EAU Guidelines on Male Hypogonadism

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European Association of Urology

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1.   INTRODUCTION

1.1   Aim
Androgens play a crucial role in the development and maintenance of male reproductive and sexual functions, body composition, erythropoiesis, muscle and bone health, and cognitive functions. Low levels of circulating androgens *in utero* can cause disturbances in male sexual development, resulting in congenital abnormalities of the male reproductive tract, such as testicular dysfunction, testicular maldescensus and hypospadias. Later in life, this may result in reduced male fertility, sexual dysfunction, decreased muscle formation and bone mineralisation, disturbances of fat metabolism and cognitive dysfunction and may contribute to the development of testicular tumours. Testosterone levels decrease slightly as a process of ageing; risks factors for developing adult onset hypogonadism are: obesity, chronic diseases and a poor general health. Symptomatic hypogonadal patients may benefit from testosterone treatment. This document presents the European Association of Urology (EAU) Guidelines on the diagnosis and treatment of male hypogonadism, with the aim to provide practical recommendations on how to deal with primary and secondary forms of hypogonadism, ageing-related decline in testosterone in men, as well as the treatment of testosterone deficiencies.

It must be emphasised that clinical guidelines present the best evidence available to the experts. However following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2   Publication history
These Guidelines are a series of revisions of the first edition of the EAU Guidelines on Male Hypogonadism published in 2012 [1].

1.3   Available Publications
A quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the Male Hypogonadism Guidelines. These are abridged versions which may require consultation together with the full text versions. All available material can be viewed for personal use at the EAU website. The EAU website also includes a selection of EAU guidelines articles as well as translations produced by national urological associations: http://www.uroweb.org/guidelines/online-guidelines/.

1.4   Panel composition
The EAU Male Hypogonadism Panel consists of a multidisciplinary group of experts, including urologists specialising in andrology, and endocrinologists.

2.   METHODS

2.1   Introduction
For the 2018 edition of the EAU Guidelines, the Guidelines Office have transitioned to a modified GRADE methodology across all 20 guidelines [2, 3]. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:

1.   the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [4];
2.   the magnitude of the effect (individual or combined effects);
3.   the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4.   the balance between desirable and undesirable outcomes;
5.   the impact of patient values and preferences on the intervention;
6.   the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [5]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be made available online. Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

The recommendations provided in these guidelines are based on a systematic literature search and review performed by the panel members in 2016. For the 2018 update, a scoping search was performed, covering all areas of the guideline and the search terms 'hypogonadism', 'eugonadal or hypogonadism or hypogonadal or gonadal', and 'low or lower testosterone', starting from April 2016 with a cut-off date of July 2017. Embase, Medline and the Cochrane Central Register of Controlled Trials databases were searched, with a limitation to reviews or meta-analysis of randomised controlled trials (RCTs). A total of 542 unique records were identified, retrieved and screened for relevance. A detail search strategy is available online: http://www.uroweb.org/guideline/male-hypogonadism/.

2.2 Review
This document was subject to peer review prior to publication in 2015.

2.3 Future goals
The results of ongoing and new systematic reviews will be included in the 2019 update of the Male Hypogonadism Guidelines. Ongoing systematic reviews are:
• What are the risks of major cardiovascular events from testosterone replacement therapy (TRT)? [6].
• What are the benefits and harms of testosterone treatment for male sexual dysfunction? 7].

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology
Definition: male hypogonadism is a clinical syndrome caused by androgen deficiency which may adversely affect multiple organ functions and quality of life (QoL) [8]. A diagnosis of male hypogonadism must comprise both persistent clinical symptoms and biochemical evidence of testosterone deficiency [9].

Androgen deficiency increases slightly with age also in healthy men [10, 11]. In middle-aged men, the incidence of biochemical hypogonadism varies from 2.1-12.8% [12]. The incidence of low testosterone and symptoms of hypogonadism in men aged 40-79 varies form 2.1-5.7% [11, 12]. Hypogonadism is more prevalent in older men, in men with obesity, those with comorbidities, and in men with poor health status.

3.1.1 Role of testosterone for male reproductive health
Androgens, which are produced by the testis and by the adrenal glands, play a pivotal role in male reproductive and sexual function. Androgens are 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 [13].

3.2 Physiology
Male sexual development starts between the seventh and twelfth week of gestation. The undifferentiated gonads develop into a foetal testis through expression of multiple genes, including the sex-determining region of the Y chromosome (SRY gene complex) and the SOX genes [14]. The foetal testis produces three hormones: testosterone, insulin-like peptide 3 (INSL3) and anti-Müllerian hormone (AMH). Testosterone is needed for the stabilisation of the Wolffian ducts, resulting in formation of the epididymis, vas deferens and seminal vesicle. Anti-Müllerian hormone activity results in regression of the Müllerian ducts (Figure 1). Insulin-like peptide 3, AMH and testosterone regulate testicular descent.

Under the influence of intratesticular testosterone, the number of gonocytes per tubule increases threefold during the foetal period [15]. 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 5α-dihydrotestosterone (DHT) by the enzyme 5α-reductase. Testosterone and DHT are required for penile growth, both activating the androgen receptor [16].

During puberty, intratesticular testosterone is needed to initiate and then maintain the spermatogenic process and to inhibit germ cell apoptosis [17]. The seminiferous tubules of the testes are exposed to concentrations of testosterone 25-100 times greater than circulating levels. Suppression of gonadotropins (e.g. through excessive testosterone abuse) results in a reduced number of spermatozoa in the ejaculate and hypospermatogenesis [18]. Complete inhibition of intratesticular testosterone results in full cessation of meiosis up to the level of round spermatids [19, 20].

Testosterone does not appear to act directly on the germ cells, but functions through the Sertoli cells by expression of the androgen receptor (AR) and by influencing the seminiferous tubular microenvironment [19]. Testosterone can also be metabolised into oestradiol by aromatase, present in fat tissue, the prostate, the testes and bone. Oestradiol is also essential for bone mineralisation in men [21]. The production of testosterone is controlled in the foetus by placental chorion gonadotropin (hCG) and after birth by luteinising hormone (LH) from the pituitary gland. Immediately after birth, serum testosterone levels reach adult concentrations over several months (mini puberty). Thereafter and until puberty, testosterone levels are low, thus preventing male virilisation. Puberty starts with the production of gonadotropins, initiated by gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus and results in testosterone production, male sexual characteristics and spermatogenesis [22]. Figure 1 shows the development of the male reproductive system.

3.2.1 *The androgen receptor*
Testosterone exerts its action through the AR, located in the cytoplasm and nucleus of target cells. During the foetal period, testosterone increases the number of ARs by increasing the number of cells with the AR and by increasing the number of ARs in each individual cell [16, 21]. 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 (i.e. disorder of sexual development (DSD)). Less severe mutations in the AR gene may cause mild forms of androgen resistance and male infertility [23]. 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 [23]. Shorter repeats have been associated with an increased risk for prostate disease, and longer repeats with reduced androgen action in several tissues [24]. Cytosine-adenine-guanine repeat number may influence androgenic phenotypical effects, even in case of normal testosterone levels [25].

