Guidelines on
Male Hypogonadism

G.R. Dohle (chair), S. Arver, C. Bettocchi,
S. Kliesch, M. Punab, W. de Ronde

European
Association
of Urology

TABLE OF CONTENTS PAGE

1. INTRODUCTION AND DEFINITION

Definition: male hypogonadism is a clinical syndrome caused by androgen deficiency which may adversely affect multiple organ functions and quality of life (1).

Androgens play a crucial role in the development and maintenance of male reproductive and sexual functions. Low levels of circulating androgens can cause disturbances in male sexual development, resulting in congenital abnormalities of the male reproductive tract. Later in life, this may cause reduced fertility, sexual dysfunction, decreased muscle formation and bone mineralisation, disturbances of fat metabolism, and cognitive dysfunction. Testosterone levels decrease as a process of ageing: signs and symptoms caused by this decline can be considered a normal part of ageing. However, low testosterone levels are also associated with several chronic diseases, and symptomatic patients may benefit from testosterone treatment.

This document presents the European Association of Urology (EAU) guidelines on the diagnosis and treatment of male hypogonadism. These guidelines aim to provide practical recommendations on how to deal with primary low testosterone and age-related decline in testosterone in male patients, as well as the treatment of testosterone disruption and deficiencies caused by other illnesses.

1.1 Reference

1. Nieschlag E, Behre HM (eds). *Andrology: male reproductive health and dysfunction*. 3rd edn. Heidelberg: Springer, 2010.

2. METHODOLOGY

The EAU Male Hypogonadism panel consists of a multidisciplinary group of experts, including urologists specialising in the treatment of infertility, endocrinologists and andrologists. There is a need for ongoing re-evaluation of the information presented in the current guidelines by an expert EAU panel. It must be emphasised that clinical guidelines present the best evidence available to the experts at the time of writing. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when treatment decisions for individual patients are being taken. Guidelines help to focus decisions. Clinical decisions must also take into account patients' personal values and preferences and their individual circumstances.

2.1 Data identification

The recommendations provided in the current guidelines are based on a systematic literature search performed by the panel members. MedLine, Embase and Cochrane databases were searched to identify original articles and review articles. The controlled vocabulary of the Medical Subject Headings (MeSH) database was used alongside a 'free-text' protocol, combining 'male hypogonadism' with the terms 'diagnosis', 'epidemiology', 'investigations', 'treatment', 'testosterone', 'androgens' and 'hypogonadism'.

All articles published before January 2012 were considered for review. The expert panel reviewed these records and selected articles with the highest level of evidence in accordance with a rating schedule adapted from the Oxford Centre for Evidence-Based Medicine levels of evidence.

2.2 Levels of evidence and grades of recommendation

References used in the text have been assessed according to their level of scientific evidence (Table 1). Guideline recommendations have been graded (Table 2) in accordance with the Oxford Centre for Evidence-Based Medicine levels of evidence (LE) (1). The aim of grading recommendations (GR) is to provide transparency between the underlying evidence and the recommendation given.

Table 1: Levels of evidence*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials.
1b	Evidence obtained from at least one randomised trial.
2a	Evidence obtained from one well-designed controlled study without randomisation.
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study.
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.

** Modified from Sackett et al. (1).*

It should be noted that when recommendations are graded, there is not an automatic relationship between the level of evidence and the grade of recommendation. The availability of RCTs may not necessarily translate into a grade A recommendation if there are methodological limitations or disparities in the published results. Conversely, an absence of high-level evidence does not necessarily preclude a grade A recommendation if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations in which corroborating studies cannot be performed, perhaps for ethical or other reasons. In this case, unequivocal recommendations are considered helpful for the reader. Whenever this occurs, it has been clearly indicated in the text with an asterisk as 'upgraded based on panel consensus'. The quality of the underlying scientific evidence is a very important factor, but it has to be balanced against benefits and burdens, values and preferences and costs when a grade is assigned (2-4).

The EAU Guidelines Office does not perform cost assessments, nor can they address local/national preferences in a systematic fashion. However, whenever such data are available, the expert panels will include the information.

Table 2: Grades of recommendation*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

** Modified from Sackett et al. (1).*

2.3 Publication history

The present male hypogonadism guidelines are a new publication that underwent a blinded peer-review process before publication. The standard procedure will be an annual assessment of newly published literature in this field, guiding future updates. An ultra-short reference document is published alongside this publication. All documents are available with free access through the EAU website Uroweb (http://www.uroweb.org/guidelines/online-guidelines/).

2.4 References

1. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2009). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009. http://www.cebm.net/index.aspx?o=1025 [Access date January 2014]
2. Atkins D, Best D, Briss PA, et al; GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004 Jun;328(7454):1490. http://www.ncbi.nlm.nih.gov/pubmed/15205295
3. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336(7650):924-6. http://www.ncbi.nlm.nih.gov/pubmed/18436948
4. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. Going from evidence to recommendations. BMJ 2008 May;336(7652):1049-51. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2376019/

3. EPIDEMIOLOGY

3.1 Introduction

Androgen deficiency increases with age; an annual decline in circulating testosterone of 0.4-2.0% has been reported (1,2). In middle-aged men, the incidence was found to be 6% (3). It is more prevalent in older men, in men with obesity, those with co-morbidities, and in men with a poor health status.

3.2 Role of testosterone for male reproductive health

Androgens, which are produced by the testis and the adrenal glands, play a pivotal role in male reproductive and sexual function. Androgens are also crucial for the development of male reproductive organs, such as the epididymis, vas deferens, seminal vesicle, prostate and penis. In addition, androgens are needed for puberty, male fertility, male sexual function, muscle formation, body composition, bone mineralisation, fat metabolism, and cognitive functions (4).

3.3 Physiology

Male sexual development starts between the 7th and 12th week of gestation. The undifferentiated gonads develop into a foetal testis through expression of the sex-determining region Y gene (SRY), a gene complex located on the short arm of the Y chromosome (5). The foetal testis produces two hormones: testosterone and anti-Müllerian hormone (AMH).

Testosterone is needed for the development of the Wolffian ducts, resulting in formation of the epididymis, vas deferens and seminal vesicle. AMH activity results in regression of the Müllerian ducts (Figure 1). Under the influence of intratesticular testosterone, the number of gonocytes per tubule increases threefold during the foetal period (6).

In addition, testosterone is needed for development of the prostate, penis and scrotum. However, in these organs testosterone is converted into the more potent metabolite dihydrotestosterone (DHT) by the enzyme 5α-reductase (7). The enzyme is absent in the testes, which explains why 5α-reductase inhibitors do not have a marked effect on spermatogenesis. Testosterone and DHT are required for penile growth, both activating the androgen receptor. The androgen receptor (AR) in the penis disappears after puberty, thus preventing further growth of the penis (8).

Intratesticular testosterone is needed to maintain the spermatogenic process and to inhibit germ cell apoptosis (9). The seminiferous tubules of the testes are exposed to concentrations of testosterone 25-100 times greater than circulating levels. Suppression of gonadotrophins (e.g. through excessive testosterone abuse) results in a reduced number of spermatozoa in the ejaculate and hypospermatogenesis (10). Complete inhibition of intratesticular testosterone results in full cessation of meiosis up to the level of spermatids (11,12). Testosterone does not appear to act directly on the germ cells, but functions through the Sertoli cells by expression of the AR and influencing the seminiferous tubular microenvironment (12).

Testosterone can also be metabolised into oestradiol by aromatase, present in fatty tissue, the prostate and bone. Oestradiol is essential for bone mineralisation, also in men (13).

The production of testosterone is controlled by luteinizing hormone (LH) from the pituitary gland. Immediately after birth, serum testosterone levels reach adult concentrations over several months. Thereafter and until puberty, testosterone levels are low, thus preventing male virilisation. Puberty starts with the production of gonadotrophins, initiated by GnRH secretion from the hypothalamus and resulting in testosterone production, male sexual characteristics and spermatogenesis (14). Figure 1 shows the development of the male reproductive system.

