

EAU Guidelines on Male Hypogonadism

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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, bone health, and behaviour. Low levels of circulating androgens in utero 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 slightly 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 obesity and several chronic diseases, and some 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, with the aim to provide practical recommendations on how to deal with primary hypogonadism and ageing-related decline in testosterone in male patients, 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.

1.2 Publication history

The present Male Hypogonadism Guidelines are a revision of the first edition of the EAU Guidelines on Male Hypogonadism published in 2012.

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 and downloaded 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 and clinical andrologists.

2. METHODS

References used in this text are assessed according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR) according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence. Additional methodology 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 the current guidelines are based on a systematic literature search and review performed by the panel members in 2014. 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 November 2014 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.

2.1 Review

This document was subject to peer review prior to publication in 2015. The decision to re-review is made based on the extent of the revision. A major revision resulting in significant changes to the clinical recommendations presented in the text will warrant re-review.

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) [1].

Androgen deficiency increases slightly with age also in healthy men [2, 3]. In middle-aged men, the incidence of biochemical hypogonadism varies from 2.1-12.8% [4]. The incidence of low testosterone and symptoms of hypogonadism in men aged 40-79 varies from 2.1-5.7% [3, 4]. Hypogonadism is more prevalent in older men, in men with obesity, those with co-morbidities, and in men with a 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 [5].

3.2 Physiology

Male sexual development starts between the 7th and 12th week of gestation. The undifferentiated gonads develop into a foetal testis through expression of multiple genes located on the short arm of the Y chromosome, including the sex-determining region of the Y chromosome (SRY gene complex) and the SOX gene on chromosome 17 [6]. 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. AMH activity results in regression of the Müllerian ducts (Figure 1). INSL3 and AMH regulate testicular descent.

Under the influence of intratesticular testosterone, the number of gonocytes per tubule increases threefold during the foetal period [7]. 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 5 α -dihydrotestosterone (DHT) by the enzyme 5 α -reductase. Testosterone and DHT are required for penile growth, both activating the androgen receptor [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 gonadotropins (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 round spermatids [11, 12]. 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 influencing the seminiferous tubular microenvironment [11]. 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 [13]. The production of testosterone is controlled in the foetus by placental choriongonadotropin (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 [14]. Figure 1 shows the development of the male reproductive system.

