologies not only share particular genes and/or molecular pathways with other pathologies but they have distinct clinical relationships with other diseases appearing after infertility is manifested. In particular, (1) testicular and high-grade prostate cancer in male infertility; (2) non-fatal stroke and endometrial cancer, and likely non-fatal coronary heart disease and ovarian cancer in polycystic ovary syndrome; (3) osteoporosis, psychosexual dysfunction, mood disorders and dementia in premature ovarian failure; (4) breast and ovarian cancer in carriers of BRCA1/2 mutations in diminished ovarian reserve; (5) clear cell and endometrioid histologic subtypes of invasive ovarian cancer, and likely low-grade serous invasive ovarian cancer, melanoma and non-Hodgkin lymphoma in endometriosis; and (6) endometrial and ovarian cancer in idiopathic infertility. The present data endorse the principle that the occurrence of a disease (in our case infertility) is non-random in the population and suggest that different infertility etiologies are genetically and clinically linked with other diseases in single meta-diseases. This finding opens new insights for clinicians and reproductive biologists to treat infertility problems using a phenomic approach instead of considering infertility as an isolated and
exclusive disease of the reproductive system/hypothalamic-pituitary-gonadal axis. In agreement with a previous validation analysis of the utility of DiseaseConnect web server, the present study does not show a univocal correspondence between common gene expression and clinical comorbid relationship. Further work is needed to untangle the potential genetic, epigenetic and phenotypic relationships that may be present among different infertility etiologies, morbid conditions and physical/cognitive traits.

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417.
Embase
PloS one. 10 (5) (pp e0127451), 2015. Date of Publication: 2015.
[Article]
BACKGROUND: Little is known regarding the effects of environmental exposure of chemicals on androgenic system in the general population. We studied 5,107 subjects included in the National Health and Nutrition Examination Survey (2011-2012). METHODS: Urinary, serum, and blood levels of 15 subclasses comprising 110 individual chemicals were analyzed for their association with serum testosterone levels. The subjects were divided into high and low testosterone groups according to the median testosterone concentration (374.51 ng/dL). Odds ratios (ORs) of individual chemicals in association with testosterone were estimated using logistic regression after adjusting for age, ethnicity, cotinine, body mass index, creatinine, alcohol, and the poverty income ratio.

RESULTS: Adjusted ORs for the highest versus lowest quartiles of exposure were 2.12 (95% CI: 1.07, 4.21; Ptrend = 0.044), 1.84 (95% CI: 1.02, 3.34; Ptrend = 0.018) for the association between urinary mandelic acid, and strontium quartiles with low testosterone concentrations in adult men, respectively. However, no association was observed for the remaining chemicals with testosterone.

CONCLUSIONS: The National Health and Nutrition Examination Survey data suggest that elevations in urinary mandelic acid, and strontium levels are negatively related to low serum testosterone levels in adult men.


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20170428

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2015
Role of testis sparing surgery in the conservative management of small testicular masses: oncological and functional perspectives.

Borghesi M., Brunocilla E., Schiavina R., Gentile G., Dababneh H., Della Mora L., del Prete C., Franceschelli A., Colombo F., Martorana G.

Embase

Actas urologicas espanolas. 39 (1) (pp 57-62), 2015. Date of Publication: 01 Jan 2015.

[Review]

AN: 615600771

INTRODUCTION: Radical orchiectomy (RO) is still considered the standard of care for malignant germ cell tumours, which represent the vast majority of the palpable testicular masses. In those patients diagnosed with small testicular masses (STMs), testis-sparing surgery (TSS) could be an alternative treatment to RO. The aim of this updated review is to evaluate the current indications for TSS, and discuss the oncological and functional results of patients who had undergone organsparing surgery for STMs. EVIDENCE ACQUISITION: A non-systematic review of the Literature using the Medline database has been performed, including a free-text protocol using the terms "testis-sparing surgery", "testicular sparing surgery", "partial orchiectomy", "testis tumour", "sex cord tumour", and "testis function". Other significant studies cited in the reference lists of the selected papers were also evaluated.

EVIDENCE SYNTHESIS: No randomized controlled trials comparing TSS with radical orchiectomy have been reported yet. In those patients with normal contra-lateral testis, the use of TSS is still controversial. In selected cases of gonadal masses < 2 cm, TSS seems to be a safe and feasible treatment option. Frozen section examination allows us to discriminate between benign and malignant neoplasms during TSS. Intermediate and long-term follow-up results showed no significant risk of local and distant recurrences in the main series reported in the literature.

CONCLUSIONS: TSS is an effective treatment for STMs in selected patients, limiting the unnecessary surgical over-treatments, without compromising the oncological and functional outcomes. Further studies are needed in order to confirm the oncological safety.

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Institution
419.
Embase
[Article]
AN: 615027181
Background Metabolic syndrome (MS) constitutes a major determinant of cardiovascular (CV) morbidity and mortality in adults. This phenomenon in women before menopause is attenuated by gonadal hormonal activity. After menopause the CV disease (CVD) incidence among women increases dramatically, and often overtakes the prevalence observed among men. Little is known about the CV-risk characteristic of early postmenopausal women in our country. Therefore the aim of our study was to investigate the frequency and distribution of metabolic syndrome components in early postmenopausal women residing urban-rural area in central Poland. Material and Methods All women aged 65-75 years, opted for one general practice form an urban-rural area in Central Poland were invited to participate. The anthropometric measures, blood pressure and blood sampling were performed. For the purpose of the study, the modified NCEP ATP III criteria for the diagnosis of metabolic syndrome were used. Results 59.5% of eligible women accepted the invitation. Additional 5.2% of randomly selected women from initially non-responders group were added to the investigated population. In the studied group only 15.7% had normal body weight and 82.4% met the criteria for abdominal obesity (92% according to IDF). 81.9% of women were characterized by hypertension, even more met the NCEP ATP III criterion for elevated blood pressure (BP) (91.5%). Only 24.2% of studied women were treated effectively;
moreover, despite treatment with three antihypertensive drugs 17.4% hypertensive women did not reach target BP values. Over one quarter of studied women suffered from diabetes mellitus, among whom 25.5% were not aware of the presence of the disease. Another 37.1% of women presented with prediabetic condition. Lipid disturbances were noted in the 25.3% and 18.4% of women for triglycerides (TG) increase and low HDL-C levels, respectively. According to modified NCEP ATP III criteria we were able to diagnose 58.8% of studied women with metabolic syndrome. Additionally, 31.9% of postmenopausal women were active cigarette smokers.

Conclusions Metabolic profile of early postmenopausal women in central Poland is strikingly abnormal. High incidence of metabolic syndrome is mainly determined by extremely prevalent increased blood pressure and abdominal obesity. With relation to all identified metabolic syndrome components, the strategy aimed at the improvement of body mass status, diabetes diagnosis and especially blood pressure control appear to be of highest priority.

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20170422
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2015

420.
Diagnosis and Treatment of Low Testosterone among Patients with End-Stage Renal Disease. Bao Y., Johansen K.L.
Embase
Seminars in dialysis. 28 (3) (pp 259-265), 2015. Date of Publication: 01 May 2015.
The prevalence of low testosterone level is particularly high among patients with end-stage renal disease (ESRD) and has been associated with mortality. In populations without ESRD, low testosterone level has also been associated with a number of morbidities including cardiovascular disease, diabetes mellitus, low muscle mass, low bone mass, low physical performance, and frailty. However, there is controversy regarding what constitutes low testosterone level in the aging population and at what level replacement therapy with testosterone is indicated. There are no randomized controlled trials investigating long-term outcomes of testosterone replacement therapy in populations with or without ESRD. Available trial results suggest equivocal improvements in sexual function. Muscle mass and bone mineral density appear to improve, but results in physical function and performance are mixed and there are no data on fracture prevention. Some recent data suggest harm when testosterone was given to men with limited mobility. Finally, there is little evidence that testosterone adds to existing erythropoietin agents in the treatment of anemia in ESRD. Due to lack of evidence supporting long-term use of testosterone, the authors recommend against the routine use of testosterone in ESRD patients with low testosterone levels. Testosterone treatment can be considered in those with low bone mass and total testosterone level <200 ng/dl, or in younger patients with sexual complaints with total testosterone level lower than the reference range. It is important to engage patients in discussion of risks and benefits before initiating testosterone therapy; testosterone therapy should be discontinued if the intended treatment effect is not observed after short-term use. Copyright © 2014 Wiley Periodicals, Inc.

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20170414

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Importance of measuring testosterone in enzyme-inhibited plasma for oral testosterone undecanoate androgen replacement therapy clinical trials.

Lachance S., Dhingra O., Bernstein J., Gagnon S., Savard C., Pelletier N., Boudreau N., Levesque A.

Embase
Future Science OA. 1 (4) (no pagination), 2015. Article Number: FSO55. Date of Publication: November 2015.

[Aarticle]
AN: 614411718

Aim: Testosterone undecanoate (TU) is metabolized by nonspecific esterases in blood to testosterone (T). Typical clinical practice has been to analyze testosterone in human serum. The degradation of TU to testosterone was evaluated in conditions typically used in clinical studies.

Methods & Results: Freshly collected whole blood was fortified with TU at known concentration. Serum was prepared and T concentration was determined by LC-MS/MS. It was observed that TU degrades extensively to T in human blood under conditions typical of harvesting serum causing overestimation of T concentration of up to 243%. These results were confirmed in a clinical study in which serum and plasma samples were compared. Conclusion: It was demonstrated that T must be analyzed in enzyme-inhibited plasma when TU is the administered medication. Testosterone undecanoate (TU) is metabolized into testosterone. Its degradation in whole blood into testosterone was studied in conditions typically used in clinical trials. It was observed that TU degrades extensively to testosterone in human blood under conditions typical of harvesting serum, causing overestimation of testosterone concentration. It was demonstrated that testosterone must be analyzed in enzyme-inhibited plasma when TU is the administered medication. Using serum for testosterone quantitation in a clinical trial for androgen replacement therapy would bias the conclusions on formulations adjustment and use.