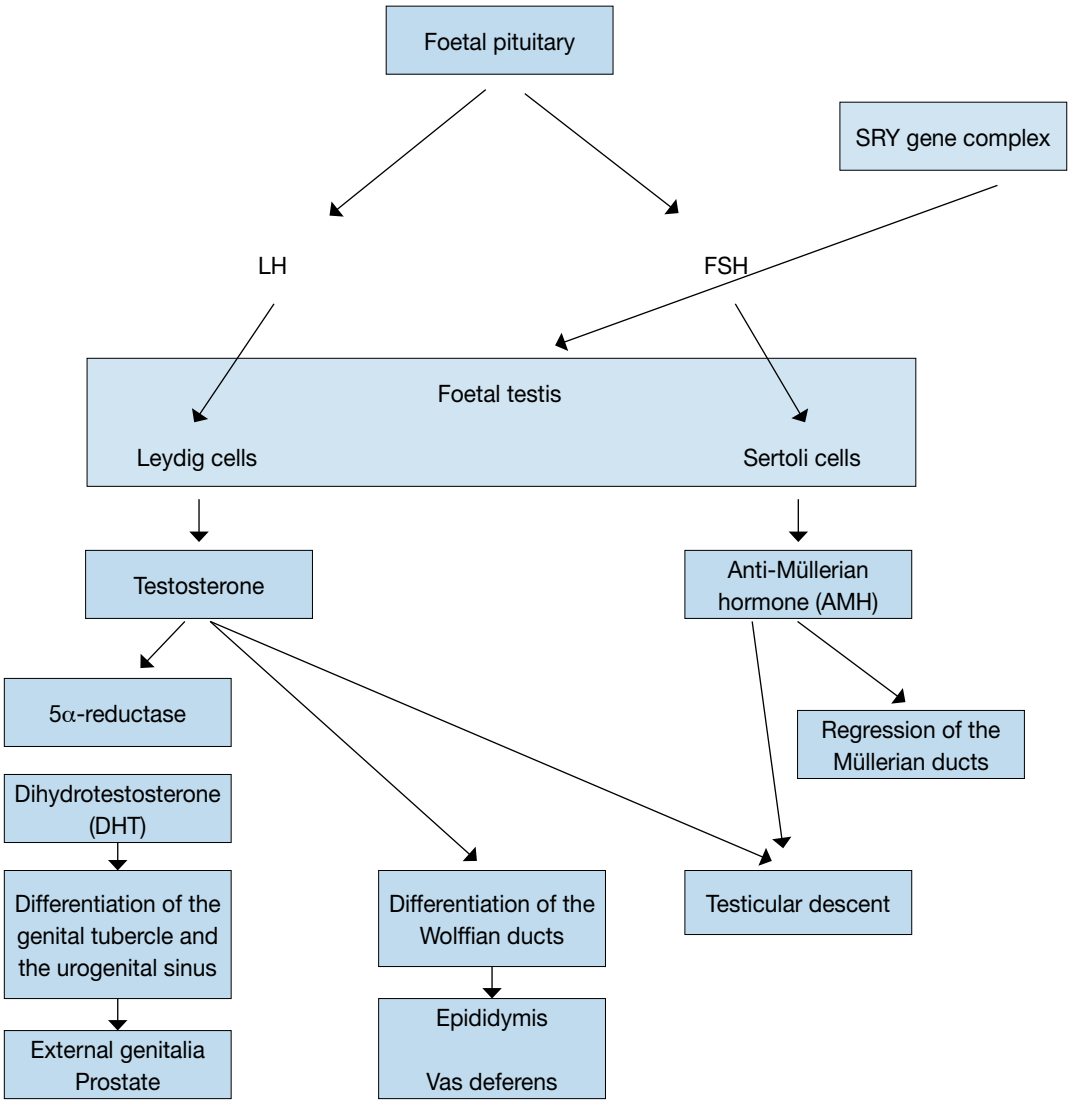
3.4 The androgen receptor

Testosterone exerts its action through the androgen receptor (AR), located in the cytoplasm and nucleus of target cells. During the foetal period, testosterone increases the number of androgen receptors by increasing the number of cells with the AR, but also by increasing the number of ARs in each individual cell (8,13).

The AR gene is located on the X chromosome (Xq 11-12): defects and mutations in the AR gene can result in male sexual maldevelopment, which may cause testicular feminisation or low virilisation. Less severe mutations in the AR gene may cause mild forms of androgen resistance and male infertility (15). In exon 1 of the gene, the transactivation domain consists of a trinucleotide tract (cytosine-adenine-guanine [CAG-repeats]) of variable length. Androgen sensitivity may be influenced by the length of the CAG repeats in exon 1 of the AR gene (15). The AR CAG repeat length is inversely correlated with serum total and bioavailable testosterone in ageing men. Shorter repeats have been associated with an increased risk for prostate disease, and longer repeats with reduced androgen action in several tissues (16). CAG repeat number may influence androgenic phenotypical effects, even in case of normal testosterone levels (17).

Conclusion
Testosterone is essential for normal male development.

Figure 1: Development of the male reproductive system



FSH = follicle-stimulating hormone; LH = luteinizing hormone; SRY = sex region of the Y chromosome.

3.5 References

1. Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. Endocr Rev 2005 Oct;26(6):833-76. http://www.ncbi.nlm.nih.gov/pubmed/15901667
2. Wu FC, Tajar A, Pye SR, et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. J Clin Endocrinol Metab 2008 Jul;93(7):2737-45. http://www.ncbi.nlm.nih.gov/pubmed/18270261
3. Hall SA, Esche GR, Araujo AB, et al. Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. J Clin Endocrinol Metab 2008 Oct;93(10):3870-7. http://www.ncbi.nlm.nih.gov/pubmed/18664536
4. Nieschlag E, Behre H, Nieschlag S. *Testosterone: action, deficiency, substitution*. Cambridge: Cambridge University Press, 2004.
5. Parker KL, Schimmer BP, Schedl A. Genes essential for early events in gonadal development. Cell Mol Life Sci 1999 Jun;55(6-7):831-8. http://www.ncbi.nlm.nih.gov/pubmed/10412366

6. Brinkmann AO. Molecular mechanisms of androgen action - a historical perspective. Methods Mol Biol 2011;776:3-24.
http://www.ncbi.nlm.nih.gov/pubmed/21796517
7. Rey RA, Grinspon RP. Normal male sexual differentiation and aetiology of disorders of sex development. Best Pract Res Clin Endocrinol Metab 2011 Apr;25(2):221-38.
http://www.ncbi.nlm.nih.gov/pubmed/21397195
8. Bentvelsen FM, McPhaul MJ, Wilson JD, et al. The androgen receptor of the urogenital tract of the fetal rat is regulated by androgen. Mol Cell Endocrinol 1994 Oct;105(1):21-6.
http://www.ncbi.nlm.nih.gov/pubmed/7821714
9. Singh J, O'Neill C, Handelsman DJ. Induction of spermatogenesis by androgens in gonadotropin-deficient (hpg) mice. Endocrinology 1995 Dec;136(12):5311-21.
http://www.ncbi.nlm.nih.gov/pubmed/7588276
10. Sun YT, Irby DC, Robertson DM, et al. The effects of exogenously administered testosterone on spermatogenesis in intact and hypophysectomized rats. Endocrinology 1989 Aug;125(2):1000-10.
http://www.ncbi.nlm.nih.gov/pubmed/2502373
11. Weinbauer GF, Nieschlag E. Gonadotrophin-releasing hormone analogue-induced manipulation of testicular function in the monkey. Hum Reprod 1993 Nov;8 Suppl 2:45-50.
http://www.ncbi.nlm.nih.gov/pubmed/8276968
12. McLachlan RI, O'Donnell L, Meachem SJ, et al. Hormonal regulation of spermatogenesis in primates and man: insights for development of the male hormonal contraceptive. J Androl 2002 Mar-Apr:23(2): 149-62.
http://www.ncbi.nlm.nih.gov/pubmed/11868805
13. de Ronde W, de Jong FH. Aromatase inhibitors in men: effects and therapeutic options. Reprod Biol Endocrinol 2011 Jun 21;9:93.
http://www.ncbi.nlm.nih.gov/pubmed/21693046
14. Brinkmann AO. Molecular basis of androgen insensitivity. Mol Cell Endocrinol 2001 Jun;179(1-2): 105-9.
http://www.ncbi.nlm.nih.gov/pubmed/11420135
15. Zitzmann M. Mechanisms of disease: pharmacogenetics of testosterone therapy in hypogonadal men. Nat Clin Pract Urol 2007 Mar;4(3):161-6.
http://www.ncbi.nlm.nih.gov/pubmed/17347661
16. Rajender S, Singh L, Thangaraj K. Phenotypic heterogeneity of mutations in androgen receptor gene. Asian J Androl 2007 Mar;9(2):147-79.
http://www.ncbi.nlm.nih.gov/pubmed/17334586
17. Canale D, Caglieresi C, Moschini C, et al. Androgen receptor polymorphism (CAG repeats) and androgenicity. Clin Endocrinol (Oxf) 2005;63(3):356-61.
http://www.ncbi.nlm.nih.gov/pubmed/16117826

4. AETIOLOGY (PRIMARY AND SECONDARY FORMS AND LATE-ONSET HYPOGONADISM)

4.1 Introduction

Hypogonadism results from testicular failure, or is due to the disruption of one or several levels of the hypothalamic-pituitary-gonadal axis (Table 3).

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

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

4.2 Male hypogonadism of hypothalamic-hypopituitary origin (secondary hypogonadism)

Central defects of the hypothalamus or pituitary cause secondary testicular failure. Identifying secondary hypogonadism is of clinical importance, as it can be a consequence of pituitary pathology (including prolactinomas) and can cause infertility, which can be restored by hormonal stimulation in most patients with secondary hypogonadism.

The most relevant forms of secondary hypogonadism are:

- *Hyperprolactinemia* (HP), caused by prolactin-secreting pituitary adenomas (prolactinomas) (microprolactinomas < 10 mm in diameter vs. macroprolactinomas) or drug-induced (by dopamine-antagonistic effects of substances such as phenothiazine, imipramine and metoclopramide); additional causes may be chronic renal failure or hypothyroidism.
- *Isolated* (formerly termed idiopathic) *hypogonadotrophic hypogonadism* (IHH).
- *Kallmann syndrome* (hypogonadotrophic hypogonadism with anosmia, genetically determined, prevalence one in 10,000 males).

These disorders are characterised by disturbed hypothalamic secretion or action of GnRH, as a pathophysiology common to the diseases, resulting in impairment of pituitary LH and FSH secretion. An additional inborn error of migration and homing of GnRH-secreting neurons results in Kallmann syndrome (1,2).