Summary of evidence
Testosterone is essential for normal male development.

Figure 1: Development of the male reproductive system
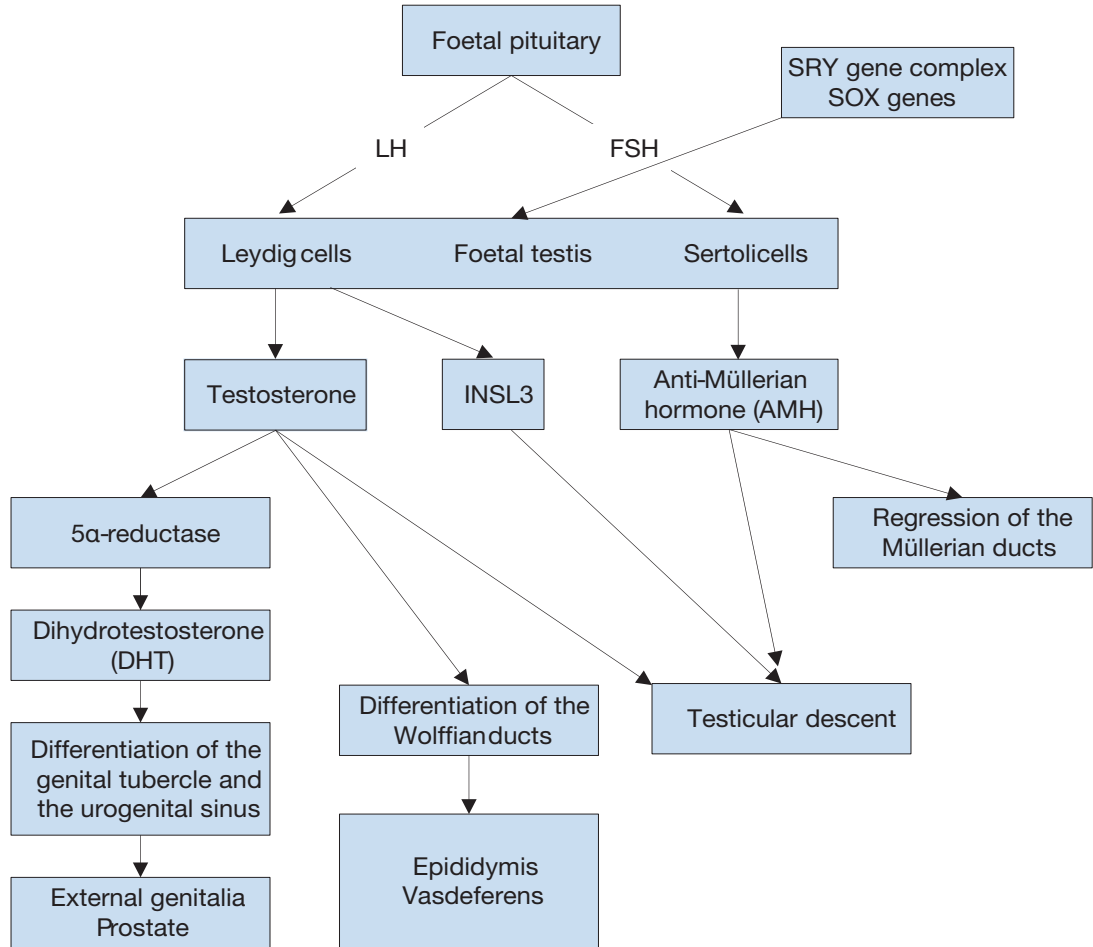
FSH = follicle-stimulating hormone; LH = luteinising hormone; SRY = sex determining region of the Y chromosome; INSL3= insulin-like peptide 3.

3.3 Aetiology

Hypogonadism results from testicular failure, or is due to the disruption of one or several levels of the hypothalamic-pituitary-gonadal axis (Figure 2).

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 (common in adult-onset hypogonadism);
* androgen target organs (androgen insensitivity/resistance).

3.4 Classification

3.4.1 Male hypogonadism of testicular origin (primary hypogonadism)

Primary testicular failure is the most frequent cause of hypogonadism and results in low testosterone levels, impairment of spermatogenesis and elevated gonadotropins (high LH and FSH). Male infertility is accompanied by hypogonadism in up to 32% of patients and and is an associated risk factor for hypogonadism, depending on the severity of the underlying causes [26, 27]. The most common clinical forms of primary hypogonadism are Klinefelter syndrome and testicular tumours.

* 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 [28]. It arises due to non-disjunction during paternal or maternal meiotic division of germ cells [29].
* Testicular germ cell tumours are the most frequent type of cancer in young males after puberty. Risk factors are contralateral germ cell cancer, maldescended testes, gonadal dysgenesis, infertility, testicular atrophy and familial germ cell cancer. Twenty-five per cent of men with testicular tumours develop testosterone deficiency after treatment [30-32].

The main reasons for primary hypogonadism are summarised in Table 1.

3.4.2 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. Fertility 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 dopamineantagonistic effects of substances such as phenothiazine, imipramine, risperidone and metoclopramide); additional causes may be chronic renal failure or hypothyroidism. Testosterone levels may, however, be normal despite the presence of a prolactinoma [33].
- *Isolated* (formerly termed idiopathic) or congenital hypogonadotrophic hypogonadism (IHH, CHH).
- *Kallmann's syndrome* (hypogonadotrophic hypogonadism with anosmia, genetically determined, prevalence one in 10,000 males).

These disorders are characterised by disturbed hypothalamic secretion (low levels of gonadatropin-releasing hormone, followed by low levels of the gonadotropins LH and FSH). An inborn error of migration and homing of GnRH-secreting neurons results in Kallmann's syndrome [34, 35]. The most important symptom is the constitutional delay of puberty: it is the most common cause of delayed puberty (pubertas tarda) [36]. Other rare forms of secondary hypogonadism are listed in Table 2.

3.4.3 Male hypogonadism due to mixed dysfunction of hypothalamus/pituitary and gonads (Adult-onset hypogonadism)

Combined primary and secondary testicular failure results in low testosterone levels and variable gonadotropin levels. Gonadotropin levels depend predominantly on primary or secondary failure. What has also been labelled as late-onset hypogonadism and age-related hypogonadism is comprised of these two types of hypogonadism [37-39].

3.4.4 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) [40].