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(Lachance, Gagnon, Savard, Pelletier, Boudreau, Levesque) InVentiv Health Clinical, QC, Canada (Dhingra, Bernstein) SOV Therapeutics, Morrisville, NC, United States
Publisher
Future Medicine Ltd. (E-mail: info@future-science.com)

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20170221
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2015
Influence of a D-aspartic acid/sodium nitrate/vitamin D3 dietary supplement on physiological parameters in middle-aged men: A pilot study.
Bloomer R.J., Gunnels T.A., Moran R.G., Schriefer J.M.
Embase
[Article]
AN: 612372663
D-aspartic acid (DAA), nitrate, and vitamin D3 have received considerable attention in recent years for their potential health-enhancing properties. Using an open-label design, we evaluated the impact of a DAA/sodium nitrate/ vitamin D3 dietary supplement on blood testosterone and nitrate/nitrite, as well as subjective indicators of health, in middle-aged men. Methods: 10 overweight or obese men (mean age: 42 years) were assigned to ingest a DAA/sodium nitrate/ vitamin D3 supplement (either one or two servings per day) for 28 days. Blood total and free testosterone and nitrate/nitrite was measured before and after 14 and 28 days of supplementation. Subjective assessment of to health indicators (e.g., energy level, libido) was included at each collection time. Results: Total and free testosterone increased on average 5-10%, which was not of statistical significance (p>0.05). The response was highly variable; some men failed to respond to treatment, while men with relatively low basal testosterone values experienced increases exceeding 20%. Plasma nitrate/nitrite was increased approximately 6-10 fold after treatment with the supplement, with a trend noted for a time effect (p=0.07). Men reported a significantly better feeling following supplement use, as evidenced by a time effect for both vitality (p=0.02) and libido (p=0.04), with a trend noted for increased energy level (p=0.08) and mental outlook and mood (p=0.10). Conclusion: Twenty-eight days of treatment with a DAA/sodium nitrate/ vitamin D3 dietary supplement increased blood nitrate/nitrite and improved subjective feelings of vitality and libido in middle-aged men. In selected men with low basal testosterone values, the supplement increased circulating levels of this hormone. Copyright © Bloomer et al.
Status
INPROCESS
Institution
Testosterone levels have become a much more available and frequent screening test in clinical practice. There is greater awareness of testosterone deficiency symptoms both among the medical community and among the patients themselves. Several studies have described the effects of testosterone on carbohydrate and lipid metabolism and the disturbances that occur in patients with hypogonadism. However, whether testosterone replacement reverts such alterations is less clear. In this article, we review the effects of testosterone replacement therapy on glucose and lipid metabolism.

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Publisher
Lippincott Williams and Wilkins (E-mail: kathiest.clai@apta.org)

Date Created
Testosterone replacement and cardiovascular disease risk: What do endocrinologists need to know?.
Gonzalez J.R., Goldstein I.
Embase
Cardiovascular Endocrinology. 4 (3) (pp 100-107), 2015. Date of Publication: September 2015.
[Article]
AN: 612342752
Testosterone deficiency (or hypogonadism) affects millions of men worldwide. Consensus regarding an appropriate biochemical cutoff for the definition and treatment of hypogonadism has been challenging. Several recent, well-publicized studies have called into question the long recognized benefits of testosterone replacement therapy. The aim of the current article is to review the data on testosterone treatment, paying specific attention to the potential cardiovascular effects of this increasingly common therapy. We examine some of the most common cardiovascular diseases including hypertension, metabolic syndrome, coronary artery disease, atherosclerosis, congestive heart failure, myocardial infarction, and stroke. This review will also investigate the potential effect of testosterone replacement therapy on cardiovascular and all-cause mortality and address a growing fear among the medical community about the safety of testosterone replacement.
Status
EMBASE
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Publisher
Lippincott Williams and Wilkins (E-mail: kathiest.clai@apta.org)
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20161009
Year of Publication
2015
Defining the best candidates for testosterone replacement?
Krakowsky Y., Grober E.D.
Embase
Cardiovascular Endocrinology. 4 (3) (pp 77-82), 2015. Date of Publication: September 2015.
[Review]
AN: 612342740
It is widely known that re-establishing physiologic levels of testosterone in symptomatic men with testosterone deficiency (TD) improves the undesirable symptoms associated with low testosterone. The indications for testosterone replacement therapy (TRT) have been evolving as research continues to find out who are the best candidates for therapy. Recently, concerns on the association of TRT and cardiovascular disease have received considerable attention. Before this, considerable attention had focused on the potential dangers of TRT and the risk of prostate cancer. The vast majority of contemporary evidence suggests that men with treated prostate cancer and no evidence of active disease are appropriate candidates for TRT in the context of symptomatic TD. Further, current evidence does not support denying TRT to symptomatic men with TD based on stable cardiac disease. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved. Cardiovascular Endocrinology 2015, 4:77-82.
Status
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Lippincott Williams and Wilkins (E-mail: kathiest.clai@apta.org)
Date Created
20161019
Year of Publication
2015
The term male hypogonadism is defined as the failure to maintain physiological concentrations of testosterone, a physiological quantity of sperm or the combination of both. Aetiologically, androgen deficiency can originate from the testes (primary hypogonadism) or from the hypothalamic-pituitary regulation of the testicular function (secondary hypogonadism). The causes of hypogonadism are very diverse and may be genetically determined (e.g. Klinefelter's syndrome) or acquired (tumours, infections, haemochromatosis). Classical hypogonadism linked to an underlying disease, such as a pituitary tumour, is a distinct indication for androgen substitution. But how about the aging male? It is known that there is a highly variable age-related decline in testosterone levels; whether this represents a variation of normality or has a true disease value requiring therapy has been disputed over more than a decade. The key questions surrounding this debate concern not only the age-dependent threshold for serum testosterone but, more importantly, the risks and benefits of testosterone replacement therapy in the aging male. We searched the literature for randomised controlled trials of testosterone administration in aging males with a size of at least 100 patients and a follow-up of at least 6 months, and identified eight studies. These studies mostly tried to evaluate the effect of testosterone on bone density, muscle strength and body composition, rather than clinically meaningful endpoints. Moreover, these trials have provided evidence for relevant cardiovascular adverse events in elderly men. This supports the need for further studies to define the treatment threshold for testosterone levels in the aging male, as well as with regard to the long-term risks and relevant benefits of testosterone therapy in this population. Until we have more solid data in aging males, testing for testosterone deficiency and testosterone replacement should remain reserved for patients with predisposing conditions, symptoms and signs of bona fide hypogonadism.
Sex-different abnormalities in the right second to fourth digit ratio in Japanese individuals with autism spectrum disorders.
Masuya Y., Okamoto Y., Inohara K., Matsumura Y., Fujioka T., Wada Y., Kosaka H.
Embase
Molecular Autism. 6 (1) (no pagination), 2015. Article Number: 34. Date of Publication: 09 Jun 2015.
[Article]
AN: 604889179

Background: The prevalence of autism spectrum disorders (ASDs) is higher in men than in women. The extreme male brain theory proposes that excessive prenatal testosterone activity could be a risk factor for ASDs. However, it is unclear whether prenatal sex hormone activity is a risk factor for women. The ratio of the length of the second to fourth digits (2D:4D) is considered to be a biomarker of the prenatal ratio of testosterone to estrogen. Therefore, this study compared the 2D:4D ratios of women with and without ASDs to determine if prenatal sex hormone activity could be a risk factor for ASDs in women. Methods: The study included 35 Japanese men with ASDs, 17 Japanese women with ASDs, 59 typically developed (TD) Japanese men, and 57 TD Japanese women. We measured digit lengths and compared the 2D:4D ratios among the four groups. We also examined the relationship between the 2D:4D ratio and the autism-spectrum quotient score of each group. Results: In our cohort, men with ASDs tended to have lower right-hand 2D:4D ratios relative to TD men. In contrast, the right 2D:4D ratios in women with ASDs were higher compared to those of TD women. No significant correlations were found between the 2D:4D ratios and the autism-spectrum quotient scores in
any group. The higher right 2D:4D ratios in women could not be explained by age or full-scale intelligent quotients. This group difference was not found for the left 2D:4D or right-left 2D:4D ratios. Conclusions: We found a reverse direction of abnormality in the right 2D:4D ratio for men and women with ASDs. It has been posited that high prenatal testosterone levels lead to a lower 2D:4D ratio. However, a recent animal study showed that testosterone injection to dam leads to a higher right 2D:4D ratio especially for female offspring, which might be mediated by abnormal adipose accumulation in the fingertip. Therefore, the present findings suggest that high prenatal testosterone could be a risk factor both for Japanese men and women with ASDs, elucidating one potential etiology of ASDs in women. Copyright © 2015 Masuya et al.

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Publisher
BioMed Central Ltd. (E-mail: info@biomedcentral.com)

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20161004

Year of Publication
2015

428.
The relationship between serum hormone levels (follicle-stimulating hormone, luteinizing hormone, total testosterone) and semen parameters.