The most important differential diagnosis is the constitutional delay of puberty, as it is the most common cause of delayed puberty (pubertas tarda) with a prevalence of one in 40 in males, caused by a delayed increase in pulsatile GnRH secretion with an autosomal-dominant pattern of inheritance (3). Other rare forms of secondary hypogonadism are listed in Table 3.

4.3 Male hypogonadism of gonadal origin (primary hypogonadism)

Primary testicular failure results in low testosterone levels, impairment of spermatogenesis and elevated gonadotrophins. The most important clinical forms of primary hypogonadism are Klinefelter syndrome (one in 500 males) and testicular tumours (12 in 100,000 males).

- *Klinefelter syndrome* affects 0.2% of the male population. It is the most frequent form of male hypogonadism and the most common numerical chromosomal aberration, with 47,XXY in 90% of cases (4). It arises due to non-disjunction during paternal or maternal meiotic division of germ cells (5).
- *Testicular tumours* are the most frequent type of cancer in young males during reproductive age. Risk factors are contralateral germ cell cancer, maldescended testes, gonadal dysgenesis, infertility and familial germ cell cancer. Twenty-five per cent of patients suffer from testosterone deficiency after treatment (6-8).

Other reasons for primary testicular failure are summarised in Table 4.

4.4 Male hypogonadism due to mixed dysfunction of hypothalamus/pituitary and gonads

Combined primary and secondary testicular failure results in low testosterone levels, impairment of spermatogenesis and variable gonadotrophin levels. Gonadotrophin levels depend on the predominant primary or secondary failure. This form was named late-onset hypogonadism some years ago (9,10).

4.5 Male hypogonadism due to defects of androgen target organs

These forms are primarily rare defects and will not be further discussed in detail in these guidelines. There are AR defects with complete, partial and minimal androgen insensitivity syndrome; Reifenstein syndrome; bulbospinal muscular atrophy (Kennedy disease); as well as 5α-reductase deficiency (for a review, see Nieschlag et al. 2010) (11).

The classification of hypogonadism has therapeutic implications. In patients with secondary hypogonadism, hormonal stimulation with hCG and FSH or alternatively GnRH can restore fertility in most cases (12,13). However, fertility options for males with primary hypogonadism are limited. Detailed evaluation may for example detect pituitary tumours, systemic disease, or testicular tumours.

Combined forms of primary and secondary hypogonadism can be observed in older men, with a concomitant age-related decline in testosterone levels resulting from defects in testicular as well as hypothalamic-pituitary function. A significant percentage of men over the age of 60 years have serum testosterone levels below the lower reference limits in young adults (14-18).

Table 3: Forms of secondary hypogonadism

Disease	Causes for deficiency
Hyperprolactinemia	Prolactin-secreting pituitary adenomas (prolactinomas) or drug-induced.
Isolated hypogonadotrophic hypogonadism (IHH) (formerly termed idiopathic hypogonadotrophic hypogonadism, IHH)	GnRH deficiency.
Kallmann syndrome (hypogonadotrophic 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 from the pituitary or pituitary stalk.
Prader-Willi syndrome (PWS) (formerly Prader-Labhart-Willi syndrome) (prevalence 1 in 10,000 individuals)	Congenital disturbance of GnRH secretion.
Congenital adrenal hypoplasia with hypogonadotrophic hypogonadism (prevalence 1 in 12,500 individuals)	X-chromosomal recessive disease, in the majority of patients caused by mutations in the DAX1 gene.
Pasqualini syndrome	Isolated LH deficiency.

Table 4: Forms of primary hypogonadism

Disease	Causes of deficiency
Maldescended or ectopic testes	Failure of testicular descent, 85% idiopathic.
Orchitis	Viral or unspecific orchitis.
Acquired anorchia	Traumatic, 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.
46,XY disorders of sexual development (DSD) (formerly male pseudohermaphroditism)	Disturbed testosterone synthesis due to enzymatic defects of steroid biosynthesis (17,20-desmolase defect, 17β-hydroxsteroid dehydrogenase defect).
Gonadal dysgenesis (synonym 'streak gonads')	XY gonadal dysgenesis can be caused by mutations in different genes.
46,XX male syndrome (prevalence of 1 in 10,000-20,000)	Males with presence of genetic information from the Y chromosome after translocation of a DNA segment of the Y to the X chromosome during paternal meiosis.
47,XYY syndrome (prevalence of 1 in 2,000)	Caused by non-disjunction in paternal meiosis.
Noonan syndrome (prevalence of 1 in 1,000 to 1 in 5,000)	Genetic origin.
Inactivating LH receptor mutations, Leydig cell hypoplasia (prevalence of 1 in 1,000,000 to 1 in 20,000)	Leydig cells are unable to develop due to the mutation (19).

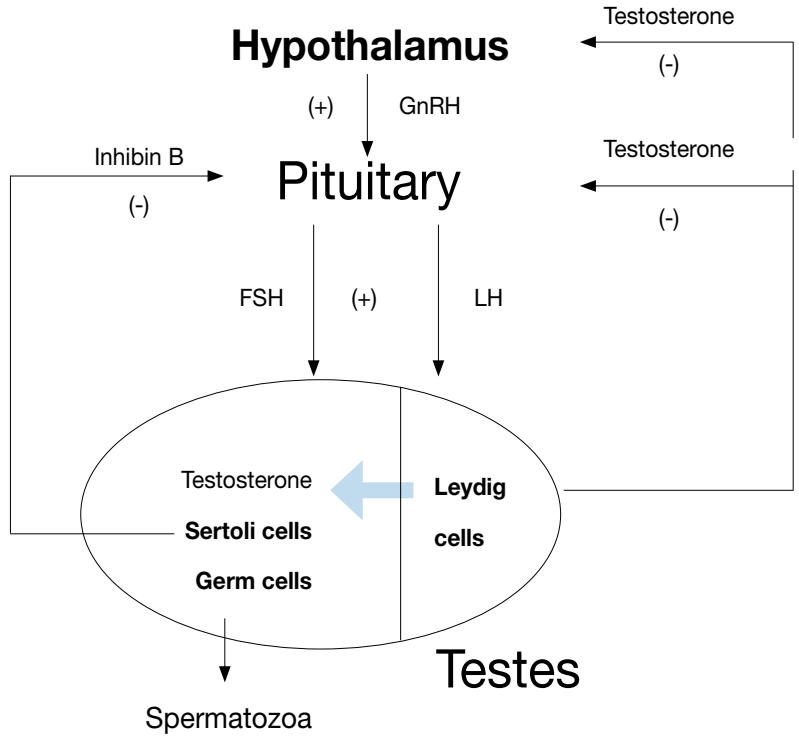
Recommendation	LE	GR
The two forms of hypogonadism have to be differentiated, as this has implications for patient evaluation and treatment and makes it possible to identify patients with associated health problems and infertility.	1b	B

4.6 References

1. Behre HM, Nieschlag E, Partsch CJ, et al. Diseases of the hypothalamus and the pituitary gland. In: Nieschlag E, Behre HM, Nieschlag S (eds). *Andrology - male reproductive health and dysfunction*. 3rd edn. Berlin: Springer, 2010:169-92.
2. Pitteloud N, Durrani S, Raivio T, et al. Complex genetics in idiopathic hypogonadotrophic hypogonadism. Front Horm Res 2010;39:142-53. http://www.ncbi.nlm.nih.gov/pubmed/20389092
3. Sedlmeyer IL, Hirschhorn JN, Palmert MR. Pedigree analysis of constitutional delay of growth and maturation: determination of familial aggregation and inheritance pattern. J Clin Endocrinol Metab 2002 Dec;87(12):5581-6. http://www.ncbi.nlm.nih.gov/pubmed/12466356
4. Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. J Clin Endocrinol Metab 2003 Feb;88(2):622-6. http://www.ncbi.nlm.nih.gov/pubmed/12574191
5. Tüttelmann F, Gromoll J. Novel genetic aspects of Klinefelter's syndrome. Mol Hum Reprod 2010 Jun;16(6):386-95. http://www.ncbi.nlm.nih.gov/pubmed/20228051
6. Nord C, Bjøro T, Ellingsen D, et al. Gonadal hormones in long-term survivors 10 years after treatment for unilateral testicular cancer. Eur Urol 2003 Sep;44(3):322-8. http://www.ncbi.nlm.nih.gov/pubmed/12932930
7. Eberhard J, Ståhl O, Cwikiel M, et al. Risk factors for post-treatment hypogonadism in testicular cancer patients. Eur J Endocrinol 2008 Apr;158(4):561-70. http://www.ncbi.nlm.nih.gov/pubmed/18362304
8. Pühse G, Secker A, Kemper S, et al. Testosterone deficiency in testicular germ-cell cancer patients is not influenced by oncological treatment. Int J Androl 2011 Oct;34(5 Pt 2):e351-7. http://www.ncbi.nlm.nih.gov/pubmed/21062302
9. Nieschlag E, Swerdloff R, Behre HM, et al.; International Society of Andrology (ISA); International Society for the Study of the Aging Male (ISSAM); European Association of Urology (EAU). Investigation, treatment and monitoring of late-onset hypogonadism in males. ISA, ISSAM, and EAU recommendations. Eur Urol 2005 Jul;48(1):1-4. http://www.ncbi.nlm.nih.gov/pubmed/15951102
10. Wang C, Nieschlag E, Swerdloff R, et al.; International Society of Andrology; International Society for the Study of Aging Male; European Association of Urology; European Academy of Andrology; American Society of Andrology. Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. Eur Urol 2009 Jan;55(1):121-30. http://www.ncbi.nlm.nih.gov/pubmed/18762364
11. Nieschlag E, Behre HM, Wieacker P, et al. Disorders at the testicular level. In: Nieschlag E, Behre HM, Nieschlag S (eds). *Andrology - male reproductive health and dysfunction*. 3rd edn. Berlin: Springer, 2010:193-238.
12. Büchter D, Behre HM, Kliesch S, et al. Pulsatile GnRH or human chorionic gonadotropin/human menopausal gonadotropin as effective treatment for men with hypogonadotrophic hypogonadism: a review of 42 cases. Eur J Endocrinol 1998 Sep;139(3):298-303. http://www.ncbi.nlm.nih.gov/pubmed/9758439
13. Sykiotis GP, Hoang XH, Avbelj M, et al. Congenital idiopathic Hypogonadotrophic hypogonadism: evidence of defects in the hypothalamus, pituitary, and testes. J Clin Endocrinol Metab 2010 Jun;95(6):3019-27. http://www.ncbi.nlm.nih.gov/pubmed/20382682
14. Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab 2007 Nov;92(11):4241-7. http://www.ncbi.nlm.nih.gov/pubmed/17698901
15. Gray A, Feldman HA, McKinlay JB, et al. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. J Clin Endocrinol Metab 1991 Nov;73(5):1016-25. http://www.ncbi.nlm.nih.gov/pubmed/1719016

16. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. J Clin Endocrinol Metab 2002 Feb;87(2):589-98.
http://www.ncbi.nlm.nih.gov/pubmed/11836290
17. Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001 Feb;86(2):724-31.
http://www.ncbi.nlm.nih.gov/pubmed/11158037
18. Wu FC, Tajar A, Pye SR, et al. Hypothalamic-pituitary-testicular axis disruptions in older man are differentially linked to age and modifiable risk factors: the European Male Aging Study. J Clin Endocrinol Metab 2008 Jul;93(7):2737-45.
http://www.ncbi.nlm.nih.gov/pubmed/18270261
19. Huhtaniemi I, Alevizaki M. Gonadotrophin resistance. Best Pract Res Clin Endocrinol Metab 2006 Dec;20(4):561-76.
http://www.ncbi.nlm.nih.gov/pubmed/17161332

Figure 2: The hypothalamic-pituitary-testes axis



FSH = follicle-stimulating hormone; GnRH = Gonadotrophin-relasing hormone; LH = luteinizing hormone.

5. DIAGNOSIS

5.1 Introduction

Hypogonadism is diagnosed on the basis of persistent signs and symptoms related to androgen deficiency and assessment of consistently low testosterone levels (at least on two occasions) with a reliable method (1-5).

5.2 Clinical symptoms

Low levels of circulating androgens may be associated with signs and symptoms (Table 5).

Table 5: Clinical symptoms and signs suggestive for androgen deficiency

Delayed puberty
Small testes
Male-factor infertility
Decreased body hair
Gynaecomastia
Decrease in lean body mass and muscle strength
Visceral obesity
Decrease in bone mineral density (osteoporosis) with low trauma fractures
Reduced sexual desire and sexual activity
Erectile dysfunction
Diminished nocturnal erections
Hot flushes
Changes in mood, fatigue and anger
Sleep disturbances
Metabolic syndrome
Insulin resistance and type 2 diabetes mellitus
Diminished cognitive function

The most prevalent symptoms of male hypogonadism in ageing men are reduced sexual desire and sexual activity, erectile dysfunction, and hot flushes (1).

Signs and symptoms of androgen deficiency vary depending on age of onset, duration and the severity of the deficiency. Reference ranges for the lower normal level of testosterone (2.5%) have recently been compiled from three large community-based samples, suggesting a cut-off of 12.1 nmol/L for total serum testosterone and for free testosterone 243 pmol/L, to distinguish between normal levels and levels possibly associated with deficiency (6). Symptoms suggesting the presence of hypogonadism (1,7) are summarised in Table 5.

In men aged 40-79 years, the threshold for total testosterone was 8 nmol/L for decreased frequency of sexual thoughts, 8.5 nmol/L for erectile dysfunction, 11 nmol/L for decreased frequency of morning erections and 13 nmol/L for diminished vigour (8). The strongest predictor for hypogonadism in this age group was three sexual symptoms (decreased sexual thoughts, weakened morning erections, erectile dysfunction) and either a total testosterone level of < 8 nmol/L or serum testosterone in the range of 8-11 nmol/L and free testosterone < 220 pmol/L. These data are based on serum samples taken in the morning, when levels are highest and most reproducible (9).

Hypogonadism may be more subtle and not always evident by low testosterone levels. For example, men with primary testicular damage often have normal testosterone levels but high LH: this could be considered a subclinical or compensated form of hypogonadism. The clinical consequences of an isolated elevation of LH is not clear yet, but potentially these men may already have signs or symptoms of hypogonadism or will become hypogonadal in the future.

To differentiate between primary and secondary forms of hypogonadism and to clarify late-onset hypogonadism determination of LH serum levels is required. Both LH and testosterone serum levels should be analysed twice.

5.3 History-taking and questionnaires

Symptoms of hypogonadism are listed in Table 5 and should be addressed during history-taking. Early onset of hypogonadism causes a lack of or minimal pubertal development, lack of development of secondary sex characteristics, possibly eunuchoid body proportions and a high-pitched voice. These signs and symptoms strongly suggest hypogonadism. Postpubertal development of hypogonadism causes a loss of androgen-dependent functions and symptoms that may have other etiological backgrounds than low testosterone levels. Published questionnaires are unreliable and have low specificity, whilst their sensitivity is high they are not effective for case-finding (10-13). It is important to assess and exclude systemic illnesses, signs of malnutrition and malabsorption, as well as ongoing acute disease. Pharmacological treatments with corticosteroids, abuse of drugs such as marihuana, opiates and alcohol and previous treatment or use of testosterone or abuse of anabolic steroids should also be included in history-taking.

5.4 Physical examination

Assessment of body mass index (BMI), the waist-hip ratio (or sagittal abdominal diameter), body hair, male-pattern hair loss, presence of gynaecomastia and testicular size (measured with an orchidometer or ultrasound [US]) and a structural examination of the penis as well as a digital rectal examination (DRE) of the prostate should be included.

Conclusion
The diagnosis of male hypogonadism is based on signs and symptoms of androgen deficiency, together with consistently low serum testosterone levels.

Recommendations	**LE**	**GR**
The diagnosis of testosterone deficiency should be restricted to men with persistent symptoms suggesting hypogonadism (Table 5) (1-7).	3	C
Total testosterone assessment should be repeated at least on two occasions with a reliable method in men with: - Total testosterone levels close to the lower normal range (8-12 nmol/L), the free testosterone level should be measured to strengthen the laboratory assessment. - Suspected or known abnormal sex hormone-binding globulin (SHBG) levels, free testosterone should also be included (6,8).	1	A
Currently available diagnostic instruments (questionnaires) are not reliable as case-finding tools (10), as they have not been validated.	3	C
Testosterone assessment is recommended in men with a disease or treatment in which testosterone deficiency is common and in whom treatment may be indicated. This includes men with: - 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. - Osteoporosis or low-trauma fractures. - HIV infection with sarcopenia. - Type 2 diabetes (14-18).	2	B
LH serum levels should be analysed to differentiate between primary, secondary, and late-onset hypogonadism.		

5.5 References

1. Hall SA, Esche GR, Araujo AB, et al. Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. J Clin Endocrinol Metab 2008 Oct;93(10):3870-7. http://www.ncbi.nlm.nih.gov/pubmed/18664536
2. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010 Jun;95(6):2536-59. http://www.ncbi.nlm.nih.gov/pubmed/20525905
3. Wang C, Catlin DH, Demers LM, et al. Measurement of total serum testosterone in adult men: comparison of current laboratory methods versus liquid chromatography-tandem mass spectrometry. J Clin Endocrinol Metab 2004 Feb;89(2):534-43. http://www.ncbi.nlm.nih.gov/pubmed/14764758
4. Rosner W, Auchus RJ, Azziz R, et al. Position statement: Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. J Clin Endocrinol Metab 2007 Feb;92(2): 405-13. http://www.ncbi.nlm.nih.gov/pubmed/17090633
5. Rosner W, Vesper H. Toward excellence in testosterone testing: a consensus statement. J Clin Endocrinol Metab 2010 Oct;95(10):4542-8. http://www.ncbi.nlm.nih.gov/pubmed/20926540