The classification of hypogonadism has therapeutic implications. In patients with secondary hypogonadism, hormonal stimulation with hCG and FSH or alternatively pulsatile GnRH treatment can restore fertility in most cases [41, 42]. Detailed evaluation may, for example, detect pituitary tumours, systemic disease, or testicular tumours (see table 2). Combined forms of primary and secondary hypogonadism can be observed in ageing, mostly obese men, with a concomitant age-related decline in testosterone levels resulting from defects in testicular as well as hypothalamic-pituitary function.

Table 1: Forms of primary hypogonadism

Disease	Causes of deficiency
Maldescended or ectopic testes	Failure of testicular descent, maldevelopment of the testis [43]
Klinefelter syndrome 47,XXY	Sex-chromosomal non-disjunction in germ cells
Germ Cell Tumour	Testicular maldevelopment
Orchitis	Viral or unspecific orchitis
Acquired anorchia	Trauma, tumour, torsion, inflammation, iatrogenic, surgical removal
Secondary testicular dysfunction	Medication, drugs, toxins, systemic diseases, varicocele
(Idiopathic) testicular atrophy/testicular dysgenesis	Male infertility (idiopathic or specific causes)
Congenital anorchia (bilateral in 1 in 20,000 males, unilateral four times as often)	Intra-uterine 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- hydroxlyase defect, 17β-hydroxysteroid 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
Noonan syndrome (prevalence of 1 in 1,000 to 1 in 5,000)	Short stature, congenital heart diseases, cryptorchidism
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 [44]

Table 2: Forms of secondary hypogonadism

Disease	Causes of deficiency
Hyperprolactinemia	Prolactin-secreting pituitary adenomas (prolactinomas) or drug-induced
Isolated (congenital) hypogonadotropic hypogonadism (IHH/CHH) (formerly termed idiopathic hypogonadotrophic hypogonadism)	Specific (or unknown) mutations affecting GnRH synthesis or action
Kallmann's 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
Haemocromatosis, Thalassaemia	Second most common endocrine abnormality in haemocromatosis in a relatively advanced stage of iron overload [45]
Prader-Willi syndrome (PWS) (formerly Prader-Labhart-Willi syndrome, prevalence 1 in 10,000 individuals)	Congenital disturbance of GnRH secretion
Congenital adrenal hypoplasia with hypogonadotropic 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

Recommendation	Strength rating
Differentiate the two forms of hypogonadism (primary and secondary hypogonadism) by determining luteinising hormone and follicle-stimulating hormone levels, as this has implications for patient evaluation and treatment and makes it possible to identify patients with associated health problems and infertility.	Strong

Figure 2: The hypothalamic-pituitary-testes axis
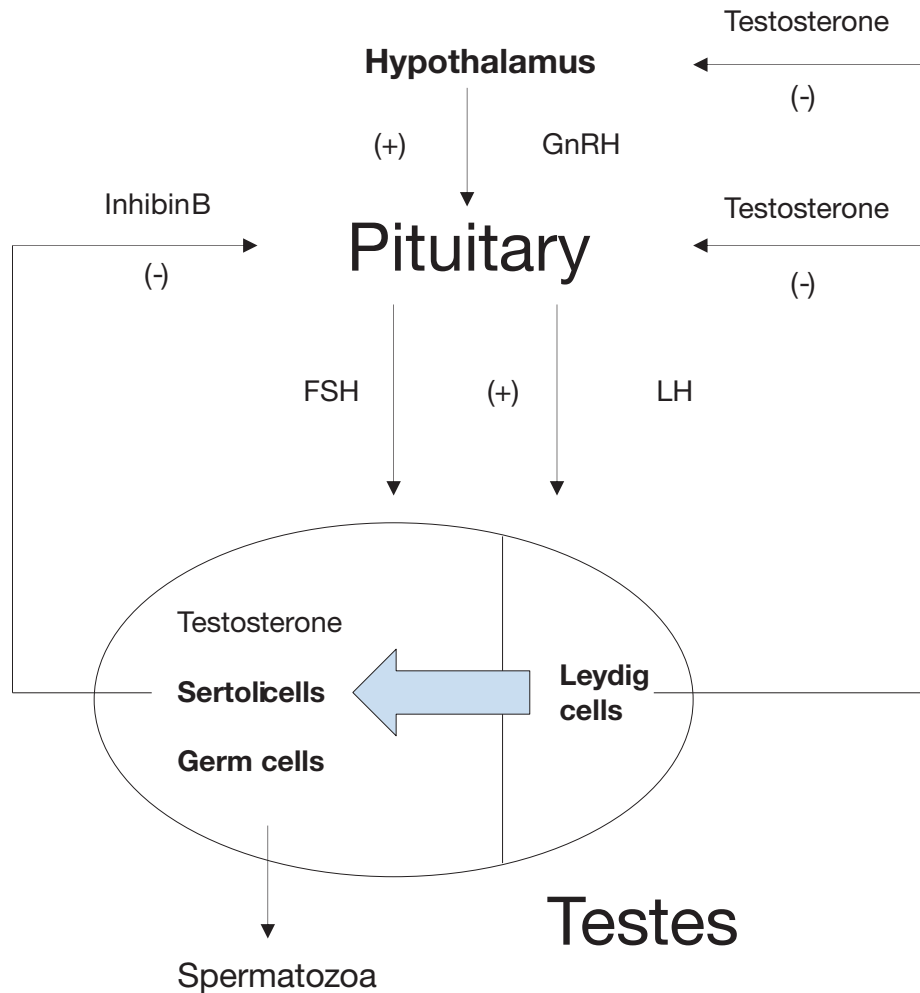
FSH = follicle-stimulating hormone; GnRH = Gonadotropin-releasing hormone; LH = luteinising hormone.

4. DIAGNOSTIC EVALUATION

Hypogonadism is diagnosed on the basis of persistent signs and symptoms related to androgen deficiency and assessment of consistently low testosterone levels (on at least two occasions) with a reliable method [12, 46-49]. It should be noted that over time, there is a substantial portion of men who recover from secondary hypogonadism, prompting the importance of re-evaluation if testosterone therapy has been instituted in men without defined hypothalamic or pituitary disease [50].

4.1 Clinical symptoms and laboratory testing
Low levels of circulating androgens may be associated with signs and symptoms (Table 3) [12, 51, 52].

Table 3: Clinical symptoms and signs suggestive for androgen deficiency

Clinical symptoms and signs suggestive for androgen deficiency:
Reduced testis volume
Male-factor infertility
Decreased body hair
Gynaecomastia
Decrease in lean body mass and muscle strength
Visceral obesity
Metabolic syndrome
Insulin resistance and type 2 diabetes mellitus
Decrease in bone mineral density (osteoporosis) with low trauma fractures
Mild anaemia
Sexual symptoms:
Reduced sexual desire and sexual activity
Erectile dysfunction
Fewer and diminished nocturnal erections
Cognitive and psychovegetative symptoms:
Hot flushes
Changes in mood, fatigue and anger
Sleep disturbances
Depression
Diminished cognitive function

The most prevalent symptoms of male hypogonadism in ageing men are reduced sexual desire and sexual activity, erectile dysfunction, loss of vigour and changes in mood [12, 52]. Other factors found associated with low testosterone are obesity and a poor general health status [12]. 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 been compiled from three large community-based samples, suggesting a cut-off of 12.1 nmol/L for total serum testosterone and 243 pmol/L for free testosterone, to distinguish between normal levels and levels possibly associated with deficiency [53]. Symptoms suggesting the presence of hypogonadism [12, 52] are summarised in Table 3. It should, however, be noted that these symptoms are also found in men with normal testosterone levels and may have causes other than androgen deficiency.