Embase
Objective: The aim of this study was to investigate the effect of serum gonadotropin and total testosterone levels on semen parameters. Materials and Methods: Three hundred and eighty-two patients that applied to a male infertility polyclinic were included in our study. Serum gonadotropin and total testosterone levels and semen parameters of the patients were analyzed during the first visit to the clinic. The reference FSH value was 1.5-12.4 mIU/mL, that of LH was 1.7-8.6 mIU/mL and the reference value for total testosterone was 249-836 ng/dL. Results: While there was no statistically significant difference between the patients with low gonadotropin levels and the controls regarding any of the semen parameters (p > 0.05), there was a strong statistically significant difference between the patients with high gonadotropin levels and the controls regarding sperm concentration (p = 0.000), total motility (p = 0.000), progressive motility (p = 0.000), and morphology (p = 0.000). There was a strong statistically significant difference between the patients with low testosterone levels and the controls regarding total motility (p = 0.012) and progressive motility (p = 0.010), and a weak statistically significant difference in morphology (p = 0.042). There was no statistically significant difference in semen volume or sperm concentration (p > 0.05). There was no statistically significant difference in any of the semen parameters between the patients with high testosterone levels and the controls (p > 0.05). Conclusions: Our findings especially regarding LH and T levels are not in agreement with previous reports. In this regard, there is a need for larger-scale and randomized trials to resolve this discrepancy.

PMID

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20160724

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2015
429.
Prediction of Long-term Post-operative Testosterone Replacement Requirement Based on the Pre-operative Tumor Volume and Testosterone Level in Pituitary Macroadenoma.
Lee C.-C., Chen C.-M., Lee S.-T., Wei K.-C., Pai P.-C., Toh C.-H., Chuang C.-C.
Embase
Scientific reports. 5 (pp 16194), 2015. Date of Publication: 2015.
[Article]
AN: 612306827
Non-functioning pituitary macroadenomas (NFPAs) are the most prevalent pituitary macroadenomas. One common symptom of NFPA is hypogonadism, which may require long-term hormone replacement. This study was designed to clarify the association between the pre-operative tumor volume, pre-operative testosterone level, intraoperative resection status and the need of long-term post-operative testosterone replacement. Between 2004 and 2012, 45 male patients with NFPAs were enrolled in this prospective study. All patients underwent transsphenoidal surgery. Hypogonadism was defined as total serum testosterone levels of <2.4ng/mL. The tumor volume was calculated based on the pre- and post-operative magnetic resonance images. We prescribed testosterone to patients with defined hypogonadism or clinical symptoms of hypogonadism. Hormone replacement for longer than 1 year was considered as long-term therapy. The need for long-term post-operative testosterone replacement was significantly associated with larger pre-operative tumor volume (p=0.0067), and lower pre-operative testosterone level (p=0.0101). There was no significant difference between the gross total tumor resection and subtotal resection groups (p=0.1059). The pre-operative tumor volume and testosterone level impact post-operative hypogonadism. By measuring the tumor volume and the testosterone level and by performing adequate tumor resection, surgeons will be able to predict post-operative hypogonadism and the need for long-term hormone replacement.
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(Chen) Institute of Biomedical Engineering, National Taiwan University, Taiwan, ROC
American Association of Clinical Endocrinologists and American College of Endocrinology Position Statement on the Association of Testosterone and Cardiovascular Risk.

Goodman N., Guay A., Dandona P., Dhindsa S., Faiman C., Cunningham G.R.

Endocrine practice: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 21 (9) (pp 1066-1073), 2015. Date of Publication: 01 Sep 2015.

[Article]

AN: 611702441

This document represents the official position of the American Association of Clinical Endocrinologists and the American College of Endocrinology. Where there were no randomized controlled trials or specific U.S. FDA labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. Position statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician.
High estrogen in men after injectable testosterone therapy: the low T experience.
Tan R.S., Cook K.R., Reilly W.G.

Embase
American journal of men's health. 9 (3) (pp 229-234), 2015. Date of Publication: 01 May 2015.
[Article]
AN: 611578920

Testosterone replacement improves quality of life and is aromatized in men in adipose tissues to estrogen. Hyperestrogenism is believed to be harmful to male sexuality. This is a description of our experience of screening 34,016 men in the Low T Centers, of which approximately 50% were converted to treatment. Men were treated with injectable testosterone, and we have available data from 2009 to 2014. The data were extracted from our electronic health record (AdvancedMD) of 35 Low T Centers across the United States. In all, 7,215 (20.2%) out of the 34,016 patients had high estradiol levels defined as >=42.6 pg/ml. Estradiol was measured using electro-chemiluminescence immunoassay. Of the patients who had high estradiol levels, the age distribution was as follows: 132/989 (13.3%) were older than 65 years, 3,753/16,955 (22.1%) were between 45 and 65 years; 2,968/15,857 (18.7%) were between 25 and 44 years, 7/215 (3.3%) were younger than 25 years. The difference between extreme age groups (<25 and >=65) was statistically significant using a chi-square test (p = .013). The correlation coefficient of serum estradiol to age was .53, SD = 8.21. It was observed that practitioners used aromatase inhibitor and selective estrogen receptor modulator to treat symptoms of hyperestrogenism, irrespective of blood estradiol levels. Gynecomastia was rarely documented as a reason for the prescription. Our finding was that high estradiol levels were not associated with higher rates of low libido but established higher rates of documented low libido with those with normal or lower estradiol levels. The difference was statistically significant (p < .05). Copyright © The Author(s) 2014.
UNLABELLED: AIMS OF REVIEW: the intent of the current manuscript is to critically review the studies on pituitary gland dysfunction in early childhood following traumatic brain injury (TBI), in comparison with those in adults. Search of the literature: The MEDLINE database was accessed through PubMed in April 2015. Results were restricted to the past 15 years and English language of articles. Both transient and permanent hypopituitarisms are not uncommon after TBI. Early after the TBI, pituitary dysfunction/s differ than those occurring after few weeks and months. Growth hormone deficiency (GHD) and alterations in puberty are the most common. After the one to more years of TBI, pituitary dysfunction tends to improve in some patients but may deteriorate in others. GH deficiency as well as Hypogonadism and thyroid dysfunction are the most common permanent lesions. Many of the symptoms of these endocrine defects can pass unnoticed because of the psychomotor defects associated with the TBI like depression and apathy. Unfortunately pituitary defects appear to negatively affect psycho-neuro-motor recovery as well as growth and pubertal development of children and adolescents after TBI. Therefore, the
current review highlights the importance of closely following patients, especially children and adolescents for growth and other symptoms and signs suggestive of endocrine dysfunction. In addition, all should be screened serially for possible endocrine disturbances early after the TBI as well as few months to a year after the injury. Risk factors for pituitary dysfunction after TBI include relatively serious TBI (Glasgow Coma Scale score < 10 and MRI showing damage to the hypothalamic pituitary area), diffuse brain swelling and the occurrence of hypotensive and/or hypoxic episodes. IN CONCLUSION: There is a considerable risk of developing pituitary dysfunction after TBI in children and adolescents. These patients should be clinically followed and screened for these abnormalities according to an agreed protocol of investigations. Further multicenter and multidisciplinary prospective studies are required to explore in details the occurrence of permanent pituitary dysfunction after TBI in larger numbers of children with TBI. This requires considerable organisation and communication between many disciplines such as neurosurgery, neurology, endocrinology, rehabilitation and developmental paediatrics.

OBJECTIVE: Our aim was to investigate the thyroid function tests and thyroid volume differences among males with isolated hypogonadotropic hypogonadism (IHH) who take androgen replacement treatment (ART).

MATERIALS AND METHODS: Forty-four male with IHH with a mean age 33.2 (18-54), diagnosed in Endocrinology and Metabolism Department between September 2013 and September 2014 and 40 healthy male control with a mean age 27.77 (18-55) were involved to study. Patient group was divided to testosterone-treated patients (n = 19) and human chorionic gonadotropine (hCG)-treated patients (n = 25). Patient group was compared in terms of total testosterone, thyroid function tests [thyroid stimulating hormone (TSH), free thyroxine (fT4)] and thyroid volume, before and 6 months after treatment. Patient group was compared with control group as well.

RESULTS: When we compared the patient group with the control group, there was no significant difference for age, Body mass index, TSH, fT4 and thyroid volume between two groups before treatment. There was no difference in terms of TSH, but fT4, testosterone levels and thyroid volume were significantly higher after treatment, when the patient group was compared before and after treatment (p < 0.05). When we compared testosterone-treated patients and hCG-treated patients; thyroid volume was higher among hCG-treated patients (p = 0.001) but there was no difference for thyroid volume before and after testosterone treatment (p > 0.05). There
was no statistically significant correlation between testosterone levels with TSH, fT4 and thyroid volume ($r = 0.09$, $p = 0.32$; $r = 0.14$, $p = 0.11$; $r = 0.15$, $p = 0.09$, respectively).

CONCLUSION: Our study showed that ART increases the thyroid volume especially in hCG-treated patients. Therefore, we suggest that thyroid volume changes should be followed up in hCG-treated patients.

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434.
Clozapine and risperidone influence on cortisol and estradiol levels in male patients with schizophrenia.