6. Bhasin S, Pencina M, Jasuja GK, et al. Reference ranges for testosterone in men generated using liquid chromatography tandem mass spectrometry in a community-based sample of healthy nonobese young men in the Framingham Heart Study and applied to three geographically distinct cohorts. J Clin Endocrinol Metab 2011 Aug;96(8):2430-9. http://www.ncbi.nlm.nih.gov/pubmed/21697255
7. Wu FC, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010 Jul 8;363(2):123-35. http://www.ncbi.nlm.nih.gov/pubmed/20554979
8. Vesper HW, Bhasin S, Wang C, et al. Interlaboratory comparison study of serum total testosterone [corrected] measurements performed by mass spectrometry methods. Steroids 2009 Jun;74(6): 498-503. http://www.ncbi.nlm.nih.gov/pubmed/19428438
9. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab 1983 Jun;56(6):1278-81. http://www.ncbi.nlm.nih.gov/pubmed/6841562
10. Morley JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism 2000 Sep:49(9):1239-42. http://www.ncbi.nlm.nih.gov/pubmed/11016912
11. Buvat, J, Lemaire A. Endocrine screening in 1,022 men with erectile dysfunction: clinical significance and cost-effective strategy. J Urol 1997 Nov;158(5):1764-7. http://www.ncbi.nlm.nih.gov/pubmed/9334596
12. Moore C, Huebler D, Zimmerman T, et al.The Aging Males' Symptoms scale (AMS) as outcome measure for treatment of androgen deficiency. Eur Urol 2004 Jul;46(1):80-7. http://www.ncbi.nlm.nih.gov/pubmed/15183551
13. Smith KW, Feldman HA, McKinlay JB. Construction and field validation of a self-administered screener for testosterone deficiency (hypogonadism) in ageing men. Clin Endocrinol (Oxf) 2000 Dec;53(6): 703-11. http://www.ncbi.nlm.nih.gov/pubmed/11155092
14. Dobs AS, Few WL 3rd, Blackman MR, et al. Serum hormones in men with human immunodeficiency virus-associated wasting. J Clin Endocrinol Metab 1996 Nov;81(11):4108-12. http://www.ncbi.nlm.nih.gov/pubmed/8923868
15. Arver S, Sinha-Hikim I, Beall G, et al. Serum dihydrotestosterone and testosterone concentrations in human immunodeficiency virus-infected men with and without weight loss. J Androl 1999 Sep-Oct;20(5):611-8. http://www.ncbi.nlm.nih.gov/pubmed/10520573
16. Reid IR. Serum testosterone levels during chronic glucocorticoid therapy. Ann Intern Med 1987 Apr;106(4):639-40. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/3826973
17. Dhindsa S, Prabhakar S, Sethi M, et al. Frequent occurrence of hypogonadotrophic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab 2004 Nov;89(11):5462-8. http://www.ncbi.nlm.nih.gov/pubmed/15531498
18. Katznelson L, Finkelstein JS, Schoenfeld DA, et al. Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. J Clin Endocrinol Metab 1996 Dec;81(12):4358-65. http://www.ncbi.nlm.nih.gov/pubmed/8954042

6. CLINICAL CONSEQUENCES OF HYPOGONADISM

6.1 Introduction

The clinical consequences of hypogonadism are determined by the age of onset and the severity of hypogonadism.

6.2 Foetal androgen deficiency

During the first 14 weeks of gestation, the presence of testosterone is crucial for normal virilisation of the external male genitalia. Androgen deficiency or androgen resistance due to deficient AR function during this

stage of life may result in abnormal genital development, ranging from hypospadias to female external genitalia with intra-abdominal testis. Frequently, patients with disorders of sexual development are diagnosed at an early age because of clearly abnormal external genitalia. However, patients at both ends of the phenotypic spectrum may go unnoticed in childhood and are diagnosed during puberty because of delayed pubertal development in phenotypic men or primary amenorrhoea in XY women.

6.3 Prepubertal onset of androgen deficiency

At the start of puberty, rising gonadotrophin levels result in increasing testicular volume and the activation of spermatogenesis and testosterone secretion. During puberty, rising testosterone levels result in the development of male secondary sex characteristics, comprising deepening of the voice, development of terminal body hair, stimulation of hair growth in sex-specific regions, facial hair, increasing penile size, increase in muscle mass and bone size and mass, growth spurt induction and eventually closing of the epiphyses. In addition, testosterone has explicit psychosexual effects, including increased libido.

Delayed puberty is defined as an absence of testicular enlargement at the age of 14. As this is a 'statistical' definition, based on reference ranges for the onset of puberty in the normal population, delayed puberty does not necessarily indicate the presence of a disease. In cases of severe androgen deficiency, the clinical picture of prepubertal-onset hypogonadism is evident (Table 6) and diagnosis and treatment are fairly straightforward. The major challenge in younger individuals with presumed idiopathic hypogonadotrophic hypogonadism is to differentiate the condition from a constitutional delay in puberty and to determine when to start androgen treatment. In milder cases of androgen deficiency, such as are seen in patients with Klinefelter syndrome, pubertal development can be incomplete or delayed, resulting in a more subtle phenotypic picture. In these patients, several clues may lead to a diagnosis of hypogonadism. These include: small testes, (a history of) cryptorchidism, gynaecomastia, sparse body hair, eunuchoid habitus, low bone mass and subfertility (1).

Table 6: Signs and symptoms suggesting prepubertal-onset hypogonadism

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

6.4 Late-onset hypogonadism

Definition: Late-onset hypogonadism is defined as hypogonadism in a person who has had normal pubertal development and as a result developed normal male secondary sex characteristics.

Depending on the underlying cause of hypogonadism, the decline in gonadal function may be gradual and partial. The resulting clinical picture may be variable, and the signs and symptoms may be obscured by the physiological phenotypic variation. Symptoms that have been associated with late-onset hypogonadism include: loss of libido, erectile dysfunction, sarcopenia, low bone mass, depressive thoughts, fatigue, loss of vigour, erectile dysfunction, loss of body hair, hot flushes and reduced fertility (Table 7). Most of these symptoms have a multifactorial aetiology, are reminiscent of normal ageing and can also be found in men with completely normal testosterone levels (2). As a result, signs and symptoms of adult-onset hypogonadism may be non-specific, and confirmation of a clinical suspicion by hormonal testing is mandatory. For most of the symptoms mentioned above, the probability of their presence increases with lower plasma testosterone levels. Most studies indicate a threshold level below which the prevalence of symptoms starts to increase (3,4). This threshold level is near the lower level of the normal range for plasma testosterone levels in young men, but there appears to be a wide variation between individuals, and even within one individual the threshold level may be different for different target organs.

Table 7: Signs and symptoms associated with late-onset hypogonadism

Loss of libido
Erectile dysfunction
Sarcopenia
Low bone mass
Depressive thoughts
Fatigue
Loss of body hair
Hot flushes
Loss of vigour

Recommendations	LE	GR
Screening of testosterone deficiency is only recommended in adult men with consistent and preferably multiple signs and symptoms listed in Table 7.	3	C
Adult men with established severe hypogonadism should be screened for concomitant osteoporosis.	2	B

6.5 References

1. Lanfranco F, Kamischke A, Zitzmann M, et al. Klinefelter's syndrome. Lancet 2004 Jul;364(9430): 273-83. http://www.ncbi.nlm.nih.gov/pubmed/15262106
2. Kaufman J, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. Endocr Rev 2005 Oct;26(6):833-76. http://www.ncbi.nlm.nih.gov/pubmed/15901667
3. Wu FC, Tajar A, Beynon M, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010 Jul;363(2):123-35. http://www.ncbi.nlm.nih.gov/pubmed/20554979
4. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab 2006 Nov;91(11):4335-43. http://www.ncbi.nlm.nih.gov/pubmed/16926258

7. INDICATIONS AND CONTRAINDICATIONS FOR TREATMENT

Testosterone treatment aims to restore testosterone levels to the physiological range in men with consistently low levels of serum testosterone and associated symptoms of androgen deficiency. The aim is to improve quality of life, sense of well-being, sexual function, muscle strength and bone mineral density. Table 8 highlights the main indications for testosterone treatment. Table 9 lists the main contraindications against testosterone therapy.

Table 8: 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 consistent and preferably multiple signs and symptoms of hypogonadism (listed in Table 7)
Hypopituitarism
Testicular dysgenesis and hypogonadism

Table 9: Contraindications against testosterone treatment

Prostate cancer
PSA > 4 ng/mL
Male breast cancer
Severe sleep apnoea
Male infertility
Haematocrit > 50%
Severe lower urinary tract symptoms due to benign prostatic hyperplasia

8. BENEFITS OF TREATMENT

Testosterone replacement therapy (TRT) provides several benefits in relation to body composition, metabolic control and psychological and sexual parameters. Randomised trials have shown a correlation between restored physiological testosterone levels, muscle mass and strength measured as leg press strength and quadriceps muscle volume (1-4). Similar positive results have been reported in meta-analyses evaluating the role of exogenous testosterone in relation to bone mineral density: it is evident that testosterone therapy improves mineral density at the lumbar spine, producing a reduction in bone resorption markers. The available trials failed to demonstrate a similar effect at the femoral neck (4-6). Body composition is influenced by testosterone therapy in hypogonadal men, with a consequent decrease in fat mass and an increase in lean body mass (4). Several studies based on experience with testosterone undecanoate have demonstrated a significant reduction in trunk and waist fat, with a clear decrease in waist size (7,8). In the same trials, testosterone undecanoate administration was associated with an improvement in body weight, body mass index and lipid profile after 3 months of therapy. Testosterone replacement therapy has positive effects on glycaemic and lipid control, insulin resistance and visceral adiposity in hypogonadal men with impaired glucose tolerance and lipid profiles, with a consequent decrease in the cardiovascular risk (9). Benefits on libido, erection and ejaculation have been reported in several retrospective studies and case reports. In a multicentre prospective study, Moon et al. (10) reported a significant increase in the International Index of Erectile Function (IIEF) score for sexual desire, intercourse satisfaction and overall satisfaction starting 6 weeks after the beginning of treatment. Testosterone replacement therapy has also shown encouraging results in several case reports in which satisfactory sexual intercourse was reported after at least 3 months from therapy induction in hypogonadal men suffering from veno-occlusive erectile dysfunction (4,11). Significant improvement in depressive symptoms in men treated with testosterone undecanoate is reported in a randomised trial, while benefits in relation to the cognitive spectrum have been reported in studies with a lower impact (12,13).