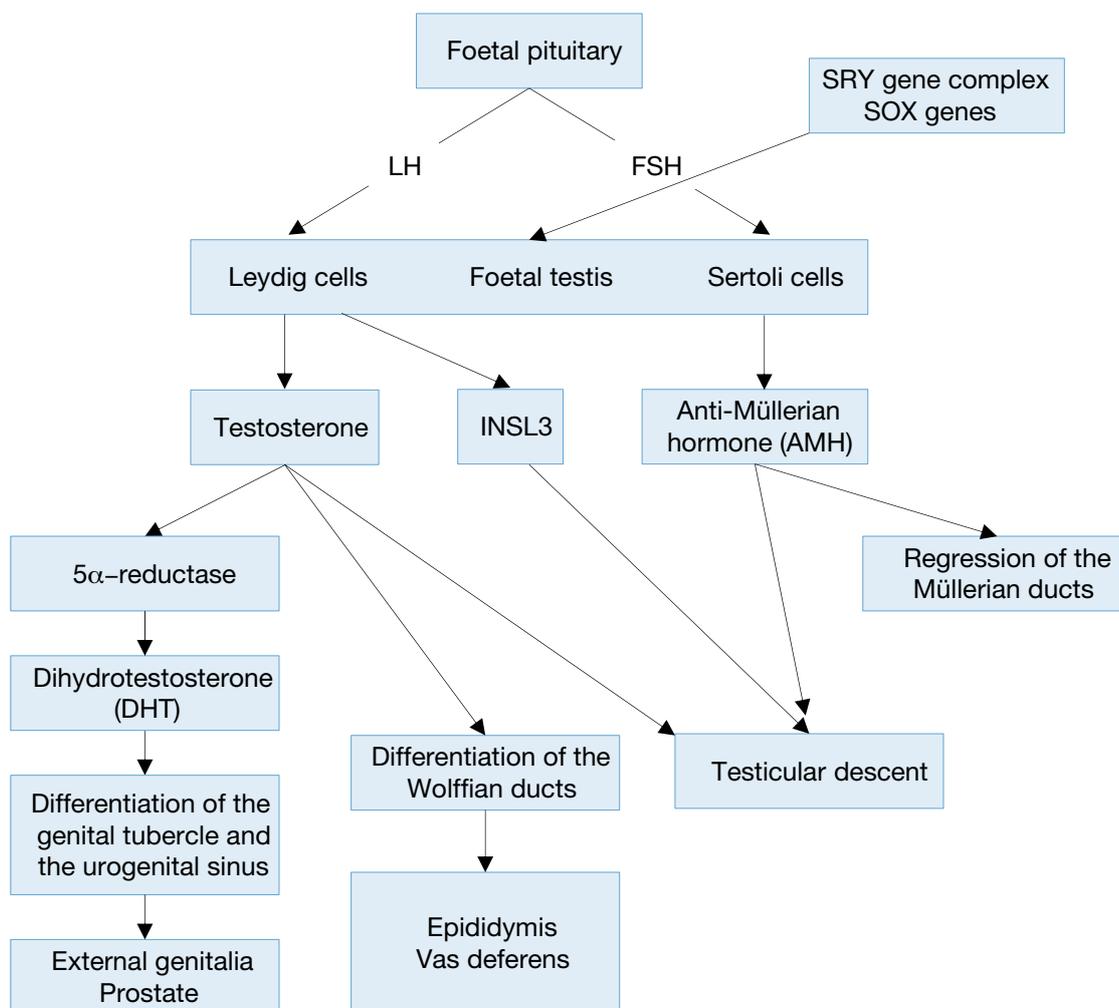
3.2.1 *The androgen receptor*

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 [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 (i.e. disorder of sexual development (DSD)). 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 and oestradiol in 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].

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. The most important 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,XXX in 90% of cases [18]. It arises due to non-disjunction during paternal or maternal meiotic division of germ cells [19].
- Testicular 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 [20-22].

The main reasons for primary testicular failure 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, 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, risperidone 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 gonadotropin-releasing hormone (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 [23, 24]. The most important symptom is the constitutional delay of puberty: it is the most common cause of delayed puberty (pubertas tarda) [25]. 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**

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 been labelled as late-onset hypogonadism and age-related hypogonadism is comprised of three types of hypogonadism and formally secondary hypogonadism is the most prevalent [26, 27]. It should however be stated that low testosterone and low gonadotropin levels do not exclude a compromised gonadal response to LH stimulation as has been demonstrated in obesity, corticosteroid induced hypogonadism etc.

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 5 α -reductase deficiency (for a review, see Nieschlag *et al.* 2010) [28].

The classification of hypogonadism has therapeutic implications. In patients with secondary hypogonadism, hormonal stimulation with human chorionic gonadotropin (hCG) and FSH or alternatively pulsatile GnRH treatment can restore fertility in most cases [29, 30]. Detailed evaluation may for example detect pituitary tumours, systemic disease, or testicular tumours. 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: Most common forms of primary hypogonadism