Piriu G., Torac E., Gaman L.E., Iosif L., Tivig I.C., Delia C., Gilca M., Stoian I., Atanasiu V.
Estrogens role in schizophrenia patients is a subject, which has gained an increased attention from the medical community. Estrogens have been shown to inhibit dopamine actions, improve neuronal regeneration, and overall, have a protective role in the pathology of schizophrenia. The adjunctive estrogen therapy for men is currently under debate. Antipsychotic medication is known to influence the hypothalamo-hypophyseal - gonadal axis by inducing variable degrees of hyperprolactinemia. Several studies have found that some of the atypical antipsychotics lower cortisol levels in patients and also in healthy controls. We have investigated the effects of clozapine and risperidone on estradiol levels in men with schizophrenia. We have also evaluated the levels of prolactin and cortisol, taking into account the possible influence of antipsychotic drugs on both these hormones. Both prolactin and cortisol also have the potential to regulate sexual hormones biosynthesis. Our study found decreased estradiol levels in men with schizophrenia treated with clozapine and risperidone, while prolactin levels were increased only in the risperidone treated group. Cortisol levels are not statistically significant different between groups.

PMID
Male sexual dysfunction in patients with chronic end-stage renal insufficiency and in renal transplant recipients.
Antonucci M., Palermo G., Recupero S.M., Bientinesi R., Presicce F., Foschi N., Bassi P., Gulino G.
Embase
[Article]
AN: 610874274
RESULTS: In patients undergoing dialysis and in recently transplanted patients a higher instance of ED was found (70% and 65% of cases respectively). Amongst dialyzed patients, patients aged over 50 suffer from ED more frequently. Patients aged over 50s represent 61% of the total number of patients suffering from ED, and just 31% of patients not suffering from ED, (p = 0.006); Hyperprolactinemia was found in 23% and 20% of both groups respectively. Fifty nine % of the dialyzed patients presented values of testosterone serum levels of less than 250 ng/dl with a significant difference between those who were suffering from ED and those who were not (65% of ED patients vs. 46%,of patients not affected from ED p = 0.019). This was found in only 37% of transplanted patients and there does not appear to be a statistically significant correlation with the onset of ED (p = 0.12). In patients over the age of 50, diabetes and a condition of hypotestosteronemia were significantly correlated with ED at univariate and multivariate analyses. CONCLUSIONS: The ED in patients with end stage chronic kidney failure (CKF) continues to have a strong prevalence, either in the patients who are undergoing dialysis or in those who have received transplants. In literature this issue is not sufficiently considered if not at all. Hypotestosteronemia is a risk factor for the onset of ED in end stage CKF patients. A significantly lower prevalence of hypogonadism among dialyzed patents and transplant recipients suggests that renal transplantation may be protective for the sexual capabilities of these patients.
MATERIALS AND METHODS: The study was conducted from December 2011 to December 2012 on 95 patients between the ages of 20 and 65 years: 44 of which had been undergoing dialysis for over a year and 51 of whom had undergone kidney transplants more than 6 months before. Comorbidities were carefully recorded, erectile function was evaluated with IIEF5 questionnaire and serum levels of total testosterone / free and prolactin were tested at early morning (7 AM). To assess the relationship between erectile dysfunction (ED) and clinical laboratory tests, Student's t-test statistical (quantitative variables), chi-square (qualitative variables), the uni and multivariate analysis were used.


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436.
Dynamics of body composition in male patients during chronic obstructive pulmonary disease (COPD) development.
Makarevich A.E., Lemiasheuskaya S.
Embase
Pneumonologia i alergologia polska. 83 (6) (pp 424-430), 2015. Date of Publication: 2015.
[Article]
AN: 610830077
INTRODUCTION: The various distribution of fat mass (FM) and lean mass (LM) during COPD development is not yet researched. MATERIAL AND METHODS: 82 male patients (40-67 years) with acute exacerbation of COPD and 19 comparable healthy males (the control group) were examined by dual-energy X-ray absorptiometry. The patients were divided into 3 groups according to COPD severity: 1st - 19 (GOLD I stage); 2nd - 43 (GOLD II) and 3rd - 20 (GOLD III). RESULTS: The patients of 3rd group had lower indices of FM, LM, bone mineral component (BMC) vs. the control and 1st, 2nd groups. A significant increase in FM share was noted in
android and gynoid regions, trunk, legs and arms in 2nd groups vs. the control with the decline of these parameters in the 3rd group below the control level. A greater proportion of FM in 1st and 2nd groups was distributed in android and trunk regions vs. the control. TNF-a and leptin levels were significantly increased by 12%, 15% 17% and by 18%, 75%, 79% respectively in 1st, 2nd, 3rd groups vs. the control, while free testosterone level was lower in these groups vs. the control (by 28%, 30% and 47% respectively; p < 0.05).

CONCLUSIONS: Body mass index (BMI) was within the control range in mild-moderate COPD patients in spite of LM, FM and BMC changes. The level of LM and BMC was decreased during COPD progression, while FM was increased in mild-moderate COPD and then it was decreased in severe COPD.

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437.

Polyorchidism with presumed contralateral intrauterine testicular torsion.
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[Journal Article]

UI: 25462053

INTRODUCTION: Polyorchidism was first described by Blasius in 1670(1) during a routine autopsy. We report a child with unilateral polyorchidism and a contralateral absent testis, a combination not reported previously.

PRESENTATION OF CASE: A 2-year-old boy was referred to the outpatient clinic with an impalpable left testis. At laparoscopy, the left vas deferens and testicular vessels ended blindly proximal to a closed internal ring. No gonadal tissue was identified. On the right side, a single vas
deferens and testicular vessels were seen entering the internal ring as normal. The right side of the scrotum was explored and two testes were identified within a single tunica vaginalis. Discussion: Polyorchidism is rare with a literature search identifying approximately 230 reported cases. Whilst prenatal testicular torsion is increasing being recognized and treated as a surgical emergency, (9) prenatal testicular torsion in association with polyorchidism has not been previously reported. Conclusion: We describe a unique case of a 2-year-old boy with right-sided polyorchidism and an absent left testis associated with a blind ending vas deferens and testicular vessels, presumed secondary to intrauterine testicular torsion.

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438.
Mutational Analysis of the Genes Encoding RFAmide-Related Peptide-3, the Human Orthologue of Gonadotrophin-Inhibitory Hormone, and its Receptor (GPR147) in Patients with Gonadotrophin-Releasing Hormone-Dependent Pubertal Disorders.
RFamide-related peptide-3 (RFRP-3), the orthologue of avian gonadotrophin-inhibitory hormone, and its receptor GPR147 have been recently identified in the human hypothalamus, and their roles in the regulation of reproductive axis has been studied. The present study aimed to investigate whether the presence of variants in the genes encoding human RFRP-3 (NPVF gene) and its receptor, GPR147 (NPFFR1 gene), is associated with the occurrence of gonadotrophin-releasing hormone-dependent pubertal disorders. Seventy-eight patients with idiopathic central precocious puberty (CPP) and 51 with normosmic isolated hypogonadotrophic hypogonadism (nIHH) were investigated. Fifty healthy subjects comprised the control group. The coding sequences of the NPVF and NPFFR1 genes were amplified and sequenced. Odds ratios (OR) were used to estimate the likelihood of CPP or nIHH in the presence of the described polymorphisms. All such polymorphisms have already been registered in the National Center for Biotechnology Information database. A three-nucleotide in frame deletion was identified in the NPVF gene (p.I71_K72), with a smaller proportion in the CPP (5%) compared to the nIHH (15%) group (P = 0.06). This results in the deletion of the isoleucine at position 71, adjacent to lysine at an endoproteolytic cleavage site of the precursor peptide. This polymorphism was associated with a lower risk of CPP (OR = 0.33; 95% confidence interval = 0.08-0.88); interestingly, only two men with nIHH were homozygotes for this variant. A total of five missense polymorphisms were found in the NPFFR1 gene, which encodes GPR147, with similar frequencies among groups and no association with pubertal timing. Our data suggest that RFRP-3/GPR147 may play secondary, modulatory roles on the regulation of pubertal development; a restraining modulatory effect of the NPVF p.I71_K72 variant on the activation of the gonadotrophic axis cannot be ruled out and deserves further investigation. Copyright © 2014 British Society for Neuroendocrinology

PMID
Endocrine dysfunction among adult patients with tuberculosis: An African experience.
Kibirige D.
Embase
Indian Journal of Endocrinology and Metabolism. 18 (3) (pp 288-294), 2014. Date of Publication: May-June 2014.
[Review]
AN: 613335731
A broad spectrum of endocrine conditions has been reported among adult patients with tuberculosis in Africa. This review aims to describe the magnitude and pathogenesis of the following endocrinopathies among patients with tuberculosis in Africa: adrenal insufficiency, diabetes mellitus, disorders of calcium and vitamin D metabolism, thyroid dysfunction and hypogonadism. PubMed database and Google scholar were used to search for the relevant published English language studies and case reports relating to endocrine abnormalities and tuberculosis in Africa up to July 2013. The search terms used were endocrine dysfunction, endocrine abnormalities, adrenal insufficiency, diabetes mellitus, thyroid dysfunction, hypogonadism, disorders of calcium and vitamin D metabolism, tuberculosis, Africa. Reference lists of the identified articles were further used to identify other studies. Adrenal insufficiency, diabetes mellitus and calcium-vitamin D abnormalities were the most prevalent and frequently reported endocrine disorders among adult patients with tuberculosis in Africa. A meticulous endocrine evaluation among tuberculosis patients with suspected endocrine abnormalities should be encouraged in Africa and other high TB endemic regions. Treatment of these endocrine disorders has generally been shown to improve quality of life and reduce mortality.
Mechanism-based treatment in complex regional pain syndromes.
Gierthmuhlen J., Binder A., Baron R.