Conclusion	**LE**
Benefits including a reduction in BMI and waist size and improved glycaemic control and lipid profile are observed in hypogonadal men receiving TRT.	2a

Recommendations	LE	GR
Testosterone replacement therapy is recommended in patients with:		
A decline in muscle mass and strength	1b	A
Reduced bone mineral density at the lumbar spine	1a	A
Decreased libido and erection	3	B

8.1 References

1. Bhasin S, Woodhouse L, Casaburi R, et al. Testosterone dose-response relationships in healthy young men. Am J Physiol Endocrinol Metab 2001 Dec;281(6):E1172-81. http://www.ncbi.nlm.nih.gov/pubmed/11701431
2. Caminiti G, Volterrani M, Iellano F, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance and baroflex sensitivity in elderly patients with chronic heart failure: a double-blind, placebo-controlled, randomized study. J Am Coll Cardiol 2009 Sep;54(10):919-27. http://www.ncbi.nlm.nih.gov/pubmed/19712802
3. Storer TW, Woodhouse L, Magliano L, et al. Changes in muscle mass, muscle strength and power but not physical function are related to testosterone dose in healthy older men. J Am Geriatr Soc 2008 Nov;56(11):1991-9. http://www.ncbi.nlm.nih.gov/pubmed/18795988
4. Saad F, Aversa A, Isidori AM, et al. Onset of effects of testosterone treatment and time span until maximum effects are achieved. Eur J Endocr 2011 Nov;165(5):675-85. http://www.ncbi.nlm.nih.gov/pubmed/21753068
5. Tracz MJ, Sideras K, Bolona ER, et al. Testosterone use in men and its effects on bone health. A systematic review and meta-analysis of randomized placebo-controlled trials. J Clin Endocrinol Metab 2006 Jun;91(6):2011-6. http://www.ncbi.nlm.nih.gov/pubmed/16720668
6. Isidori AM, Giannetta E, Greco EA, et al. Effects of testosterone on body composition, body metabolism and serum lipid profile in middle-aged men: a meta-analysis. Clin Endocrinol (Oxf) 2005 Sep;63(3):280-93. http://www.ncbi.nlm.nih.gov/pubmed/16117815
7. Saad F, Gooren L, Haider A, et al. An exploratory study of the effect of 12 months administration of the novel long-acting testosterone undecanoate on measures of sexual function and the metabolic syndrome. Arch Androl 2007 Nov-Dec;53(6):353-7. http://www.ncbi.nlm.nih.gov/pubmed/18357966
8. Haider A, Gooren LJ, Padungton P, et al. Improvement of the metabolic syndrome and of non-alcoholic liver steatosis upon treatment of hypogonadal elderly men with parenteral testosterone undecanoate. Exp Clin Endocrinol Diabetes 2010 Mar;118(3):167-71. http://www.ncbi.nlm.nih.gov/pubmed/19472103
9. Kapoor D, Goodwin E, Channer KS, et al. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol 2006 Jun;154(6):899-906. http://www.ncbi.nlm.nih.gov/pubmed/16728551
10. Moon du G, Park MG, Lee SW, et al. The efficacy and safety of testosterone undecanoate (Nebido®) in testosterone deficiency syndrome in Korean: a multicenter prospective study. J Sex Med 2010 Jun;7(6):2253-60. http://www.ncbi.nlm.nih.gov/pubmed/20345732
11. Yassin AA, Saad F, Traish A. Testosterone undecanoate restores erectile function in a subset of patients with venous leakage: a series of case report. J Sex Med 2006 Jul;3(4):727-35. http://www.ncbi.nlm.nih.gov/pubmed/16839330
12. Giltay EJ, Tishova YA, Mskhalaya GJ, et al. Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in men with metabolic syndrome. J Sex Med 2010 Jul;7(7):2572-82. http://www.ncbi.nlm.nih.gov/pubmed/20524974
13. Zitzmann M, Weckesser M, Schoner O, et al. Changes in cerebral glucose metabolism and visuospatial capability in hypogonadal males under testosterone substitution therapy. Exp Clin Endocrinol Diabetes 2001;109(5):302-4. http://www.ncbi.nlm.nih.gov/pubmed/11507655

9. CHOICE OF TREATMENT

9.1 Introduction

The aim of TRT is to restore physiological testosterone levels in hypogonadal men (1). During TRT, periodic observation of the serum concentration of the hormone and its metabolites is recommended in order to alleviate treatment-related side effects (1). Several preparations are available, which differ in the route of administration and pharmacokinetics, and the selection should be a joint decision by both the patient and the physician (2). Short-acting preparations may be preferred to long-acting depot administration in the initial treatment phase, so that any adverse events that may develop can be observed and treatment can be discontinued if needed (3).

Testosterone replacement therapy is safe and effective and the agents are available as oral preparations, intramuscular injections and transdermal gel or patches (4).

9.2 Preparations

*9.2.1 **Testosterone undecanoate***

Testosterone undecanoate is the most widely used and safest oral delivery system. It rarely causes a rise in testosterone levels above the mid-range and it is therefore infrequently associated with side effects (1). In oral administration, resorption depends on simultaneous intake of fatty food.

Testosterone undecanoate is also available as a long-acting intramuscular injection (with intervals of up to 3 months). This long period of action ensures a normal testosterone serum concentration for the entire period, but the relatively long wash-out period may cause problems if complications appear (5).

*9.2.2 **Testosterone cypionate and enanthate***

Testosterone cypionate and enanthate are available as short-acting intramuscular delivery systems (with intervals of 2-3 weeks) and represent safe and valid preparations. However, these preparations may cause fluctuations in serum testosterone from high levels to subnormal levels, and they are consequently associated with periods of well-being alternating with periods of unsatisfactory clinical response (6,7).

*9.2.3 **Transdermal testosterone***

Transdermal testosterone preparations are available as skin patches or gel. They provide a uniform and normal serum testosterone level for 24 hours (daily interval). Common side effects consist of skin irritation at the site of application (patches) and risk of interpersonal transfer if appropriate precautions are not taken (gel) (8,9).

*9.2.4 **Sublingual and buccal testosterone***

Sublingual and buccal testosterone tablets are effective and well-tolerated delivery systems that can provide a rapid and uniform achievement of a physiological testosterone level with daily administration (10,11).

*9.2.5 **Subdermal depots***

Subdermal depots need to be implanted every 5-7 months and offer a long period of action without significant serum fluctuation of the testosterone level. The risk with this kind of delivery system lies in infections and extrusions, which may occur in up to 10% of cases (1,12,13).

9.3 Hypogonadism and fertility issues

Exogenous testosterone reduces endogenous testosterone production by negative feedback on the hypothalamic-pituitary-gonadal axis. If hypogonadism coincides with fertility issues, hCG treatment should be considered.

Human chorionic gonadotrophin (hCG) stimulates testosterone production of Leydig cells. Its administration should be restricted to patients with secondary hypogonadism, if fertility issues are important. Normal physiological serum levels can be achieved with a standard dosage of 1500-5000 IU administered intramuscularly or subcutaneously twice weekly. In patients with secondary hypogonadism, hCG treatment is combined with FSH treatment (usually 150 IU three times weekly i.m. or s.c.) to induce spermatogenesis.

In patients with secondary hypogonadism and fertility issues, and in selected cases of primary hypogonadism, hCG treatment can be chosen to support endogenous testosterone production for the period of infertility treatment. The dosage has to be adjusted individually to prevent suppression of FSH serum levels. Human chorionic gonadotrophin treatment has higher costs than testosterone treatment. There is insufficient information about the therapeutic and adverse effects of long-term hCG treatment. This type of treatment can therefore not be recommended for male hypogonadism, except in patients in whom fertility treatment is an issue.

Table 10: Testosterone preparations for replacement therapy

Formulation	Administration	Advantages	Disadvantages
Testosterone undecanoate	Oral; 2-6 cps every 6 h	Absorbed through the lymphatic system, with consequent reduction of liver involvement.	Variable levels of testosterone above and below the mid-range (1). Need for several doses per day with intake of fatty food.
Testosterone cypionate	Intramuscular; one injection every 2-3 weeks	Short-acting preparation that allows drug withdrawal in case of onset of side effects.	Possible fluctuation of testosterone levels (5,6).
Testosterone enanthate	Intramuscular; one injection every 2-3 weeks	Short-acting preparation that allows drug withdrawal in case of onset of side effects.	Possible fluctuation of testosterone levels (5,6).
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 (7).
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 (8,9).
Sublingual testosterone	Sublingual; daily doses	Rapid absorption and achievement of physiological serum level of testosterone.	Local irritation (10,11).
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 (10,11).
Subdermal depots	Subdermal implant every 5-7 months	Long duration and constant serum testosterone level.	Risk of infection and extrusion of the implants (1,12,13).