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 [54, 55]. 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 mean levels are highest and most reproducible in younger men [56].

Laboratory testing of testosterone should reflect on the diurnal variation of testosterone. In most cases two morning (7.00 a.m. to 11.00 a.m.) samples are sufficient, but should trigger further evaluation if the difference is > 20% [57]. Both immuno-assay and mass spectrometry based assays can produce reliable results, as long as they are well-validated. Evaluation should be based on reference ranges for normal men provided by the laboratory measuring the samples.

In cases with discrepancy between testosterone levels and symptoms, free testosterone (FT) levels should be analysed. For determination of FT levels, the calculation of FT with the help of the sex hormone binding globulin (SHBG) is recommended.

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 are not clear yet, but potentially, these men may become hypogonadal in the future.

To differentiate between primary and secondary forms of hypogonadism and to clarify hypogonadism in adult men, determination of LH serum levels is required. Both LH and testosterone serum levels should be analysed twice within 30 days, preferably in a fasting state [58].

4.2 History-taking and questionnaires

Symptoms of hypogonadism are listed in Table 3 and 4 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 secondary hypogonadism. Adult-onset hypogonadism is characterised by sexual dysfunction, obesity and loss of vigour. Published questionnaires are unreliable, have low specificity and are not effective for case-finding [59-62]. 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, previous treatment or use of testosterone, and abuse of anabolic steroids should also be included in history-taking [63, 64].

4.3 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, testicular size (measured with an orchidometer or ultrasound [US]) and examination of the penis, as well as a digital rectal examination (DRE) of the prostate should be included.

4.4 Summary of evidence and recommendations for the diagnostic evaluation

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

Recommendations	Strength rating
Restrict the diagnosis of testosterone deficiency to men with persistent symptoms suggesting hypogonadism (Tables 3 and 4).	Strong
Measure testosterone in the morning before 11.00 hours, preferably in the fasting state.	Strong
Repeat total testosterone 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 levels.	Strong
Consider assessing 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: - Sexual dysfunction. - Type 2 diabetes. - Metabolic syndrome. - Obesity. - Pituitary mass, following radiation involving the sellar region and other diseases in the hypothalamic and sellar region. - 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.	Strong
Analyse LH and FSH serum levels to differentiate between primary and secondary forms of hypogonadism.	Strong

4.5 Clinical consequences of hypogonadism

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

4.5.1 Prenatal androgen deficiency

During the first fourteen 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 or LH receptor 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 DSD 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.

4.5.2 *Prepubertal-onset of androgen deficiency*

At the start of puberty, rising gonadotropin 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, 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 fourteen [65]. 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 4) and diagnosis and treatment are fairly straightforward. The major challenge in younger individuals with presumed isolated (congenital) 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, as seen in patients with Klinefelter syndrome, pubertal development can be normal, 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 sub-fertility [66].

Table 4: Signs and symptoms suggesting prepubertal-onset hypogonadism

Delayed puberty
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

4.5.3 *Adult-onset hypogonadism*

Adult-onset hypogonadism is defined as testosterone deficiency, usually associated with clinical symptoms or signs 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 adult-onset hypogonadism are summarised in Table 3. Most of these symptoms have a multi-factorial aetiology, are reminiscent of normal ageing and can also be found in men with completely normal testosterone levels [10]. 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 many 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 [52, 67]. 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. Androgen receptor activity may also contribute to this variance [68, 69].

4.5.4   ***Hypogonadism in Type 2 Diabetes***

There is a high prevalence of hypogonadism in men with type 2 diabetes mellitus [70-72]. The commonest symptom and main indication for treatment is that of sexual dysfunction. Erectile dysfunction has been reported in up to 70% of men with diabetes but may be caused by different or combined aetiologies (vasculopathy, neuropathy, medications and psychological factors) as well as hypogonadism in approximately 30%. Testosterone therapy alone may be insufficient and a combination with phosphodiesterase type 5 inhibitors (PDE5Is) may be necessary. Testosterone deficiency is also associated with a failure of PDE5Is therapy [73]. Randomised controlled trials of at least six months duration of TRT have reported significant improvement in sexual desire, but not erectile function [74-76] in men with type 2 diabetes, although one study did not find a benefit on sexual desire [77].

        Testosterone deficiency is associated with an adverse cardiovascular risk profile in men with type 2 diabetes and TRT can improve insulin resistance and glycaemic control in some studies, reduce percentage body fat, and waist circumference and lower total and LDL-cholesterol, lipoprotein (a), and a small fall in HDL-cholesterol may occur. There is some evidence that it may reduce mortality [76, 78, 79]. These benefits, however, are not currently stand alone indications for TRT in type 2 diabetes and require further research but, could be considered as potential added benefits when used in conjunction when subjects are treated for sexual dysfunction [80].

4.5.4.1   *Recommendations for screening men with adult-onset hypogonadism*

Recommendations	Strength rating
Screen for testosterone deficiency only in adult men with consistent and multiple signs and symptoms listed in Table 3.	Weak
Young men with testicular dysfunction and men older than 50 years of age with low testosterone should additionally be screened for osteoporosis.	Strong

5.   DISEASE MANAGEMENT

5.1   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 of testosterone treatment is to restore physiological androgen dependent functions and to improve QoL, e.g. sense of well-being, sexual function, muscle strength and bone mineral density. Table 5 highlights the main indications for testosterone treatment. Table 6 lists the main contraindications against testosterone treatment.

Table 5: Main indications for testosterone treatment

Delayed puberty (constitutional or congenital forms (HH, Kallmann's syndrome))
Klinefelter syndrome with hypogonadism
Sexual dysfunction and low testosterone, not responding to PDE5Is
Low bone mass in hypogonadism
Adult men with low testosterone and consistent and preferably multiple signs and symptoms of hypogonadism following unsuccessful treatment of obesity and comorbidities (listed in Table 3)
Hypopituitarism

Table 6: Contraindications against testosterone treatment

Locally advanced or metastatic prostate cancer
Male breast cancer
Men with an active desire to have children
Haematocrit > 0.54%
Severe chronic cardiac failure (New York Heart Association Class IV)

5.2 Benefits of treatment

In congenital HH, treatment is usually indicated. In these patients hormonal stimulation with hCG and FSH or alternatively pulsatile GnRH treatment can induce puberty, restore fertility in most cases and normalise bone mineralisation [42, 81, 82]. If active desire to have children is not the focus of treatment after puberty induction, life-long testosterone substitution is recommended [83].