Nature Reviews Neurology. 10 (9) (pp 518-528), 2014. Date of Publication: September 2014.
[Review]
AN: 612205023

Complex regional pain syndromes (CRPS) are multifactorial disorders with complex aetiology and pathogenesis. Management of CRPS is challenging, partly because of a lack of clinical data regarding the efficacy of the various therapies, and partly because successful treatment of CRPS requires a multidisciplinary, patient-tailored approach. The pain in CRPS is often described as typical 'burning' neuropathic pain, and is accompanied by a variety of sensory, motor and autonomic signs and symptoms. Because research into therapies specifically in CRPS has been scarce, treatment for these syndromes has been largely based on therapeutic strategies adapted from neuropathic pain states; however, increased understanding of the pathogenesis of CRPS has provided the opportunity to develop mechanism-based treatments. The interactions between the multiple pathophysiological mechanisms that contribute to the development, progression and maintenance of CRPS remain poorly understood. This Review describes the challenges in linking the current theories and knowledge of pathophysiological mechanisms to the mode of actions of the different treatment approaches. We discuss the current treatment strategies for CRPS, including pharmacotherapy, sympathetic ganglion block interventions, psychological support,
Practical considerations and patient selection for intrathecal drug delivery in the management of chronic pain.

Saulino M., Kim P.S., Shaw E.

Embase

Journal of Pain Research. 7 (pp 627-638), 2014. Date of Publication: 10 Nov 2014.

[Review]

AN: 600441490

Chronic pain continues to pose substantial and growing challenges for patients, caregivers, health care professionals, and health care systems. By the time a patient with severe refractory pain sees a pain specialist for evaluation and management, that patient has likely tried and failed several nonpharmacologic and pharmacologic approaches to pain treatment. Although relegated to one of the interventions of "last resort", intrathecal drug delivery can be useful for improving pain control, optimizing patient functionality, and minimizing the use of systemic pain medications in appropriately selected patients. Due to its clinical and logistical requirements, however, intrathecal drug delivery may fit poorly into the classic pain clinic/interventional model and may be
perceived as a “critical mass” intervention that is feasible only for large practices that have specialized staff and appropriate office resources. Potentially, intrathecal drug delivery may be more readily adopted into larger practices that can commit the necessary staff and resources to support patients’ needs through the trialing, initiation, monitoring, maintenance, and troubleshooting phases of this therapy. Currently, two agents - morphine and ziconotide - are approved by the United States Food and Drug Administration for long-term intrathecal delivery. The efficacy and safety profiles of morphine have been assessed in long-term, open-label, and retrospective studies of >400 patients with chronic cancer and noncancer pain types. The efficacy and safety profiles of ziconotide have been assessed in three double-blind, placebo-controlled trials of 457 patients, and safety has been assessed in 1,254 patients overall, with severe chronic cancer, noncancer, and acquired immunodeficiency syndrome pain types. Both agents are highlighted as first-line intrathecal therapy for the management of neuropathic or nociceptive pain. The purpose of this review is to discuss practical considerations for intrathecal drug delivery, delineate criteria for the identification and selection of candidates for intrathecal drug delivery, and consider which agent may be more appropriate for individual patients.

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2014
Hypothalamic-pituitary hormones during critical illness: a dynamic neuroendocrine response.
Langouche L., Van den Berghe G.

Embase
[Review]
AN: 611427519

Independent of the underlying condition, critical illness is characterized by a uniform dysregulation of the hypothalamic-pituitary-peripheral axes. In most axes a clear biphasic pattern can be distinguished. The acute phase of critical illness is characterized by low peripheral effector hormone levels such as T3, IGF-1 and testosterone, despite an actively secreting pituitary. The adrenal axis with high cortisol levels in the presence of low ACTH levels is a noteworthy exception. In the prolonged phase of critical illness, low peripheral effector hormone levels coincide with a uniform suppression of the neuroendocrine axes, predominantly of hypothalamic origin. The severity of the alterations in the different neuroendocrine axes is associated with a high risk of morbidity and mortality, but it remains unknown whether the observed changes are cause or consequence of adverse outcome. Several studies have identified therapeutic potential of hypothalamic releasing factors, but clinical outcome remains to be investigated with sufficiently powered randomized controlled trials. Copyright © 2014 Elsevier B.V. All rights reserved.

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Date Created
20160802

Year of Publication
2014

443.
Luteinizing hormone and follicle stimulating hormone synergy: A review of role in controlled ovarian hyper-stimulation.
Luteinizing hormone (LH) in synergy with follicle stimulating hormone (FSH) stimulates normal follicular growth and ovulation. FSH is frequently used in assisted reproductive technology (ART). Recent studies have facilitated better understanding on the complementary role of the LH to FSH in regulation of the follicle; however, role of LH in stimulation of follicle, optimal dosage of LH in stimulation and its importance in advanced aged patients has been a topic of discussion among medical fraternity. Though the administration of exogenous LH with FSH is obligatory for controlled ovarian stimulation in patients with hypogonadotropic hypogonadism, there is still a paucity of information of its usage in other patient population. In this review we looked in to the multiple roles that LH plays complementary to FSH to better understand the LH requirement in patients undergoing ART.

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Selenium and reproductive function. A systematic review.
Mirone M., Giannetta E., Isidori A.M.
Embase
[Review]
AN: 611900889
Selenium (Se) is an essential element involved in normal gonadal development, gametogenesis, and fertilization. Molecular studies show that the gonads actively take up and store Se, most of which is incorporated in the glutathione peroxidase enzymes. We provide a systematic review of the original molecular studies, prospective observational data and randomized controlled trials on the role of Se in reproductive function conducted in the past 30 years. A critical appraisal of these findings suggests that Se supplementation produces a bell-shaped response curve, with negative effects observed for both low and high concentrations. The few available clinical trials support the use of Se supplementation (<200 mug/d) to improve male infertility, although their pre-treatment assessment of Se levels in enrolled subjects is inconsistent and their quality and size are insufficient to enable general recommendations. In females, a putative role in oocyte maturation and fertilization is suggested, but no large controlled trials have yet been performed. The role of Se supplementation on pregnancy outcomes is promising, and ongoing studies and meta-analysis should soon enable proper recommendations to be suggested. How best to assess Se in terms of cut-off value, sample type (serum, semen, other fluids) and the specific outcome of interest remains to be clarified. In the meantime, assessment of serum Se levels followed by low-dose replacement therapy when necessary is a reasonable approach to improve male idiopathic infertility and gestational outcome. Copyright © 2013, Editrice Kurtis.
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Recent advances in opioid prescription for chronic non-cancer pain.
Snidvongs S., Mehta V.
Embase
Postgraduate Medical Journal. 88 (1036) (pp 66-72), 2012. Date of Publication: February 2012.
[Article]
AN: 51508249

Chronic pain is pain that persists past the normal time of healing, and is seen as a common problem with a significant socioeconomic impact. Pharmacological management for chronic non-cancer pain also involves the prescription of opioids, with the aim of an improved quality of life for the patient. New guidelines have been published to aid prescribing clinicians improve opioid safety and patient care, and include recommendations on when to refer patients to a pain specialist. In recent years there has been a rapid increase in opioid prescription in the UK and USA, prompting further concern regarding opioid abuse and side effects. Opioid use may also result in physical dependence and tolerance. Earlier recognition and diagnosis of unwanted effects of long term opioid use is needed, such as opioid induced suppression of the hypothalamo-adenohypophyseal and gonadal axes, and opioid induced immunosuppression. Patients may themselves discontinue opioids, however, due to minor side effects. Recent advances in opioid prescription include the increasing use of transdermal preparations and extended release, oral, once daily preparations. New formulations of existing drugs have been developed, as well as a new chemical entity. Abuse deterrent formulations and delivery systems may prevent the artificial acceleration of drug delivery and reduce the potential for opioid addiction. Overdose concerns and the potential for fatal overdose may necessitate mandatory training for all clinicians who prescribe opioids. Despite the widespread use of opioids in the management of chronic non-cancer pain, significant research gaps remain. An improvement in the evidence base for its prescription is required.
Pharmacodynamic Effects of Intravenous Alcohol on Hepatic and Gonadal Hormones: Influence of Age and Sex.
Vatsalya V., Issa J.E., Hommer D.W., Ramchandani V.A.

Background: Growth hormone (GH)-insulin-like growth factor-1 (IGF-1) axis and gonadal hormones demonstrate extensively associated regulation; however, little is known about the effects of acute alcohol exposure on these hormones. This study examined the effects of intravenous alcohol on the GH-IGF-1 axis and gonadal hormone concentrations, and the influence of age and sex on their regulation. Methods: Forty-eight healthy volunteers (24 men and 24 women each in the 21 to 25 and 55 to 65 year age groups) underwent a 2-session single-blinded study. Subjects received in randomized counter-balanced order, alcohol infusions, individually computed based on a physiologically based pharmacokinetic model, to maintain a steady-state (“clamped”) exposure of 50mg% or saline for 3 hours in separate sessions. Blood samples collected at baseline and postinfusion in each session were assayed for levels of GH, IGF-1, free testosterone, and estradiol. Results: Acute alcohol administration resulted in changes in gonadal hormones that differed by sex. Change in free testosterone showed a significant
treatmentxbaseline interaction (p<0.001), indicating that alcohol-induced suppression of testosterone occurred predominantly in men. On the other hand, change in estradiol showed a significant treatmentxsex interaction (p=0.028), indicating that alcohol-induced increases in estradiol occurred predominantly in women. There was a trend for alcohol-induced decreases in IGF-1 levels. Change in GH showed a significant main effect of baseline (p<0.001) and a trend for treatment by baseline interaction, suggesting an alcohol-induced decrease in individuals with high baseline GH values. There was also a significant main effect of sex (p=0.046) indicating that men had greater changes in GH across treatment compared with women. Conclusions: Alcohol induced a complex pattern of hormonal responses that varied between younger and older men and women. Some of the observed sex-based differences may help improve our understanding of the greater susceptibility to alcohol-related hepatic damage seen in women. © 2011 by the Research Society on Alcoholism.