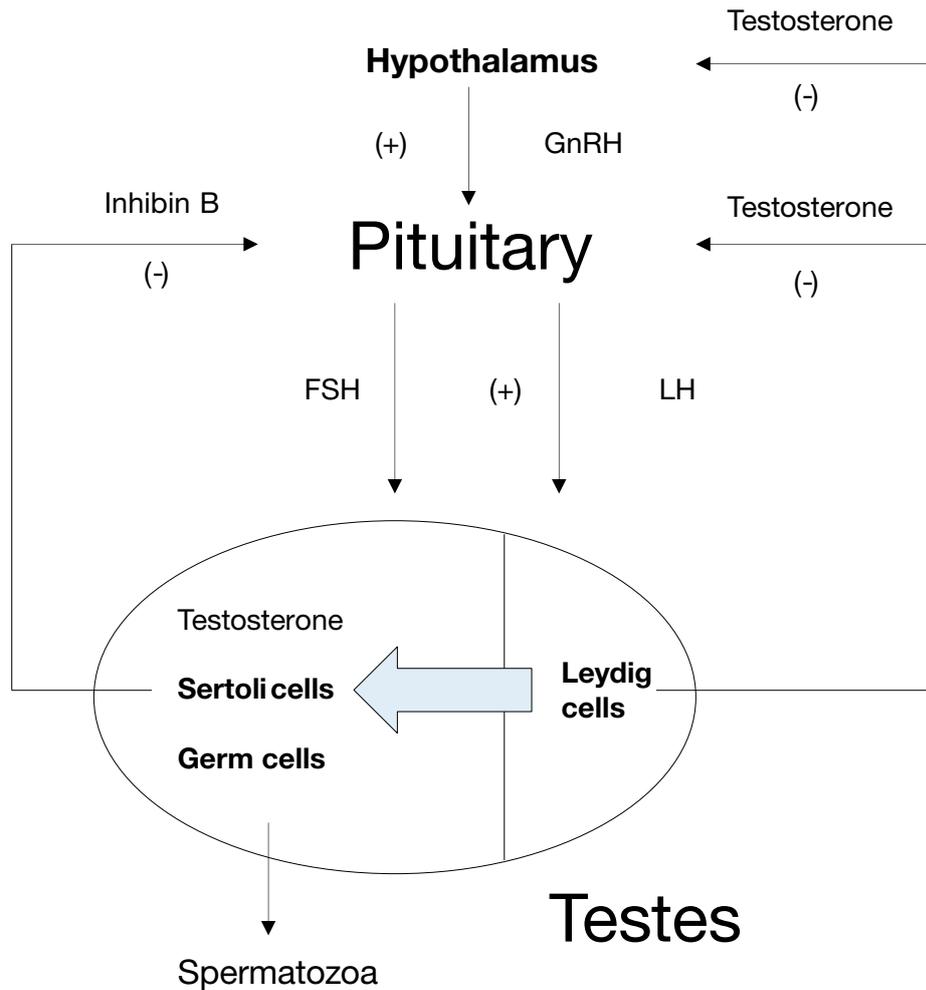
Disease	Causes of deficiency
Maldescended or ectopic testes	Failure of testicular descent, maldevelopment of the testis
Testicular cancer	Testicular maldevelopment
Orchitis	Viral or unspecific orchitis
Acquired anorchia	Trauma, tumour, torsion, inflammation, iatrogenic, surgical removal
Secondary testicular dysfunction	Medication, drugs, toxins, systemic diseases
(Idiopathic) testicular atrophy	Male infertility (idiopathic or specific causes)
Congenital anorchia (bilateral in 1 in 20,000 males, unilateral 4 times as often)	Intrauterine torsion is the most probable cause
Klinefelter syndrome 47,XXX	Sex-chromosomal non-disjunction in germ cells
46,XY disorders of sexual development (DSD) (formerly male pseudohermaphroditism)	Disturbed testosterone synthesis due to enzymatic defects of steroid biosynthesis (17,20- lyase defect, 17 β -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 [31]

Table 2: Most common forms of secondary hypogonadism

Disease	Causes of deficiency
Hyperprolactinemia	Prolactin-secreting pituitary adenomas (prolactinomas) or drug-induced
Isolated hypogonadotropic hypogonadism (IHH) (formerly termed idiopathic hypogonadotropic hypogonadism, IHH)	Specific (or unknown) mutations affecting GnRH synthesis or action
Kallmann syndrome (hypogonadotropic hypogonadism with anosmia, prevalence 1 in 10,000)	GnRH deficiency and anosmia, genetically determined
Secondary GnRH deficiency	Medication, drugs, toxins, systemic diseases.
Hypopituitarism	Radiotherapy, trauma, infections, haemochromatosis and vascular insufficiency or congenital
Pituitary adenomas	Hormone-secreting adenomas; hormone-inactive pituitary adenomas; metastases to the pituitary or pituitary stalk
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	LE	GR
Differentiate the two forms of hypogonadism (primary and secondary) (LH levels), as this has implications for patient evaluation and treatment and makes it possible to identify patients with associated health problems and infertility.	1b	B

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 [4, 32-35].

4.1 Clinical symptoms

Low levels of circulating androgens may be associated with signs and symptoms (Table 3) [4, 36, 37]

Table 3: 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
Fewer and 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 [4, 37]. Other factors found associated with low testosterone were waist circumference and health status [4]. 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 [38]. Symptoms suggesting the presence of hypogonadism [4, 37] 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 [39]. 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 [40]. Both immunoassay and mass spectrometry based assays can produce valid 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.

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 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.

4.2 History-taking and questionnaires

Symptoms of hypogonadism are listed in Table 3 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 primary hypogonadism. Adult-onset hypogonadism is characterised by sexual dysfunction, obesity and loss of vigour. Published questionnaires are unreliable and have low specificity, and they are not effective for case-finding [41-44]. 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 marijuana, opiates and alcohol and previous treatment or use of testosterone or abuse of anabolic steroids should also be included in history-taking.

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 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.