In adult-onset hypogonadism testosterone treatment may improve symptoms, but many hypogonadal men are obese and have comorbidities: weight reduction, lifestyle modification and good treatment of comorbidities are more important than just testosterone treatment [84, 85]. Reduction of BMI in obese patients, for example, is associated with significant increase of serum testosterone levels [86].

Testosterone treatment may present several benefits regarding body composition, metabolic control, psychological and sexual parameters, although the effects are usually modest. Observational trials show a correlation between restored physiological testosterone levels, muscle mass and strength measured as leg press strength and quadriceps muscle volume [51, 87-89]. Low testosterone levels are common in men with chronic renal failure on haemodialysis and there is also a worsening of prognosis associated with lower testosterone levels. There, is however, a lack of interventional studies evaluating eventual benefits of testosterone therapy in this group of men [90]. Similar positive results are shown in meta-analysis designed to address the value of the role of exogenous testosterone in bone mineral density: it is evident how testosterone therapy improves mineral density at the lumbar spine producing a reduction in bone resorption markers. Available trials failed to demonstrate a similar effect at the femoral neck. At present though, bone mineral density seems to remain a surrogate marker of bone health and there are no RCTs detailing actual bone fracture risk [88, 91-93]. Improvement in bone mineral density and bone structure in men with Klinefelter syndrome has also been reported [94]. Body composition is influenced by testosterone therapy in hypogonadal men, with a consequent decrease of fat mass and an increase in lean body mass [88, 95]. Men with hypogonadism are at an increased risk of having osteoporosis and osteopenia. Young men with testicular dysfunction and men older than 50 years of age with low testosterone should additionally be screened for osteoporosis [96].

Several observational studies based on testosterone undecanoate, demonstrate a significant reduction in trunk and waist fat with an evident decrease in waist size [97-99]. In the same trials, testosterone undecanoate administration showed an improvement in body weight, BMI and lipid profile after three months of therapy [97].

A strong correlation between decreased testosterone levels and increased cardiovascular mortality has been reported in meta-analyses and retrospective studies showing that total-testosterone and FT in the normal range are related to reduced all-cause mortality [100-106]. It is suggested that low testosterone is a biomarker for a poor health condition and as such is a marker for increased risk of cardiovascular disease [107]. Also of interest is the observation that testosterone treatment (transdermal) over a three year period compared to placebo did not cause any change in dynamics of atherosclerotic plaque development in the intima media of the carotids [108]. Normalisation of testosterone levels after testosterone replacement therapy also seems to be associated with decreased incidence of atrial fibrillation [109].

A recent double-blinded, placebo-controlled study on men 65 years or older suggests that among men with low testosterone levels, testosterone replacement therapy significantly increases haemoglobin levels thus correcting anaemia from known or unknown causes [110].

Sexual dysfunction and testosterone treatment

Male sexual dysfunction symptoms are the most predictive determinant sign of potential male hypogonadism: 23 to 36% of men with sexual dysfunction are hypogonadal [111]. Testosterone therapy was shown to moderately increase sexual function in hypogonadal men [112]. In a large RCT, testosterone therapy resulted in a significant improvement in sexual arousal, interest and drive [113]. Two RCTs have reported that testosterone therapy has a benefit on sexual function in men with type 2 diabetes [114]. In a recent meta-analyses of RCTs on testosterone therapy and sexual function, testosterone was shown to have a positive influence on sexual function but only in clearly hypogonadal men (testosterone < 8 nmol/L) [115]. In a recent RCT performed in older men with low libido and low testosterone levels, improvements in sexual desire and activity in response to testosterone treatment were related to the magnitude of increase in testosterone levels. There was no significant effect on erectile function [116]. Improvement of sexual symptoms will largely depend on the aetiology of the dysfunction: testosterone therapy in men with normal testosterone levels is not very effective, but testosterone therapy may help improve response to PDE5Is in hypogonadal men [117], although a recent meta-analyses of studies with daily PDE5Is in men with low testosterone showed that PDE5Is were equally

effective in men with low testosterone as in men with normal testosterone [118]. The advantage of the use of PDE5Is for erectile dysfunction is that these drugs are usually very effective and work fast. In contrast, testosterone treatment for erectile dysfunction may take up to several months to become effective. The use of a PDE5I may also increase serum testosterone levels [119].

In a small RCT, testosterone therapy did not improve cognitive functions but had a positive effect on verbal memory and depressive symptoms [120]. However, a recent, large, placebo-controlled study showed no significant improvement on memory and other cognitive functions in older men with symptomatic hypogonadism after one year of testosterone treatment [121]. Significant improvement of depressive symptoms in men treated with testosterone undecanoate was reported in a recent randomised trial [74]. Meta-analysis of data from randomised placebo-controlled trials has shown a significant positive impact of testosterone on mood [122].

Summary of evidence	LE
Testosterone treatment may improve symptoms, but many hypogonadal men have a chronic illness and are obese. Weight reduction, lifestyle modification and good treatment of comorbidities can increase testosterone and reduce associated risks for diabetes and cardiovascular diseases.	2
Testosterone treatment can improve body composition, bone mineralisation, signs of the metabolic syndrome, male sexual problems, diabetes regulations, memory and depressive symptoms.	3
A reduction in BMI and waist size, improved glycaemic control and lipid profile are observed in hypogonadal men receiving testosterone treatment.	2a

Recommendations	Strength rating
Improve lifestyle, reduce weight in case of obesity and treat comorbidities before starting testosterone therapy.	Strong
In hypogonadal men with erectile dysfunction start with a phosphodiesterase type 5 inhibitor (PDE5I) as first line treatment and add testosterone in case of a poor response to PDE5I treatment.	Strong

5.3 Choice of treatment

The aim of testosterone treatment is to restore physiological testosterone levels in hypogonadal men [123]. Several preparations are available, which differ in the route of administration, pharmacokinetics and adverse events, and the selection should be a joint decision by both the patient and the physician [124]. Short-acting preparations are preferred to long-acting depot administration in the initial treatment phase, so that any adverse events that may develop can be observed early and treatment can be discontinued if needed [125]. The available agents are oral preparations, intramuscular injections and transdermal gel.