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447.
Efficacy and Safety of Testosterone in the Management of Hypoactive Sexual Desire Disorder in Postmenopausal Women.
Davis S.R., Braunstein G.D.
Embase
Journal of Sexual Medicine. 9 (4) (pp 1134-1148), 2012. Date of Publication: April 2012.
Introduction. Hypoactive sexual desire disorder (HSDD) is a common problem in postmenopausal
women, but in the absence of an approved medical treatment in the United States, off-label
testosterone use is widespread. Large, randomized controlled studies have demonstrated that
transdermal testosterone improves sexual function and activity in postmenopausal women and
has favorable short-term safety. However, a longer-term safety profile of testosterone must be
established before a testosterone product for women is approved. Aim. To review current
knowledge of the efficacy and safety of transdermal testosterone based on presentations at a
satellite symposium during the 2011 annual meeting of the International Society for the Study of
Women's Sexual Health. Methods. Pertinent information included in the presentations was
augmented with relevant articles from the peer-reviewed literature. Main Outcome Measures. The
rationale for testosterone therapy and results from phase III and other clinical studies with the
testosterone patch in postmenopausal women with HSDD and findings from studies investigating
the cardiovascular, breast, and endometrial effects of testosterone therapy. Results.
Randomized, double-blind, placebo-controlled studies have established the efficacy of the
transdermal testosterone patch for relieving symptoms of HSDD in surgically and naturally
menopausal women with and without concomitant estrogen or estrogen/progestin therapy. The
main side effects reported in clinical trials were increased hair growth and acne. Available safety
data for testosterone, although not conclusive, were reassuring with respect to cardiovascular,
breast, and endometrial outcomes. Interim data from a long-term phase III safety trial of a
testosterone gel demonstrate a continued low rate of cardiovascular events and breast cancer in
postmenopausal women at increased cardiovascular risk. Conclusion. Transdermal testosterone
appears to be an effective and safe therapy for postmenopausal women with HSDD. © 2012
International Society for Sexual Medicine.
Erectile dysfunction and diabetes: A review of the current evidence-based medicine and a synthesis of the main available therapies.

Phe V., Roupret M.

Embase

Diabetes and Metabolism. 38 (1) (pp 1-13), 2012. Date of Publication: February 2012.

[Review]

AN: 51699200

Aim: This review aimed to provide an update of the epidemiology, pathophysiology and management of erectile dysfunction (ED) in diabetes patients. Methods: Data on the management of ED in diabetes patients in the literature were analyzed using Medline, and by matching the following keywords: diabetes; erectile dysfunction; endothelial dysfunction; cardiovascular disease; phosphodiesterase inhibitors; intracavernous injection; and penile prosthesis. Results: ED has a higher incidence in diabetic patients. The pathophysiology is multifactorial, involving endothelial dysfunction, specific complications of diabetes and psychological factors. Recent studies have shown that ED is able to predict future cardiovascular events not only in non-diabetics, but also in patients with diabetes. ED could also be a potential marker to screen for silent coronary artery disease. The management of ED has been revolutionized by the discovery of phosphodiesterase type-5 (PDE5) inhibitors, the first-line therapeutic options for diabetic men with ED that are efficient and safe. As a second line, intracavernous injections remain a gold-standard treatment, although a vacuum device can be used as well. In cases of failure, penile prosthesis may be considered. Hypogonadism, commonly found in diabetics, may require identification and treatment. Optimized glycaemic control, management of associated co-morbidities and lifestyle modifications are essential in all patients. As ED and diabetes negatively impact male self-esteem, and generate depression and anxiety, the psychological treatment of patients is also likely to be beneficial. Conclusion: The aetiology of diabetic ED is multifactorial. Endothelial dysfunction is the link between diabetes-induced ED and coronary artery disease. A global approach is needed for the successful management of diabetic ED. © 2011 Elsevier Masson SAS.

Status

EMBASE

Institution
Pathogenesis and causes of premature ovarian failure: An update.
Ebrahimi M., Asbagh F.A.

Embase
International Journal of Fertility and Sterility. 5 (2) (pp 54-65), 2011. Date of Publication: July-September 2011.

[Review]
AN: 615237486

Premature ovarian failure (POF) affects 1% of young women. This condition has significant psychological sequelae and major health implications. POF seriously interferes with fertility and family planning. Diverse etiologies are associated with POF. Literature review related to the causes and pathogenesis of POF, cited between the year 1900 and May 2010. POF may be either spontaneous or induced. The known causes include: Genetic disorders, which could involve the X chromosome or autosomes. However, the growing body of literature demonstrates a list of newly discovered mutations that may be responsible for causing POF. Most of these mutations are extremely rare, and most cases of POF are still considered to be idiopathic. Autoimmune causes; there is some evidence of an association of POF with lymphocytic oophoritis and other autoimmune disorders. Antiovarian antibodies are reported in POF, but their specificity and pathogenic role are obscure. Iatrogenic causes; chemotherapy, radiotherapy and pelvic surgery can lead to POF. Infectious Causes; some viral and microbial infections can be followed by POF. Environmental toxins, such as cigarette smoking are reported as risk factors of spontaneous POF. Idiopathic; in most cases, no identifiable etiology can be recognized after complete evaluation. Copyright © 2011, Royan Institute (ACECR). All rights reserved.
Oral contraceptive pill, progestogen or oestrogen pretreatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques.
We searched the following databases from inception to January 2017: Cochrane Gynaecology and Fertility Group Specialised Register, The Cochrane Central Register Studies Online, MEDLINE, Embase, CINAHL and PsycINFO. We also searched the reference lists of relevant articles and registers of ongoing trials.

Selection criteria
Randomised controlled trials (RCTs) of hormonal pretreatment in women undergoing ART.

Data collection and analysis
We used standard methodological procedures recommended by Cochrane. The primary review outcomes were live birth or ongoing pregnancy and pregnancy loss.

Main results
We included 29 RCTs (4701 women) of pretreatment with COCPs, progestogens or oestrogens versus no pretreatment or alternative pretreatments, in gonadotrophin-releasing hormone (GnRH) agonist or antagonist cycles. Overall, evidence quality ranged from very low to moderate. The main limitations were risk of bias and imprecision. Most studies did not describe their methods in adequate detail.

Authors’ conclusions
Among women undergoing ovarian stimulation in antagonist protocols, COCP pretreatment was associated with a lower rate of live birth or ongoing pregnancy than no pretreatment. There was insufficient evidence to determine whether rates of live birth or ongoing pregnancy were influenced by pretreatment with progestogens or oestrogens, or by COCP pretreatment using other stimulation protocols. Findings on adverse events were inconclusive, except that progesterone pretreatment may reduce the risk of ovarian cysts in agonist cycles, and COCP in antagonist cycles may reduce the risk of pregnancy loss compared with no pretreatment in agonist cycles.

451.
Interventions for preventing silent cerebral infarcts in people with sickle cell disease
EBM Reviews - Cochrane Database of Systematic Reviews
Cochrane Database of Systematic Reviews. 5, 2017.
[Systematic Review]
Background
Sickle cell disease (SCD) is one of the commonest severe monogenic disorders in the world, due to the inheritance of two abnormal haemoglobin (beta globin) genes. SCD can cause severe pain, significant end-organ damage, pulmonary complications, and premature death. Silent cerebral infarcts are the commonest neurological complication in children and probably adults with SCD. Silent cerebral infarcts also affect academic performance, increase cognitive deficits and may lower intelligence quotient.

Objectives
To assess the effectiveness of interventions to reduce or prevent silent cerebral infarcts in people with SCD.

Search methods
We searched for relevant trials in the Cochrane Library, MEDLINE (from 1946), Embase (from 1974), the Transfusion Evidence Library (from 1980), and ongoing trial databases; all searches current to 19 September 2016. We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register: 06 October 2016.

Selection criteria
Randomised controlled trials comparing interventions to prevent silent cerebral infarcts in people with SCD. There were no restrictions by outcomes examined, language or publication status.

Data collection and analysis
We used standard Cochrane methodological procedures.

Main results
We included five trials (660 children or adolescents) published between 1998 and 2016. Four of the five trials were terminated early. The vast majority of participants had the haemoglobin (Hb)SS form of SCD. One trial focused on preventing silent cerebral infarcts or stroke; three trials were for primary stroke prevention and one trial dealt with secondary stroke prevention.

Authors’ conclusions
We identified no trials for preventing silent cerebral infarcts in adults, or in children who do not have HbSS SCD.

Pharmacological and non-pharmacological strategies for obese women with subfertility
Taghavi, Abdolvahab Seyed. van Wely, Madelon. Jahanfar, Shayesteh. Bazarganipour, Fatemeh.Institution Fatemeh Bazarganipour .TI Pharmacological and non-pharmacological strategies for obese women with subfertility. EBM Reviews - Cochrane Database of Systematic Reviews Cochrane Database of Systematic Reviews. 4, 2017. [Protocol] AN: 00075320-100000000-11056 This is a protocol for a Cochrane Review (Intervention). The objectives are as follows: To assess the effectiveness and safety of pharmacological and non-pharmacological strategies compared with each other, placebo or no treatment, for obese women with subfertility.