Recommendations	LE	GR
The patient should be fully informed about expected benefits and side effects of each treatment option. The selection of the preparation should be a joint decision by an informed patient and the physician.	1a	A
Short-acting preparations may be preferred to long-acting depot administration when starting the initial treatment.	3	B
hCG treatment can only be recommended for hypogonadal patients with simultaneous fertility treatment.	1b	B

9.4 References

1. Bassil N, Alkaade S, Morley JE. The benefits and risks of testosterone replacement therapy: a review. Ther Clin Risk Manag 2009 Jun;5(3):427-48. http://www.ncbi.nlm.nih.gov/pubmed/19707253
2. Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A BiolSci Med Sci 2005 Nov;60(11):1451-7. http://www.ncbi.nlm.nih.gov/pubmed/16339333

3. Parsons JK, Carter HB, Platz EA, et al. Serum testosterone and the risk of prostate cancer: potential implications for testosterone therapy. Cancer Epidemiol Biomarkers Prev 2005 Sep;14(9):2257-60. http://www.ncbi.nlm.nih.gov/pubmed/16172240
4. Zitzman M, Nieschlag E. Androgen receptor gene CAG repeat length and body mass index modulate the safety of long-term intramuscolar testosterone undecanoate therapy in hypogonodal men. J Clin Endocrinol Metab 2007 Oct;92(10):3844-53. http://www.ncbi.nlm.nih.gov/pubmed/17635942
5. Wang C, Harnett M, Dobs A, et al. Pharmacokinetics and safety of long acting testosterone undecanoate injections in hypogonadal men: An 84-week phase III clinical trial. J Androl 2010 Sep-Oct;31(5):457-65. http://www.ncbi.nlm.nih.gov/pubmed/20133964
6. Bashin S, Bremner WJ. Emerging issues in androgen replacement therapy. J Clin Endocrinol Metab 1997 Jan;82(1):3-8. http://www.ncbi.nlm.nih.gov/pubmed/8989221
7. Comhaire FH. Andropause: hormone replacement therapy in the aging male. Eur Urol 2000 Dec;38(6):655-62. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/11111180
8. Lakshaman KM, Bassaria S. Safety and efficacy of testosterone gel in the treatment of male hypogonadism. Clin Interv Aging 2009;4:397-412. http://www.ncbi.nlm.nih.gov/pubmed/19966909
9. Swerdloff RS, Wang C. Transdermal androgens: pharmacology and applicability to hypogonadal elderly men. J Endocrinol Invest 2005;28(3 Suppl):112-6. http://www.ncbi.nlm.nih.gov/pubmed/16042369
10. Salhenian B, Wang C, Alexander G, et al. Pharmacokinetics, bioefficacy and safety of sublingual testosterone cyclodextrin in hypogonadal men: comparison to testosterone enanthate - a clinical research center study. J Clin Endocrinol Metab 1995 Dec;80(12):3567-75. http://www.ncbi.nlm.nih.gov/pubmed/8530600
11. Wang C, Swerdloff R, Kipnes M, et al. New testosterone buccal system (Striant) delivers physiological testosterone levels: pharmacokinetics study in hypogonadal men. J Clin Endocrinol Metab 2004 Aug;89(8):3821-9. http://www.ncbi.nlm.nih.gov/pubmed/15292312
12. Jockenhovel F, Vogel E, Kreutzer M, et al. Pharmacokinetics and pharmacodynamics of subcutaneous testosterone implants in hypogonadal men. Clin Endocrinol 1996 Jul;45(1):61-71. http://www.ncbi.nlm.nih.gov/pubmed/8796140
13. Kelleher S, Conway AJ, Handelsman DJ. Influence of implantation site and track geometry on the extrusion rate and pharmacology of testosterone implants. Clin Endocrinol (Oxf) 2001 Oct;55(4):531-6. http://www.ncbi.nlm.nih.gov/pubmed/11678837

10. RISK FACTORS IN TESTOSTERONE TREATMENT

10.1 Introduction

Physicians are often reluctant to offer TRT, especially in elderly men, due to the potential risk of this form of treatment (1). The most common doubts are associated with the possible consequences for prostatic and breast tissues, the cardiovascular system and sleep apnoea.

10.2 Male breast cancer

Male breast cancer is a rare disease, with an incidence of less than 1% of all male cancers (2). The incidence is higher in men with Klinefelter syndrome. Testosterone treatment is contraindicated in men with a history of breast cancer (3). An association between TRT and the development of breast cancer is not supported by strong evidence, although there have been some reports based on a small number of patients (4).

10.3 Prostate cancer

Prostate cancer growth may be influenced by testosterone. Studies have reported that hypogonadism is associated with a lower incidence of prostate cancer, but if prostate cancer occurs in hypogonadal men, it is usually at an advanced stage and with a higher Gleason score (5,6). Randomised controlled trials support

the hypothesis that TRT does not result in changes in prostatic histology, nor in a significant increase in intraprostatic testosterone and DHT (7,8). The most recent studies indicate that testosterone therapy does not increase the risk of prostate cancer (7-10), but long-term follow-up data are not yet available. A meta-analysis showed a higher (but not statistically significant) percentage of prostate events in middle-aged and older men receiving TRT (11). In view of these observations, PSA testing and digital examination of the prostate before and during therapy are highly recommended (11).

Testosterone therapy is clearly contraindicated in men with prostate cancer. A topic currently under debate involves the use of TRT in hypogonadal men with a history of prostate cancer and no evidence of active disease. So far, only studies with limited numbers of patients and relatively short follow-up periods are available, and these indicate no increased risk for recurrent prostate cancer. No randomised and placebo-controlled trials are available yet to document the long-term safety of the treatment in these patients (12). 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) and showing symptoms of testosterone deficiency can be cautiously considered for TRT, although this approach is still an 'off-label' treatment (13,14). In these patients, treatment should be restricted to patients with a low risk for recurrent prostate cancer (pre-surgery Gleason < 8; pT1-2; PSA < 10 ng/mL). Therapy should not start before 1 year of follow-up after surgery and there should be no PSA recurrence (13-15). Patients who have undergone brachytherapy or external-beam radiotherapy (EBRT) for low-risk prostate cancer can also be cautiously treated with TRT in case of hypogonadism, with close monitoring for prostate cancer recurrence (14-16).

10.4 Cardiovascular diseases

Testosterone treatment is not related to the development of de novo cardiovascular events (17,18). Caution, however, should be used in men with existing cardiovascular diseases, since an increase in red blood cells is a common side effect of testosterone. Haemoglobin and haematocrit measurements are recommended before treatment and periodically thereafter (9,11,19). Patients with erythrocytosis and serious congestive heart failure (NYHA classes III-IV) are at risk of developing cardiovascular deterioration, and testosterone therapy should be discontinued until the resolution of congestive heart failure (9). Cardiovascular adverse events are more frequent in patients with multiple co-morbidities and with limited physical activity (19).

10.5 Obstructive sleep apnoea

There is no consistent evidence correlating TRT with obstructive sleep apnoea (OSA). There is also no evidence that TRT can result in the onset or worsening of the condition (20).

Conclusions	LE
Case reports and small cohort studies point to a possible correlation between TRT and the onset of breast cancer, but there is as yet a lack of strong evidence for this relationship.	3
Randomised controlled trials support the hypothesis that TRT does not result in changes in prostatic histology.	1b
Testosterone therapy is not related to the development of de novo cardiovascular events.	1a
There is no evidence for a relationship between TRT and OSA.	3

Recommendations	LE	GR
Haematological, cardiovascular, breast and prostatic assessment should be performed before the start of treatment.	1a	A
Haematocrit and haemoglobin monitoring, PSA and digital rectal examination of prostate and breast examination are recommended assessments during TRT therapy.	1a	A
In patients operated on for localised prostate cancer, testosterone therapy should not start before 1 year of follow-up without PSA recurrence has been completed.	4	B

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

10.6 References

1. Raynaud JP. Testosterone deficiency syndrome: Treatment and cancer risk. J Steroid Biochem Mol Biol 2009 Jan;114(1-2):96-105. http://www.ncbi.nlm.nih.gov/pubmed/19429438
2. JohansenTaber KA, Morisy LR, Osbahr AJ 3rd, et al. Male breast cancer: risk factors, diagnosis, and management (review). Oncol Rep 2010 Nov;24(5):1115-20. http://www.ncbi.nlm.nih.gov/pubmed/20878100