5.3.1 Preparations
5.3.1.1 Testosterone undecanoate
Testosterone undecanoate (TU) 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 [123]. 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 three 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 [126]. In the recent IPASS study, a total worldwide sample of 1,438 men was evaluated during nine to twelve months of treatment with injectable TU: TU was effective and well-tolerated, with marked improvements in several psychosexual functions and waist circumference. Adverse events and adverse drug reactions (more common: increase in haematocrit, increase in Prostate-Specific Antigen (PSA), and injection site pain) were 12% and 6% respectively, mostly mild to moderate, and with no increase in prostate cancer observed [99]. A recent RCT shows that sexual function benefits are evident principally in patients with severe hypogonadism (< 8nmol/L): improvements in intercourse satisfaction and sexual desire appear by the sixth week of treatment while erectile function improvements appear after at least 30 weeks of treatment [75].

5.3.1.2 Testosterone cypionate and enanthate
Testosterone cypionate and enanthate are available as short-acting intramuscular delivery systems (with intervals of two to three weeks) and represent safe and valid preparations. However, these preparations 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 [127, 128]. They are also associated with increased rates of erytrocytosis. In fact, short-acting intramuscular injections have the highest incidence of erythrocytosis (approaching 40%). The mechanism of the pathophysiology is still unknown. In at-risk populations (type 2 diabetes, smokers, obese, thrombophilic conditions) caution should be exercised in prescribing short-acting intramuscular formulations [129].

5.3.1.3 Transdermal testosterone

Transdermal testosterone preparations are available as 1% up to 2% gel. They provide a uniform and normal serum testosterone level for 24 hours (daily interval). Common side-effects are the risk of interpersonal transfer if appropriate precautions are not taken [130, 131]. In a recent open-label phase III study, a testosterone 2% gel formulation has proven efficacious in normalising serum testosterone levels as early as the first dose in more than half the subjects, and in more than 85% of subjects by the third month of administration. Adverse events were mild-to-moderate, but care in titration and dosing is suggested to avoid supraphysiological serum testosterone levels [132]. It should be noted that patients with high BMI may require higher doses since obesity seems to affect the pharmacokinetics of transdermal testosterone preparations [133, 134].

5.3.1.4 Future perspectives

A randomised phase II clinical trial detailing the efficacy and safety of Enclomiphene Citrate (EC) as an alternative to testosterone preparations is available. Enclomiphene Citrate should provide adequate supplementation of testosterone while preventing oligospermia with a sufficient safety profile. At present it is used as an off-label medication for male hypogonadism [135-138].

5.4 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, especially in men with low gonadotropins (secondary hypogonadism). Human chorionic gonadotropin stimulates testosterone production of Leydig cells. Normal physiological serum levels can be achieved with a standard dosage of 1,500-5,000 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 intramuscular or subcutaneous) in adults as well as in adolescents [43, 139]. In the near future, long-acting FSH formulations may be available for the treatment of the male [140]. In cases of mild forms of secondary hypogonadism or in selected cases of primary hypogonadism induction of testosterone synthesis by hCG alone may lead to suppression of FSH (negative feedback of testosterone production) and has consequently also to be combined with FSH treatment if necessary.

Human chorionic gonadotropin 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 long-term treatment of male hypogonadism, except in patients in whom fertility treatment is indicated. Previous testosterone treatment does not seem to affect the efficacy of gonadotropin therapy [82, 83]. Anti-oestrogens and aromatase inhibitors are further options for hypogonadal patients with an active child wish, though evidence is limited [141].

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 [123]. 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 [127].
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 [126, 127].

Testosterone undecanoate	Intramuscular; one injection every ten to fourteen weeks	Steady-state testosterone levels without fluctuation.	Long-acting preparation that cannot allow drug withdrawal in case of onset of side-effects [128].
Transdermal testosterone	Gel; daily application	Steady-state testosterone level without fluctuation.	Risk of interpersonal transfer [130, 131].
Subdermal depots	Subdermal implant every five to seven months	Long duration and constant serum testosterone level.	Risk of infection and extrusion of the implants [123, 142, 143].

5.5 Recommendations for testosterone replacement therapy

Recommendations	Strength rating
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.	Strong
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.	Weak
Do not use testosterone therapy in patients with male infertility or active child wish since it may suppress spermatogenesis.	Strong
Only use human chorionic gonadotropin treatment for (hypogonadotrophic) hypogonadal patients with simultaneous fertility treatment.	Strong
In patients with adult-onset hypogonadism, only prescribe testosterone treatment in men with multiple symptoms and if weight loss, lifestyle modification and good treatment balance of comorbidities have proven unsuccessful.	Strong

5.6 Risk factors in testosterone treatment

Physicians are often reluctant to offer testosterone treatment especially in elderly men due to the potential risk of this therapy. The most common doubts are represented by the possible consequences on the prostate and cardiovascular risks.

5.6.1 Male breast cancer

Male breast cancer is a rare disease with an incidence of less than 1% of all male cancers [144]. The incidence is higher in men with Klinefelter syndrome. Testosterone treatment is contraindicated in men with a history of breast cancer [39]. Association between testosterone treatment and development of breast cancer is not supported by strong evidence although there are some reports based on small numbers of patients [145].

5.6.2 Risk for prostate cancer

Prostate cancer growth may be influenced by testosterone: studies report that hypogonadism is associated with a lower incidence of prostate cancer, but if prostate cancer occurs in hypogonadal men it usually has an advanced stage and a higher Gleason score [146, 147]. Short-term RCTs support the hypothesis that testosterone treatment does not result in changes in prostatic histology nor in a significant increase in intraprostatic testosterone and DHT [148, 149]. Observational studies indicate that testosterone therapy does not increase the risk of developing prostate cancer or result in more aggressive prostate tumours [99, 148, 150, 151]. In a recent meta-analysis, no increased risk in International Prostate Symptom Score (IPSS) worsening, in detection of abnormal PSA levels or in developing prostate cancer was observed [152].

Testosterone treatment is clearly contraindicated in men with advanced prostate cancer. A topic under debate is the use of testosterone treatment in hypogonadal men with a history of prostate cancer and no evidence of active disease. So far only studies with a limited number of patients and a relatively short period of follow-up are available and indicate no increased risk for prostate cancer recurrence [153, 154]. According to a recent retrospective study on hypogonadal men with previous history of prostate cancer receiving testosterone following cancer diagnosis, treatment was not associated with increased overall or cancer-specific mortality, but testosterone treatment was more likely to be prescribed in patients undergoing radical prostatectomy for well-differentiated tumours [155]. No randomised placebo-controlled trials are available yet to document its long-term safety in these patients [123]. 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) can be cautiously considered for testosterone treatment [156].

In these men, 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). It is advised that therapy should not start before one year of follow-up after surgery and patients should be without PSA recurrence [157].

Patients who underwent brachytherapy or external beam radiation (EBRT) for low-risk prostate cancer can also be cautiously considered for testosterone treatment in case of symptomatic hypogonadism with a close monitoring of prostate cancer recurrence [155, 157, 158], although no long-term safety data are available in these patients.