453.
Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility Skalkidou, Alkistis. Sergentanis, Theodoros N. Gialamas, Spyros P. Georgakis, Marios K. Psaltopoulou, Theodora. Trivella, Marialena. Siristatidis, Charalampos S. Evangelou, Evangelos. Petridou, Eleni.Institution Alkistis Skalkidou .TI Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility. EBM Reviews - Cochrane Database of Systematic Reviews Cochrane Database of Systematic Reviews. 3, 2017. [Systematic Review] AN: 00075320-100000000-09339 Background Medical treatment for subfertility principally involves the use of ovary-stimulating agents, including selective oestrogen receptor modulators (SERMs), such as clomiphene citrate, gonadotropins, gonadotropin-releasing hormone (GnRH) agonists and antagonists, as well as human chorionic gonadotropin. Ovary-stimulating drugs may act directly or indirectly upon the endometrium (lining of the womb). Nulliparity and some causes of subfertility are recognized as risk factors for endometrial cancer. Objectives To evaluate the association between the use of ovary-stimulating drugs for the treatment of subfertility and the risk of endometrial cancer. Search methods
A search was performed in CENTRAL, MEDLINE (Ovid) and Embase (Ovid) databases up to July 2016, using a predefined search algorithm. A search in OpenGrey, ProQuest, ClinicalTrials.gov, ZETOC and reports of major conferences was also performed. We did not impose language and publication status restrictions.

Selection criteria
Cohort and case-control studies reporting on the association between endometrial cancer and exposure to ovary-stimulating drugs for subfertility in adult women were deemed eligible.

Data collection and analysis
Study characteristics and findings were extracted by review authors independently working in pairs. Inconsistency between studies was quantified by estimating $I^2$. Random-effects (RE) models were used to calculate pooled effect estimates. Separate analyses were performed, comparing treated subfertile women versus general population and/or unexposed subfertile women, to address the superimposition of subfertility as an independent risk factor for endometrial cancer.

Main results
Nineteen studies were eligible for inclusion (1,937,880 participants). Overall, the quality of evidence was very low, due to serious risk of bias and indirectness (non-randomised studies (NRS), which was reflected on the GRADE assessment.

Authors’ conclusions
The synthesis of the currently available evidence does not allow us to draw robust conclusions, due to the very low quality of evidence. It seems that exposure to clomiphene citrate as an ovary-stimulating drug in subfertile women is associated with increased risk of endometrial cancer, especially at doses greater than 2000 mg and high (more than 7) number of cycles. This may largely be due to underlying risk factors in women who need treatment with clomiphene citrate, such as polycystic ovary syndrome, rather than exposure to the drug itself. The evidence regarding exposure to gonadotropins was inconclusive.

454.

Progestosterone for acute traumatic brain injury
EBM Reviews - Cochrane Database of Systematic Reviews
Cochrane Database of Systematic Reviews. 2, 2017.
Background

Traumatic brain injury (TBI) is a leading cause of death and disability, and the identification of effective, inexpensive and widely practicable treatments for brain injury is of great public health importance worldwide. Progesterone is a naturally produced hormone that has well-defined pharmacokinetics, is widely available, inexpensive, and has steroidal, neuroactive and neurosteroidal actions in the central nervous system. It is, therefore, a potential candidate for treating TBI patients. However, uncertainty exists regarding the efficacy of this treatment. This is an update of our previous review of the same title, published in 2012.

Objectives

To assess the effects of progesterone on neurologic outcome, mortality and disability in patients with acute TBI. To assess the safety of progesterone in patients with acute TBI.

Search methods

We updated our searches of the following databases: the Cochrane Injuries Group's Specialised Register (30 September 2016), the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 9, 2016), MEDLINE (Ovid; 1950 to 30 September 2016), Embase (Ovid; 1980 to 30 September 2016), Web of Science Core Collection: Conference Proceedings Citation Index-Science (CPCI-S; 1990 to 30 September 2016); and trials registries: Clinicaltrials.gov (30 September 2016) and the World Health Organization (WHO) International Clinical Trials Registry Platform (30 September 2016).

Selection criteria

We included randomised controlled trials (RCTs) of progesterone versus no progesterone (or placebo) for the treatment of people with acute TBI.

Data collection and analysis

Two review authors screened search results independently to identify potentially relevant studies for inclusion. Independently, two review authors selected trials that met the inclusion criteria from the results of the screened searches, with no disagreement.

Main results

We included five RCTs in the review, with a total of 2392 participants. We assessed one trial to be at low risk of bias; two at unclear risk of bias (in one multicentred trial the possibility of centre effects was unclear, whilst the other trial was stopped early), and two at high risk of bias, due to issues with blinding and selective reporting of outcome data.

Authors’ conclusions

This updated review did not find evidence that progesterone could reduce mortality or disability in patients with TBI. However, concerns regarding inconsistency (heterogeneity among participants and the intervention used) across included studies reduce our confidence in these results.
Clomiphene and other antioestrogens for ovulation induction in polycystic ovarian syndrome


EBM Reviews - Cochrane Database of Systematic Reviews
Cochrane Database of Systematic Reviews. 1, 2017.

[Systematic Review]
AN: 00075320-10000000-01646

Background

Subfertility due to anovulation is a common problem in women. First-line oral treatment is with antioestrogens such as clomiphene citrate, but resistance may be apparent with clomiphene. Alternative and adjunctive treatments have been used including tamoxifen, dexamethasone, and bromocriptine. The effectiveness of these is to be determined.

Objectives

To determine the relative effectiveness of antioestrogen agents including clomiphene alone or in combination with other medical therapies in women with subfertility associated with anovulation, possibly caused by polycystic ovarian syndrome.

Search methods

We conducted a search of the Cochrane Gynaecology and Fertility Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO, and CINAHL (all from inception to August 2016) to identify relevant randomised controlled trials (RCTs). We searched the United Kingdom National Institute for Clinical Excellence (NICE) guidelines and the references of relevant reviews and RCTs. We also searched the clinical trial registries for ongoing trials (inception until August 2016).

Selection criteria

We considered RCTs comparing oral antioestrogen agents for ovulation induction (alone or in conjunction with medical therapies) in anovulatory subfertility. We excluded insulin-sensitising agents, aromatase inhibitors, and hyperprolactinaemic infertility.

Data collection and analysis

Two review authors independently performed data extraction and quality assessment. The primary outcome was live birth; secondary outcomes were pregnancy, ovulation, miscarriage, multiple pregnancy, ovarian hyperstimulation syndrome, and adverse effects.
Main results
This is a substantive update of a previous review. We identified an additional 13 studies in the 2016 update. The review now includes 28 RCTs (3377 women) and five RCTs awaiting classification. Five of the 28 included trials reported live birth/ongoing pregnancy. Secondary outcomes were poorly reported.

Authors’ conclusions
We found evidence suggesting that clomiphene citrate improves the chance of a clinical pregnancy compared with placebo, but may reduce the chance of live birth or ongoing pregnancy when compared with a gonadotropin. Due to low event rates, we advise caution interpreting these data.

456.
Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews
EBM Reviews - Cochrane Database of Systematic Reviews
Cochrane Database of Systematic Reviews. 1, 2017.
[Protocol]
AN: 00075320-100000000-10912
This is a protocol for a Cochrane Review (Overview). The objectives are as follows:
To assess adverse events associated with medium- and long-term use of opioids for CNCP.

457.
Disease-modifying treatments for primary autoimmune haemolytic anaemia
EBM Reviews - Cochrane Database of Systematic Reviews
Cochrane Database of Systematic Reviews. 1, 2017.

[Protocol]
AN: 00075320-100000000-10890
This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:
To determine the effects of various disease-modifying treatment modalities in people with autoimmune haemolytic anaemia.

458.
Interventions for antipsychotic-induced amenorrhoea
EBM Reviews - Cochrane Database of Systematic Reviews
Cochrane Database of Systematic Reviews. 12, 2016.

[Protocol]
AN: 00075320-100000000-10855
This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:
To assess the clinical effectiveness and safety of various treatments for antipsychotic-induced amenorrhoea.

459.
Hydroxyurea for reducing blood transfusion in non-transfusion dependent beta thalassaemias
EBM Reviews - Cochrane Database of Systematic Reviews
Cochrane Database of Systematic Reviews. 10, 2016.

[Systematic Review]
AN: 00075320-100000000-09969
Background
Non-transfusion dependent beta thalassaemia is a subset of inherited haemoglobin disorders characterised by reduced production of the beta globin chain of the haemoglobin molecule leading to anaemia of varying severity. Although blood transfusion is not a necessity for survival, it is required when episodes of chronic anaemia occur. This chronic anaemia can impair growth and affect quality of life. People with non-transfusion dependent beta thalassaemia suffer from iron overload due to their body's increased capability of absorbing iron from food sources. Iron overload becomes more pronounced in those requiring blood transfusion. People with a higher foetal haemoglobin level have been found to require fewer blood transfusions. Hydroxyurea has been used to increase foetal haemoglobin level; however, its efficacy in reducing transfusion, chronic anaemia complications and its safety need to be established.

Objectives
To assess the effectiveness, safety and appropriate dose regimen of hydroxyurea in people with non-transfusion dependent beta thalassaemia (haemoglobin E combined with beta thalassaemia and beta thalassaemia intermedia).

Search methods
We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register, compiled from electronic database searches and handsearching of relevant journals. We also searched ongoing trials registries and the reference lists of relevant articles and reviews.

Selection criteria
Randomised or quasi-randomised controlled trials of hydroxyurea in people with non-transfusion dependent beta thalassaemia comparing hydroxyurea with placebo or standard treatment or comparing different doses of hydroxyurea.

Data collection and analysis
Two authors independently applied the inclusion criteria in order to select trials for inclusion. Both authors assessed the risk of bias of trials and extracted the data. A third author verified these assessments.