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	LE	GR
Restrict the diagnosis of testosterone deficiency to men with persistent symptoms suggesting hypogonadism (Table 3).	3	C
Measure testosterone in the morning before 11.00 hours in the fasting state.	2	A
Repeat total testosterone on at least two occasions with a reliable method. In addition, measure the free testosterone level in men with: <ul style="list-style-type: none">- Total testosterone levels close to the lower normal range (8-12 nmol/L), to strengthen the laboratory assessment.- Suspected or known abnormal sex hormone-binding globulin (SHBG) levels.	1	A
Assess testosterone in men with a disease or treatment in which testosterone deficiency is common and in whom treatment may be indicated. This includes men with: <ul style="list-style-type: none">- Type 2 diabetes.- Metabolic syndrome.- Obesity.- Pituitary mass, following radiation involving the sellar region and other diseases in the hypothalamic and sellar region.- End-stage renal disease receiving haemodialysis.- Treatment with medications that cause suppression of testosterone levels - e.g. corticosteroids and opiates.- Moderate to severe chronic obstructive lung disease.- Infertility.- Osteoporosis or low-trauma fractures.- HIV infection with sarcopenia.	2	B
Analyse LH serum levels to differentiate between primary and secondary forms of hypogonadism.	2	A

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 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 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 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.

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 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 [45]. 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 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, as 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 [46].

Table 4: Signs and symptoms suggesting prepubertal-onset hypogonadism

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

4.5.3 **Adult-onset hypogonadism**

Definition: 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 include: loss of libido, erectile dysfunction, sarcopenia, low bone mass, depressive thoughts, fatigue, loss of vigour, loss of body hair, hot flushes and reduced fertility (Table 3). 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 nonspecific, 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 [37, 47]. 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.

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

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

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 is to improve QoL, 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 therapy.

Table 5: Indications for testosterone treatment

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

Table 6: Contraindications against testosterone treatment

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

5.2 Benefits of treatment

In congenital hypogonadotrophic hypogonadism 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 [29, 30].

In adult-onset hypogonadism Testosterone Replacement Therapy (TRT) may improve symptoms, but many hypogonadal men are sick and/or obese, and weight reduction, lifestyle modification and good treatment of comorbidities are more important than just TRT.

TRT may present several benefits regarding body composition, metabolic control, psychological and sexual parameters. Randomised trials show a correlation between restored physiological testosterone levels, muscle mass and strength measured as leg press strength and quadriceps muscle volume [36, 48-50]. 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 [49, 51, 52]. Body composition is influenced by testosterone therapy in hypogonadal men, with a consequent decrease of fat mass and an increase in lean body mass [49]. Several studies based on testosterone undecanoate, demonstrate a significant reduction in trunk and waist fat with an evident decrease in waist size [53, 54]. In the same trials, testosterone undecanoate administration showed an improvement in body weight, body mass index and lipid profile after 3 months of therapy [53]. TRT presents positive effects in glycemic and lipid control, insulin resistance and visceral adiposity in hypogonadal men with impaired glucose tolerance and lipid profile with a consequent decrease in mortality [55, 56]. 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 free-testosterone in the normal range are related moreover to reduced all-cause mortality [57-61].

Benefits on libido, erection and ejaculation have been reported in hypogonadal men in several retrospective studies and case reports: Small improvements in satisfaction with erectile function and moderate

improvements in libido have been shown by a meta-analysis of 17 placebo-control trials [49, 62-64]. In a recent multicenter prospective study a significant increase in the IIEF (International Index of Erectile Function) regarding sexual desire, intercourse satisfaction and overall satisfaction was reported, starting 6 weeks from the start of treatment [63]. TRT showed encouraging results in several studies, where satisfactory sexual intercourse was reported at least three months after therapy induction in hypogonadal men suffering from erectile dysfunction [49, 64]. Improvement of sexual symptoms will largely depend on the aetiology of the dysfunction: TRT in men with normal testosterone levels seems not very effective, but TRT may help improve response to phosphodiesterase type 5 (PDE5) inhibitors in hypogonadal men [65].

Significant improvement of depressive symptoms in men treated with testosterone undecanoate were reported in a recent randomised trial [66], as well as benefits in the cognitive spectrum [67]. Meta-analysis of data from randomised placebo-controlled trials has shown a significant positive impact of testosterone on mood [68]. Benefits in relation to the cognitive spectrum have been reported in studies with lower impact.

Summary of evidence	LE
Testosterone replacement therapy (TRT) may improve symptoms, but many hypogonadal men have a chronic illness and are obese: weight reduction, lifestyle modification and good treatment of comorbidities is more important than just TRT.	2
Testosterone replacement treatment can improve body composition, bone mineralisation, signs of the metabolic syndrome and male sexual problems.	3
A reduction in BMI and waist size, improved glycaemic control and lipid profile are observed in hypogonadal men receiving TRT.	2a

5.3 Choice of treatment

The aim of TRT is to restore physiological testosterone levels in hypogonadal men [69]. 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 [70]. 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 [71]. The available agents are oral preparations, intramuscular injections and transdermal gel and patches.