5.6.3 *Cardiovascular diseases*
There is good evidence that testosterone deficiency, as well as erectile dysfunction, are both independent biomarkers, but not necessarily the cause, of cardiovascular disease and also for all-cause and cardiovascular mortality [159]. Endogenous testosterone levels within the mid-normal range are associated with the lowest risk of mortality [106].

Two studies have reported that men with testosterone levels in the upper quartile of the normal range have a reduced number of cardiovascular events when compared to the combined data from the lower three quartiles [160, 161]. The knowledge that hypogonadism and erectile dysfunction are biomarkers of cardiovascular disease demonstrates that patients should be assessed for cardiovascular risk factors and where appropriate referred to cardiology. Individual cardiovascular risk factors (e.g. lifestyle, diet, exercise, smoking, hypertension, diabetes, dyslipidaemia) should be treated in men with pre-existing cardiovascular disease. Their secondary prevention should be optimised as best possible.

Testosterone treatment has also demonstrated in some studies beneficial effects on certain cardiovascular risk factors [162]. In men with angiographically proven coronary disease those with low testosterone are at greater risk of mortality [163, 164]. Over the many years since testosterone treatment has been available up until recently, there have been no clinical studies in the medical literature, which have shown concern in regard to an increased risk of major cardiovascular events (MACE) apart from heart failure [165]. A major adverse cardiac event is defined as the composite of cardiovascular death, non-fatal acute myocardial infarction, acute coronary syndromes, stroke and cardiac failure. However, three recent studies (one placebo-controlled trial [166] and two observational studies [167, 168]) have suggested that testosterone treatment may be associated with an increased risk of cardiovascular events. These studies have recently been reviewed by the FDA who concluded that, 'each of the studies had major limitations, precluding the ability to draw definitive conclusions' [169]. These findings are supported by letters in response to the paper by Vigen *et al.* [170]. The controversy was fuelled also by a meta-analysis by Xu *et al.* [171] of 27 small studies involving 2,994 predominantly older men that demonstrated that testosterone therapy increased the risk for cardiovascular-related events and that the effect of testosterone therapy was more dependent on the source of funding of the reported trials than on underlying baseline testosterone levels [172, 173]. However, other studies demonstrated that testosterone treatment is at least not proatherogenic over a wide range of doses [174]. In order to overcome some of the limitations of the analysis of Xu *et al.*, Corona *et al.* performed an updated systematic review and meta-analysis of RCTs on testosterone treatment, using a more conventional definition of cardiovascular events similar to that used by regulatory authorities to verify the safety of newly registered drugs (including MACE). The results do not support a causal role between testosterone treatment and adverse cardiovascular events [101].

Recent studies have provided some clarification in regard to the effect of testosterone treatment on cardiovascular events. A large (n=83,010, mean follow up > 4.7 years) retrospective study of men with low testosterone that had testosterone replaced to the normal range was associated with a reduction in myocardial infarction, whereas men treated with testosterone which did not achieve normalisation had no benefit [175]. A second retrospective analysis of MACE at three years (n=4,736) in men again treated to normalise testosterone compared groups with low, normal and high testosterone. The result was that normal testosterone reduced MACE and death [176]. A third large study (population-based matched cohort 10,311 TRT vs. 28,029 controls) followed up for five years, reported that men with the highest tertile of testosterone treatment exposure decreased mortality and cardiovascular events, whereas men in the lowest tertile of testosterone treatment exposure had decreased mortality and cardiovascular events [105]. These studies demonstrate that when testosterone is used, adequate replacement should be administered in order to normalise testosterone levels and that patients must be compliant.

The European Medicines Agency (EMA) has stated 'The Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), a regulatory body representing EU Member States, has agreed by consensus that there is no consistent evidence of an increased risk of heart problems with testosterone

medicines in men who lack the hormone (a condition known as hypogonadism). However, the product information is to be updated in line with the most current available evidence on safety, and with warnings that the lack of testosterone should be confirmed by signs and symptoms and laboratory tests before treating men with these medicines.'

A recent comprehensive and detailed meta-analysis of available randomised placebo-controlled trials concluded that the data did not support a causal role between testosterone treatment and adverse cardiovascular events [101]. There are however no long-term studies or RCTs that provide a definitive answer. Observational studies have reported that testosterone treatment improves survival when compared to men who were not treated [78, 177]. These findings are supported by a large retrospective analysis of 6,355 men treated with testosterone compared to 19,065 non-users which did not demonstrate any increased risk of myocardial infarction with testosterone treatment [178]. A registry study has reported that testosterone treatment compared to untreated men with a mean follow-up of 6.5 years reported a significant improvement in cardio-metabolic risk factors and a decrease in cardiovascualr mortality [179]. A second registry study (RHYME) with adjudicated MACE events found no difference between treated or untreated MACE nor did it report any testosterone treatment related event followed for up to three years [180].

A large retrospective analysis of 76,639 men has demonstrated that testosterone therapy that achieves normalisation of levels results in a significant reduction in the incidence of atrial fibrillation, the commonest cardiac arrhythmia which is associated with an increased risk of stroke, cardiac complications and death [109].

Caution should, however, be used in men with pre-existing cardiovascular disease. Firstly, hypogonadism must be carefully diagnosed beyond reasonable doubt. Secondly, if testosterone is prescribed then testosterone levels should not exceed the mid-normal range and the haematocrit should not exceed 0.54% [181]. Testosterone dose adjustment may be required and/or venesection (500 mL) should be considered and repeated if necessary, if the haematocrit is greater than 0.54%. The haematocrit value of > 54% is based on the increased risk of cardiovascular mortality from the Framingham Heart Study [182], which was recently confirmed in another study [183]. This value is also supported by the known increased risk of thrombosis in the congenital condition of idiopathic erythropoiesis [184]. The majority of patients with cardiovascular disease will be receiving anti-platelet therapy. An electrocardiogram prior to testosterone treatment in the assessment of hypogonadism could be considered.

Adding to the controversy, a recent double-blind, placebo-controlled trial at nine academic medical centres in the United States shows that treatment with testosterone gel for one year is associated with a significantly greater increase in coronary artery non-calcified plaque volume, as measured by coronary computed tomographic angiography. However, the clinical significance remains to be determined [185]. Two large retrospective studies have not shown any evidence that testosterone treatment is associated with an increased incidence of venous thromboembolism [186, 187]. Venous thromboembolism in one study of men on testosterone treatment reported 42 (38 men) cases, 40 of which had evidence of underlying thrombophilia (which included Factor V Leiden deficiency, prothrombin mutations, homocysteinuria) of which 39 had their condition diagnosed after an event [188]. The risk of venous thromboembolism is suggested to increase soon after the start of testosterone use and peak in the first six months of treatment [189]. In addition, high endogenous levels of testosterone and/or oestradiol are not associated with an increased risk of venous thromboembolism [186, 187, 190].