Main results
No trials comparing hydroxyurea with placebo or standard care were found. However, we included one randomised controlled trial (n = 61) comparing 20 mg/kg/day with 10 mg/kg/day of hydroxyurea for 24 weeks.

Authors’ conclusions
There is no evidence from randomised controlled trials to show whether hydroxyurea has any effect compared with controls on the need for blood transfusion. Administration of 10 mg/kg/day compared to 20 mg/kg/day of hydroxyurea resulted in higher haemoglobin levels and seems safer with fewer adverse effects. It has not been reported whether hydroxyurea is capable of reducing
the need for blood transfusion. Large well-designed randomised controlled trials with sufficient duration of follow up are recommended.

460.
Hematopoietic stem cell transplantation for people with [latin sharp s]-thalassaemia major
EBM Reviews - Cochrane Database of Systematic Reviews
Cochrane Database of Systematic Reviews. 11, 2016.
[Systematic Review]
AN: 00075320-100000000-07153
Background
Thalassemia is an inherited autosomal recessive blood disorder, caused by mutations in globin genes or their regulatory regions. This results in a reduced rate of synthesis of one of the globin chains that make up haemoglobin. In [latin sharp s]-thalassaemia major there is an underproduction of [latin sharp s]-globin chains combined with excess of free [alpha]-globin chains. The excess free [alpha]-globin chains precipitate in red blood cells, leading to their destruction (haemolysis) and ineffective erythropoiesis. The conventional approach to treatment is based on the correction of haemoglobin status through regular blood transfusions and iron chelation therapy for iron overload. Although conventional treatment has the capacity to improve the quality of life of people with [latin sharp s]-thalassaemia major, allogeneic hematopoietic stem cell transplantation is the only currently available procedure which has the curative potential. This is an update of a previously published Cochrane Review.
Objectives
To evaluate the effectiveness and safety of different types of allogeneic hematopoietic stem cell transplantation, in people with severe transfusion-dependant [latin sharp s]-thalassaemia major, [latin sharp s]-thalassaemia intermedia or [latin sharp s]0/+- thalassaemia variants requiring chronic blood transfusion.
Search methods
We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Haemoglobinopathies Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.
Selection criteria
Randomised controlled trials and quasi-randomised controlled trials comparing allogeneic hematopoietic stem cell transplantation with each other or with standard therapy (regular transfusion and chelation regimen).

Data collection and analysis
Two review authors independently screened studies and had planned to extract data and assess risk of bias using standard Cochrane methodologies but no studies were identified for inclusion.

Main results
No relevant studies were retrieved after a comprehensive search of the literature.

Authors’ conclusions
We were unable to identify any randomised controlled trials or quasi-randomised controlled trials on the effectiveness and safety of different types of allogeneic stem cell transplantation in people with severe transfusion-dependant [latin sharp s]-thalassaemia major or [latin sharp s]0/+-thalassaemia variants requiring chronic blood transfusion. The absence of high-level evidence for the effectiveness of these interventions emphasises the need for well-designed, adequately-powered, randomised controlled clinical trials.

461.
Treatment for osteoporosis in people with [latin sharp s]-thalassaemia

Background
Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. Osteoporosis represents an important cause of morbidity in people with beta-thalassaemia and its pathogenesis is multifactorial. Factors include bone marrow expansion due to ineffective erythropoiesis, resulting in reduced trabecular bone tissue with cortical thinning; endocrine dysfunction secondary to excessive iron loading, leading to increased bone turnover;
and lastly, a predisposition to physical inactivity due to disease complications with a subsequent reduction in optimal bone mineralization.

Objectives
To review the evidence on the efficacy and safety of treatment for osteoporosis in people with beta-thalassaemia.

Search methods
We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.

Selection criteria
Randomised, placebo-controlled trials in people with thalassaemia with a bone mineral density z score of less than -2 standard deviations for: children less than 15 years old; adult males (15 to 50 years old); and all pre-menopausal females above 15 years and a bone mineral density t score of less than -2.5 standard deviations for post-menopausal females and males above 50 years old.

Data collection and analysis
Two review authors assessed the eligibility and risk of bias of the included trials, extracted and analysed data and completed the review. We summarised results using risk ratios or rate ratios for dichotomous data and mean differences for continuous data. We combined trial results where appropriate.

Main results
Four trials (with 211 participants) were included; three trials investigated the effect of bisphosphonate therapies and one trial investigated the effect of zinc supplementation. Only one trial was judged to be of good quality (low risk of bias); the remaining trials had a high or unclear risk of bias in at least one key domain.

Authors’ conclusions
There is evidence to indicate an increase in bone mineral density at the femoral neck, lumbar spine and forearm after administration of bisphosphonates and at the lumbar spine and hip after zinc sulphate supplementation. The authors recommend that further long-term randomised control trials on different bisphosphonates and zinc supplementation therapies in people with beta-thalassaemia and osteoporosis are undertaken.
Dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history
Chen, Hengxi. Fu, Jing. Huang, Wei.Institution Wei Huang .TI Dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history.
EBM Reviews - Cochrane Database of Systematic Reviews
Cochrane Database of Systematic Reviews. 7, 2016.
[Systematic Review]
AN: 00075320-10000000-07286
Background
Hyperprolactinemia is the presence of abnormally high circulating levels of prolactin. Idiopathic hyperprolactinemia is the term used when no cause of prolactin hypersecretion can be identified and it is causally related to the development of miscarriage in pregnant women, especially women who have a history of recurrent miscarriage. A possible mechanism is that high levels of prolactin affect the function of the ovaries, resulting in a luteal phase defect and miscarriage. A dopamine agonist is a compound with high efficacy in lowering prolactin levels and restoring gonadal function.
Objectives
To assess the effectiveness and safety of different types of dopamine agonists in preventing future miscarriage given to women with idiopathic hyperprolactinemia and a history of recurrent miscarriage.
Search methods
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 June 2016) and reference lists of retrieved studies.
Selection criteria
Randomized controlled trials (RCTs) in all languages examining the effect of dopamine agonists on preventing future miscarriage. Women who had idiopathic hyperprolactinemia with a history of recurrent miscarriages were eligible for inclusion in this review. Comparisons planned included: dopamine agonists alone versus placebo/no treatment; and dopamine agonists combined with other therapy versus other therapy alone.
Data collection and analysis
Two review authors independently assessed a single trial for inclusion, evaluated trial quality and extracted data. Data were checked for accuracy.
Main results
One study (recruiting 48 women with idiopathic hyperprolactinemia) met our inclusion criteria; 46 women (42 pregnancies - 4/46 women did not conceive during the study period) were included in the analysis. The study compared the use of a dopamine agonist (bromocriptine, 2.5 mg to 5.0 mg/day until the end of the ninth week of gestation) versus a no-treatment control. The study was
judged as being at a high risk of bias. It was not possible to carry out meta-analysis due to insufficient data.

Authors’ conclusions
Currently, there is insufficient evidence (from a single randomized trial with a small sample size, and judged to be at high risk of bias) to evaluate the effectiveness of dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and a history of recurrent miscarriage. We assessed outcomes using GRADE methodology. Miscarriage was assessed as low quality due to risk of bias concerns in the one trial contributing data (no description of allocation concealment, lack of blinding and possible reporting bias) and to imprecision (effect estimates were based on small sample size and few events). Live births and conception were assessed as of very low quality due to the same risk of bias concerns in study design and to imprecision (with a wide 95% CI consistent with either benefit or harm), and a small sample size. There were no data relating to adverse effects of the intervention for either the mother or her baby.

463.
Growth hormone therapy for people with thalassaemia
EBM Reviews - Cochrane Database of Systematic Reviews
Cochrane Database of Systematic Reviews. 7, 2016.
[Protocol]
AN: 00075320-100000000-10689
This is the protocol for a review and there is no abstract. The objectives are as follows:
To assess the risks and benefits of GH therapy in people with thalassaemia.

464.
Hematopoietic stem cell transplantation for people with sickle cell disease
Background
Sickle cell disease is a genetic disorder involving a defect in the red blood cells due to its sickled hemoglobin. The main therapeutic interventions include preventive and supportive measures. Hematopoietic stem cell transplantations are carried out with the aim of replacing the defective cells and their progenitors (hematopoietic (i.e. blood forming) stem cells) in order to correct the disorder. This is an update of a previously published review.

Objectives
To determine whether stem cell transplantation can improve survival and prevent symptoms and complications associated with sickle cell disease. To examine the risks of stem cell transplantation against the potential long-term gain for people with sickle cell disease.

Search methods
We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Group’s Haemoglobinopathies Trials Register complied from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of The Cochrane Library) and quarterly searches of MEDLINE.

Selection criteria
Randomized controlled and quasi-randomized studies that compared any method of stem cell transplantation with either each other or with any of the preventive or supportive interventions (e.g. periodic blood transfusion, use of hydroxyurea, antibiotics, pain relievers, supplemental oxygen) in people with sickle cell disease irrespective of the type of sickle cell disease, gender and setting.

Data collection and analysis
No relevant trials were identified.

Main results
Ten trials were identified by the initial search and none for the update. None of these trials were suitable for inclusion in this review.

Authors’ conclusions
Reports on the use of hematopoietic stem cell transplantation improving survival and preventing symptoms and complications associated with sickle cell disease are currently limited to observational and other less robust studies. No randomized controlled trial assessing the benefit or risk of hematopoietic stem cell transplantations was found. Thus, this systematic review
identifies the need for a multicentre randomized controlled trial assessing the benefits and possible risks of hematopoietic stem cell transplantations comparing sickle status and severity of disease in people with sickle cell disease.