3. Wang C, Nieschlag E, Swerdloff R, et al. Investigation, Treatment, and Monitoring of Late-Onset Hypogonadism in Males: ISA, ISSAM, EAU, EAA, and ASA Recommendations. Eur Urol 2009 Jan;55(1):121-30.
http://www.ncbi.nlm.nih.gov/pubmed/18762364
4. Medras M, Filus A, Jozkow P, et al. Breast cancer and long term hormonal treatment of male Hypogonadism. Breast Cancer Res Treat 2006 Apr;96(3):263-5.
http://www.ncbi.nlm.nih.gov/pubmed/16418796
5. Stattin P, Lumme S, Tenkanen L, et al. High levels of circulating testosterone are not associated with increased prostate cancer risk; a pooled prospective study. Int J Cancer 2004 Jan;108(3):418-24.
http://www.ncbi.nlm.nih.gov/pubmed/14648709
6. Severi G, Morris HA, MacInnis RJ, et al. Circulating steroid hormones and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2006 Jan;15(1):86-91.
http://www.ncbi.nlm.nih.gov/pubmed/16434592
7. Shabsigh R, Crawford ED, Nehra A, et al. Testosterone therapy in hypogonadal men and potential prostate cancer risk: a systematic review. Int J Impot Res 2009 Jan-Feb;21(1):9-23.
http://www.ncbi.nlm.nih.gov/pubmed/18633357
8. Marks LS, Mazer NA, Mostaghel E, et al. Effect of testosterone replacement therapy on prostate tissue in men with late onset hypogonadism: a randomized controlled trial. JAMA 2006 Nov 15;296(19): 2351-61.
http://www.ncbi.nlm.nih.gov/pubmed/17105798
9. Cooper CS, Perry PJ, Sparks AE, et al. Effect of exogenous testosterone on prostate volume, serum and semen prostate specific antigen levels in healthy young men. J Urol 1998 Feb;159(2):441-3.
http://www.ncbi.nlm.nih.gov/pubmed/9649259
10. Fernández-Balsells MM, Murad MH, Lane M, et al. Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2010 Jun;95(6):2560-75.
http://www.ncbi.nlm.nih.gov/pubmed/20525906
11. Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A BiolSci Med Sci 2005 Nov;60(11):1451-7.
http://www.ncbi.nlm.nih.gov/pubmed/16339333
12. Bassil N, Alkaade S, Morley JE. The benefits and risks of testosterone replacement therapy: a review. Ther Clin Risk Manag 2009 Jun;5(3):427-48.
http://www.ncbi.nlm.nih.gov/pubmed/19707253
13. Morgentaler A, Morales A. Should hypogonadal men with prostate cancer receive testosterone? J Urol 2010 Oct;184(4):1257-60. [No abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/20723918
14. Morgentaler A. Testosterone therapy in men with prostate cancer: scientific and ethical considerations. J Urol 2009 March;181(3):972-9.
http://www.ncbi.nlm.nih.gov/pubmed/19150547
15. Kaufman JM, Graydon RJ. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. J Urol 2004 Sept;172(3):920-2.
http://www.ncbi.nlm.nih.gov/pubmed/15310998
16. Sarodsy MF. Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachitherapy. Cancer 2007 Feb;109(3):536-41.
http://www.ncbi.nlm.nih.gov/pubmed/17183557
17. Haddad RM, Kennedy CC, Caples SM, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc 2007 Jan;82(1):29-39.
http://www.ncbi.nlm.nih.gov/pubmed/17285783
18. Shabsigh R, Katz M, Yan G, et al. Cardiovascular issues in hypogonadism and testosterone therapy. Am J Cardiol 2005 Dec;96(12B):67M-72M.
http://www.ncbi.nlm.nih.gov/pubmed/16387571
19. Basaria S, Coviello AD, Travison TG, et al. Adverse event associated with testosterone administration. New Engl J Med 2010 Jul;363(2):109-22.
http://www.ncbi.nlm.nih.gov/pubmed/20592293
20. Hanafy HM. Testosterone therapy and obstructive sleep apnea: is there a real connection? J Sex Med 2007 Sep;4(5):1241-6.
http://www.ncbi.nlm.nih.gov/pubmed/17645445

11. MONITORING OF PATIENTS RECEIVING TESTOSTERONE REPLACEMENT THERAPY

11.1 Introduction

Regular follow-up is needed in patients receiving testosterone therapy, as potentially androgen-dependent symptoms and conditions may occur as a result of TRT. The side effects of TRT are limited, but their incidence and clinical relevance is as yet unclear.

The primary aim of TRT is to alleviate the clinical symptoms of testosterone deficiency. Careful monitoring of changes in the clinical manifestations of testosterone deficiency should therefore be an essential part of every follow-up visit. Effects of TRT on sexual interest may already appear after 3 weeks of treatment, and reach a plateau at 6 weeks (1). Changes in erectile function and ejaculation may require up to 6 months (1). Effects on quality of life, and also on depressive mood, may become detectable within 1 month, but the maximum effect may take longer (1).

11.2 Testosterone level

There are as yet insufficient data to define optimal serum levels of testosterone during TRT. Expert opinion suggests that TRT should restore the serum testosterone level to the mid-normal range of specific age groups of men, which is usually sufficient to alleviate various manifestations of hormone deficiency. An optimal monitoring schedule for serum testosterone level is also dependent on the formulation of TRT used (LE: 4; GR: C).

11.3 Bone density

Bone mineral density (BMD) should be monitored only in men whose BMD was abnormal before initiation of TRT. An increase in lumbar spine BMD may already be detectable after 6 months of TRT and may continue for 3 more years (1).

11.4 Haematocrit

It is important to use only minimal or no venous occlusion when taking a blood sample for haematocrit measurements (2). Elevated haematocrit is the most frequent side effect of TRT. The clinical significance of a high haematocrit level is unclear, but it may be associated with hyperviscosity and thrombosis (3). The effect of erythropoiesis may become evident at 3 months and peaks at 12 months (1).

11.5 Prostate safety

Testosterone replacement therapy results in a marginal increase in PSA and prostate volume, plateauing at 12 months (1). Previous fears that TRT might increase the risk of prostate cancer have been contradicted by a number of meta-analyses (4-7). However, there are insufficient long-term data available to conclude that there is safety from prostate cancer with TRT.

11.6 Cardiovascular system

Testosterone replacement therapy is not associated with the development of any unsafe cardiovascular events, and special monitoring in this respect is not needed (7,8). There has been one study (9) indicating that testosterone therapy in older men with a high prevalence of chronic diseases may result in a higher risk of cardiovascular adverse events. These patients may need individualised monitoring schemes.

Recommendations	LE	GR
The response to treatment should be assessed 3, 6 and 12 months after the onset of treatment, and thereafter annually.	4	C
In men with an abnormal BMD, BMD measurements should be repeated 6 and 12 months after the start of TRT and thereafter annually.	4	C
Haematocrit should be monitored at 3, 6 and 12 months and thereafter annually. The testosterone dosage should be decreased, or therapy discontinued if the haematocrit increases above normal levels.	4	C
Prostate health should be assessed by digital rectal examination and PSA before the start of TRT. Follow-up by PSA at 3, 6 and 12 months and thereafter annually.	4	C
Routine screening of potential cardiovascular side effects is not indicated in men receiving TRT.	1b	A
Men with cardiovascular co-morbidity should be assessed by a cardiologist before TRT is initiated and there should be close cardiovascular monitoring during TRT.	3	C

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

11.7 References

1. Saad F, Aversa A, Isidori AM, et al. Onset of effects of testosterone treatment and time span until maximum effects are achieved. Eur J Endocrinol 2011 Nov;165(5):675-85. http://www.ncbi.nlm.nih.gov/pubmed/21753068
2. McMullin MF, Bareford D, Campbell P; General Haematology Task Force of the British Committee for Standards in Haematology. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. Br J Haematol 2005 Jul;130(2):174-95. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/16029446
3. Palacios A, Campfield LA, McClure RD, et al. Effect of testosterone enanthate on hematopoiesis in normal men. Fertil Steril1983 Jul;40(1):100-4. http://www.ncbi.nlm.nih.gov/pubmed/6862037
4. Shabsigh R, Crawford ED, Nehra A, et al. Testosterone therapy in hypogonadal men and potential prostate cancer risk: a systematic review. Int J Impot Res 2009 Jan;21(1):9-23. http://www.ncbi.nlm.nih.gov/pubmed/18633357
5. Marks LS, Mazer NA, Mostaghel E, et al. Effect of testosterone replacement therapy on prostate tissue in men with late onset hypogonadsim: a randomized controlled trial. JAMA 2006 Nov;296(19):2351-61. http://www.ncbi.nlm.nih.gov/pubmed/17105798
6. Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A BiolSci Med Sci 2005 Nov;60(11):1451-7. http://www.ncbi.nlm.nih.gov/pubmed/16339333
7. Fernández-Balsells MM, Murad MH, Lane M, et al. Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab Jun 2010;95(6):2560-75. http://www.ncbi.nlm.nih.gov/pubmed/20525906
8. Haddad RM, Kennedy CC, Caples SM, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc 2007 Jan;82(1):29-39. http://www.ncbi.nlm.nih.gov/pubmed/17285783
9. Basaria S, Coviello AD, Travison TG, et al. Adverse event associated with testosterone administration. New Engl J Med 2010 Jul;363(2):109-22. http://www.ncbi.nlm.nih.gov/pubmed/20592293

12. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

AMH	Anti-Müllerian hormone
AR	Androgen receptor
BMD	Bone mineral density
BMI	Body mass index
CAG	Cytosine-adenine-guanine
DHT	Dihydrotestosterone
DRE	Digital rectal examination
DSD	Disorders of sexual development
EAU	European Association of Urology
EBRT	External-beam radiation therapy
FSH	Follicle-stimulating hormone
GnRH	Gonadotrophin-releasing hormone
GR	Grade of recommendation
hCG	Human chorionic gonadotrophin
HIV	Human immunodeficiency virus
HP	Hyperprolactinemia
IHH	Isolated hypogonadotrophic hypogonadism
IIEF	International Index of Erectile Function
IU	International unit
LE	Level of evidence
LH	Luteinizing hormone
NYHA	New York Heart Association
OSA	Obstructive sleep apnoea
PSA	Prostate-specific antigen
PWS	Prader-Willi syndrome
RCT	Randomised controlled trial
SHBG	Sex hormone-binding globulin
SRY	Sex region of the Y chromosome
TRT	Testosterone replacement therapy

Conflict of interest statement

All members of the Male Hypogonadism Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.