A recent meta-analysis of previous RCTs does not support an increased cardiovascular risk related to testosterone replacement therapy. It also draws similar conclusions for the relationship between testosterone treatment and venous thromboembolism risk, while stating that reported cases of venous thromboembolism are frequently related to an undiagnosed thrombophilia-hypofibrinolysis status [191].

5.6.4 Cardiac Failure
Testosterone treatment is contraindicated in men with severe chronic cardiac failure as fluid retention may lead to an exacerbation of the condition. Some studies including one of twelve months duration have shown that men with moderate chronic cardiac failure (NYHA class III) may benefit from low doses of testosterone, which achieve mid-normal range testosterone levels [87, 192, 193]. If a decision is made to treat hypogonadism in men with chronic cardiac failure, it is essential that the patient is followed carefully with clinical assessment and testosterone and haematocrit measurements on a regular basis. An interesting observation is that testosterone deficiency increased the re-admission and mortality rate in men with heart failure [104].

5.6.5 *Obstructive sleep apnoea*

There is no consistent evidence correlating testosterone treatment with obstructive sleep apnoea. There is also no evidence that testosterone treatment can result in the onset or worsening of the condition [194].

5.6.6 *Anabolic steroid–induced hypogonadism*

Non-prescription anabolic-androgenic steroids (AAS) are used in order to obtain a boost in athletic performances. Use of AAS results in hypogonadotropic hypogonadism by feedback suppression of the hypothalamic-pituitary-gonadal (HPG) axis via inhibition of pulsatile GnRH release and a subsequent decrease in LH and FSH. The duration of suppression and the resultant symptomatic hypogonadism is highly variable and due to multiple factors, including differences in the choices of drugs, amounts used, and durations of use. After a complete endocrine and metabolic assessment, the condition may be treated with hCG, and selective oestrogen receptor modulators (SERM) [195], until the reproductive endocrine axis has been restored. A first systemic review and meta-analysis of the effects of AAS on athletes and recreational users shows that discontinuation of AAS prompts recovery of gonadotropin levels after 13-24 weeks, whereas serum testosterone does not seem to recover, remaining reduced even at 16 weeks from discontinuation. Moreover, AAS use is associated with persistent changes in sperm characteristics (8-30 weeks following discontinuation), reduction in testicular volume (up to 16 weeks following discontinuation) and gynecomastia (often irreversible) [196].

5.7 Summary of evidence and recommendations on risk factors in testosterone replacement treatment

Summary of evidence	LE
Case reports and small cohort studies point to a possible correlation between testosterone treatment 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 testosterone treatment does not result in changes in prostatic histology.	1b
Recent studies indicate that testosterone treatment does not increase the risk of prostate cancer, but long-term follow-up data are not yet available.	3
There is no evidence for a relationship between testosterone treatment and obstructive sleep apnoea.	3
There is no substantive evidence that testosterone treatment, when replaced to the normal physiological range, is related to the development of major adverse cardiovascular events.	1a
In hypogonadal men testosterone treatment has been demonstrated to have a positive impact on cardiovascular risks.	1b

Recommendations	Strength rating
Perform haematological, cardiovascular, breast and prostatic assessment before the start of treatment.	Strong
Monitor testosterone, haematocrit, haemoglobin and prostate-specific antigen (PSA) during testosterone treatment.	Strong
Offer testosterone treatment 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 one year of follow-up.	Weak
Assess for cardiovascular risk factors before commencing testosterone treatment and optimise secondary prevention in men with pre-existing cardiovascular disease.	Strong
Treat men with hypogonadism and either pre-existing cardiovascular disease, venous thromboembolism or chronic cardiac failure who require testosterone treatment 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.	Strong

6. FOLLOW-UP

6.1 Monitoring of patients receiving testosterone replacement therapy

Regular follow-up is needed in patients receiving testosterone treatment, as potentially androgen-dependent symptoms and conditions may occur. The side-effects of testosterone treatment are limited, but their incidence and clinical relevance is as yet unclear. The primary aim of testosterone treatment 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 testosterone treatment on sexual interest may already appear after three weeks of treatment, and reach a plateau at six weeks [88]. Changes in erectile function and ejaculation may require up to six months [88]. Effects on QoL, and also on depressive mood, may become detectable within one month, but the maximum effect may take longer [88].

6.2 Testosterone level

There are as yet insufficient data to define optimal serum levels of testosterone during testosterone treatment. Expert opinion suggests that testosterone treatment 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 testosterone used. It is of importance to evaluate symptom regression and lack of response prompts termination of treatment and eventual re-assessment of the diagnosis.

6.3 Bone density

Bone mineral density (BMD) should be monitored only in men whose BMD was abnormal before initiation of testosterone treatment. An increase in lumbar spine BMD may already be detectable after six months of treatment and may continue for three more years [88].

6.4 Haematocrit

It is important to use only minimal or no venous occlusion when taking a blood sample for haematocrit measurements [184]. Elevated haematocrit is the most frequent side-effect of testosterone treatment. The clinical significance of a high haematocrit level is unclear, but it may be associated with hyperviscosity and thrombosis [190]. The effect of erythropoiesis may become evident at three months and peaks at twelve months [88].

6.5 Prostate safety

Testosterone replacement therapy results in a marginal increase in PSA and prostate volume, plateauing at twelve months [88]. Previous fears that testosterone treatment might increase the risk of prostate cancer have been contradicted by a number of meta-analyses [124, 148, 153, 197]. However, there are insufficient long-term data available to conclude that there is safety regarding the development of prostate cancer with testosterone treatment. Prostate monitoring therefore remains indicated. Subjects with substantial or continuous increase of PSA level need to be investigated to exclude prostate cancer.

6.6 Cardiovascular monitoring

Caution should be used in men with pre-existing cardiovascular disease. In men with chronic heart failure, testosterone treatment can result in fluid retention and an exacerbation of the condition [192, 193]. If a decision is made to treat hypogonadism in men with chronic cardiac diseases it is essential that the patient is followed carefully with clinical assessment and testosterone and haematocrit measurements, on a regular basis.

6.7 Recommendations for follow-up

Recommendations	Strength rating
Assess the response to testosterone treatment at three, six and twelve months after the onset of treatment, and thereafter annually.	Strong
Monitor testosterone, haematocrit at three, six and twelve months and thereafter annually. Decrease the testosterone dosage or switch testosterone preparation from intramuscular 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.	Strong
Assess prostate health by digital rectal examination and prostate-specific antigen (PSA) before the start of testosterone replacement therapy (TRT). Follow-up by PSA tests at three, six and twelve months and thereafter annually.	Strong
Assess men with cardiovascular diseases for cardiovascular symptoms before testosterone treatment is initiated and continue close clinical assessment during treatment.	Strong

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8. CONFLICT OF INTEREST

All members of the EAU Male Hypogonadism Guidelines 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: http://www.uroweb.org/guideline/. 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.

9.   CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

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