EAU GUIDELINES ON MALE HYPOGONADISM

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Introduction

Male hypogonadism is a clinical syndrome caused by androgen deficiency which may adversely affect multiple organ functions and quality of life. Androgen deficiency increases slightly with age. In middle-aged men the incidence is 6%. Hypogonadism is more prevalent in older men, in men with obesity, those with co-morbidities, and in men with a poor health status.

Aetiology and classification

Male hypogonadism can be classified in accordance with disturbances at the level of:

- the testes (primary hypogonadism);
- the hypothalamus and pituitary (secondary hypogonadism);
- the hypothalamus/pituitary and gonads (hypogonadism in adult men);
- androgen target organs (androgen insensitivity/resistance).

Table 1: Most common forms of primary hypogonadism

Disease	Pathophysiology
Maldescended or ectopic testes	Failure of testicular descent, maldevelopment of the testis
Testicular cancer	Testicular maldevelopment
Orchitis	Viral or unspecific orchitis
Acquired anorchia	Trauma, tumour, torsion, inflammation, iatrogenic, surgical removal
Secondary testicular dysfunction	Medication, drugs, toxins, systemic diseases
(Idiopathic) testicular atrophy	Male infertility (idiopathic or specific causes)
Congenital anorchia (bilateral in 1 in 20,000 males, unilateral 4 times as often)	Intrauterine torsion is the most probable cause
Klinefelter syndrome 47,XXY	Sex-chromosomal non-disjunction in germ cells

Table 2: Most common forms of secondary hypogonadism

Disease	Pathophysiology
Hyperprolactinemia	Prolactin-secreting pituitary adenomas (prolactinomas) or drug-induced
Isolated hypogonadotropic hypogonadism (IHH) (formerly termed idiopathic hypogonadotropic hypogonadism)	SGnRH deficiency specific (or unknown) mutations affecting GnRH synthesis or action

Kallmann syndrome (hypogonadotropic hypogonadism with anosmia) (prevalence 1 in 10,000)	GnRH deficiency and anosmia, genetically determined
Secondary GnRH deficiency	Medication, drugs, toxins, systemic diseases
Hypopituitarism	Radiotherapy, trauma, infections, haemochromatosis and vascular insufficiency or congenital
Pituitary adenomas	Hormone-secreting adenomas; hormone-inactive pituitary adenomas; metastases to the pituitary or pituitary stalk

Recommendation	**LE**	**GR**
Differentiate the two forms of hypogonadism (primary and secondary) (LH levels), as this has implications for patient evaluation and treatment and makes it possible to identify patients with associated health problems and infertility.	1b	B

LH = luteinising hormone; GnRH = gonadotropin-releasing hormone.

Diagnostic evaluation

Table 3: Signs and symptoms suggesting prepubertal-onset hypogonadism

Small testes
Cryptorchidism
Gynaecomastia
High pitched voice
Unclosed epiphyses
Linear growth into adulthood
Eunuchoid habitus
Sparse body hair/facial hair
Infertility
Low bone mass
Sarcopenia
Reduced sexual desire/activity

Table 4: Signs and symptoms associated with adult-onset hypogonadism

Loss of libido
Erectile dysfunction
Fewer and decreased morning erections
Overweight or obesity
Sarcopenia
Low bone mass
Depressive thoughts
Fatigue
Loss of body hair
Hot flushes
Loss of vigour

Recommendations diagnostic evaluation	LE	GR
Restrict the diagnosis of testosterone deficiency to men with persistent symptoms suggesting hypogonadism (Table 3).	3	C
Measure testosterone in the morning before 11.00 hours in the fasting state.	2	A
Repeat total testosterone assessment on at least two occasions with a reliable method. In addition, measure the free testosterone level in men with: - Total testosterone levels close to the lower normal range (8-12 nmol/L), to strengthen the laboratory assessment. - Suspected or known abnormal sex hormone-binding globulin (SHBG) levels.	1	A
Assess testosterone in men with a disease or treatment in which testosterone deficiency is common and in whom treatment may be indicated. This includes men with: - Type 2 diabetes. - Metabolic syndrome - Obesity. - Pituitary mass, following radiation involving the sellar region and other diseases in the hypothalamic and sellar region. - End-stage renal disease receiving haemodialysis. - Treatment with medications that cause suppression of testosterone levels - e.g. corticosteroids and opiates. - Moderate to severe chronic obstructive lung disease. - Infertility.	2	B

- Osteoporosis or low-trauma fractures. - HIV infection with sarcopenia.		
Analyse LH serum levels to differentiate between primary and secondary forms of hypogonadism.	2	A

Recommendations for screening men with adult-onset hypogonadism	**LE**	**GR**
Screen for testosterone deficiency only in adult men with consistent and multiple signs and symptoms listed in Table 3 and 4.	3	C
In adult men with established hypogonadism, screen for concomitant osteoporosis.	2	B

Disease management

Table 5: Indications for testosterone treatment

Delayed puberty (idiopathic, Kallmann syndrome)
Klinefelter syndrome with hypogonadism
Sexual dysfunction and low testosterone
Low bone mass in hypogonadism
Adult men with low testosterone and consistent and preferably multiple signs and symptoms of hypogonadism (listed in Table 3 and 4) following unsuccessful treatment of obesity and comorbidities
Hypopituitarism
Testicular dysgenesis and hypogonadism
Type 2 diabetes mellitus with hypogonadism

Table 6: Contraindications against testosterone treatment

Prostate cancer
PSA > 4 ng/mL
Male breast cancer
Severe sleep apnoea
Male infertility-active desire to have children
Haematocrit > 0.54%
Severe lower urinary tract symptoms due to benign prostatic hyperplasia
Severe chronic cardiac failure/New York Heart Association Class IV
Uncontrolled cardiovascular disease

Table 7: Testosterone preparations for replacement therapy

Formulation	Administration	Advantages	Disadvantages
Testosterone undecanoate	Oral; 2-6 cps every 6 hours	Absorbed through the lymphatic system, with consequent reduction of liver involvement.	Variable levels of testosterone above and below the mid-range. Need for several doses per day with intake of fatty food.
Testosterone cypionate	Intramuscular; one injection every two to three weeks	Short-acting preparation that allows drug withdrawal in case of onset of side-effects.	Possible fluctuation of testosterone levels.

Testosterone enanthate	Intramuscular; one injection every two to three weeks	Short-acting preparation that allows drug withdrawal in case of onset of side-effects.	Fluctuation of testosterone levels.
Testosterone undecanoate	Intramuscular; one injection every 10-14 weeks	Steady-state testosterone levels without fluctuation.	Long-acting preparation that cannot allow drug withdrawal in case of onset of side-effects.
Transdermal testosterone	Gel or skin patches; daily application	Steady-state testosterone level without fluctuation.	Skin irritation at the site of application and risk of interpersonal transfer.
Sublingual testosterone	Sublingual; daily doses	Rapid absorption and achievement of physiological serum level of testosterone.	Local irritation.
Buccal testosterone	Buccal tablet; two doses per day	Rapid absorption and achievement of physiological serum level of testosterone.	Irritation and pain at the site of application.
Subdermal depots	Subdermal implant every five to seven months	Long duration and constant serum testosterone level.	Risk of infection and extrusion of the implants.

Recommendations for testosterone replacement therapy	LE	GR
Fully inform the patient about expected benefits and side-effects of the treatment option. Select the preparation with a joint decision by an informed patient and the physician.	3	A
Use short-acting preparations rather than long-acting depot administration when starting the initial treatment, so that therapy can be adjusted or stopped in case of adverse side-effects.	3	B
Do not use testosterone therapy in patients with male infertility and active child wish since it may suppress spermatogenensis.	1b	A
Only use hCG treatment for hypogonadotropic hypogonadal patients with simultaneous fertility treatment.	1b	B
In patients with adult-onset hypogonadism, only attempt testosterone treatment in men with major symptoms and if weight loss, lifestyle modification and good treatment balance of comorbidities have proven unsuccessful.	2	A

hCG = human chorionic gonadotropin.

Recommendations on risk factors in testosterone treatment (TRT)	LE	GR
Perform haematological, cardiovascular, breast and prostatic assessment before the start of treatment.	1a	A
Monitor haematocrit, and haemoglobin and PSA during TRT therapy.	3	A
Offer TRT cautiously in symptomatic hypogonadal men who have been surgically treated for localised prostate cancer and who are currently without evidence of active disease (i.e. measurable PSA, abnormal rectal examination, evidence of bone/visceral metastasis): treatment should be restricted to those patients with a low risk for recurrent prostate cancer (i.e. Gleason score <8; pathological stage pT1-2; pre-operative PSA <10 ng/mL) and should not start before 1 year of follow-up.	3	B
Assess for cardiovascular risk factors before commencing TRT and optimise secondary prevention in men with pre-existing cardiovascular disease.	1a	A
Treat men men with hypogonadism and either pre-existing cardiovascular disease, venous thromboembolism or chronic cardiac failure who require TRT with caution by monitoring carefully with clinical assessment, haematocrit (not exceeding 0.54) and testosterone levels maintained as best possible for age within the mid-normal healthy range.	1b	A

PSA = prostate-specific antigen; TRT = testosterone replacement therapy.

Recommendations for follow-up	LE	GR
Assess the response to treatment at three, six and twelve months after the onset of treatment, and thereafter annually.	4	C
Monitor haematocrit at three, six and twelve months and thereafter annually. Decrease the testosterone dosage or switch testosterone preparation from parenteral to topical or venesection, if haematocrit is above 0.54. If haematocrit remains elevated, stop testosterone and reintroduce at a lower dose once haematocrit has normalised.	4	C
Assess prostate health by digital rectal examination and PSA before the start of TRT. Follow-up by PSA at three, six and twelve months and thereafter annually.	4	C
Assess men with cardiovascular diseases for cardiovascular symptoms before TRT is initiated and continue close clinical assessment during TRT.	1b	A

BMD = bone mineral density; PSA = prostate-specific antigen; TRT = testosterone replacement therapy.

This short booklet text is based on the more comprehensive EAU Guidelines (978-90-79754-98-4), available to all members of the European Association of Urology at their website, http://www.uroweb.org.