5.3.1 Preparations

5.3.1.1 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 [69]. 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 [72].

5.3.1.2 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 [73, 74]. They are also associated with increased rates of erythrocytosis.

5.3.1.3 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) [75, 76]. The topical application of Testosterone 2% to the axillae is recently gaining more popularity: it has been demonstrated to have a safe and effective profile in a multinational open-label clinical study and has been approved in the United States and Europe [77-79].

5.3.1.4 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 [80, 81].

5.3.1.5 Subdermal depots

Subdermal depots need to be implanted every five to seven 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 [69, 82, 83].

5.4 Hypogonadism and fertility issues

Exogenous testosterone reduces endogenous testosterone production by negative feedback on the hypothalamic-pituitary-gonadal axis. If secondary hypogonadism coincides with fertility issues, hCG treatment should be considered, especially in men with low gonadotropins. 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 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) to induce spermatogenesis in patients with secondary hypogonadism and fertility issues. 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 male hypogonadism, except in patients in whom fertility treatment is an issue.

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 [69]. 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 [73].
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 [72, 73].
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 [74].
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 [75, 76].
Sublingual testosterone	Sublingual; daily doses	Rapid absorption and achievement of physiological serum level of testosterone.	Local irritation [80, 81].
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 [80, 81].
Subdermal depots	Subdermal implant every five to seven months	Long duration and constant serum testosterone level.	Risk of infection and extrusion of the implants [69, 82, 83].

5.5 Recommendations for testosterone replacement therapy

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

5.6 Risk factors in testosterone treatment

Physicians are often reluctant to offer TRT 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 [84]. The incidence is higher in men with Klinefelter syndrome. Testosterone treatment is contraindicated in men with a history of breast cancer [27]. Association between TRT and development of breast cancer is not supported by strong evidence although there are some reports based on small numbers of patients [85].

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 [86, 87]. Short-term 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 [88, 89]. Most recent studies indicate that testosterone therapy does not increase the risk of prostate cancer [88-91], but long-term follow-up data are not yet available. A recent meta-analysis showed a higher (but not statistically significant) percentage of prostate events in middle-aged and older men on TRT, but they were more likely to have a prostatic biopsy due to some increase in prostate-specific antigen (PSA), which is common in men on TRT [70].

Testosterone therapy is clearly contraindicated in men with advanced prostate cancer. A topic under debate is the use of TRT in hypogonadal men with 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 [89]. According to a recent retrospective study on hypogonadal men with previous history of prostate cancer receiving TRT following cancer diagnosis, treatment was not associated with increased overall or cancer-specific mortality, but TRT was more likely to be prescribed in patients undergoing radical prostatectomy for well-differentiated tumours [92]. No randomised placebo-controlled trials are available yet to document its long-term safety in these patients [69]. 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 TRT [93-95]. 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; preoperative PSA < 10 ng/ml). Therapy should not start before one year of follow-up after surgery and patients should be without PSA recurrence [65, 94-96].

Patients who underwent brachytherapy or external beam radiation (EBRT) for low risk prostate cancer can also be cautiously considered for TRT in case of symptomatic hypogonadism with a close monitoring of prostate cancer recurrence [92, 94, 96, 97], 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, for cardiovascular disease and also for all-cause and cardiovascular mortality [98]. Endogenous testosterone levels within the mid-normal range are associated with the lowest risk of mortality [61].

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 [99, 100]. 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.

TRT has also in some studies demonstrated beneficial effects on certain cardiovascular risk factors [101]. In men with angiographically proven coronary disease those with low testosterone are at greater risk of mortality [102, 103]. Over many years since TRT 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 [104]. MACE is defined as the composite of cardiovascular death, nonfatal acute myocardial infarction, acute coronary syndromes, stroke and cardiac failure. However, three recent studies (one placebo-controlled trial [105] and two observational studies [106, 107] have suggested that TRT may be associated 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' [108]. These findings are supported by letters in response to the paper by Vigen *et al.* [109].

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.'

The TOM trial (Basaria *et al.*) used a testosterone dose twice that recommended for initiation of treatment, so does not reflect normal clinical practise, in addition the study was underpowered to detect an increased risk of cardiovascular events. A recent comprehensive and detailed meta-analysis of available evaluable randomised placebo-controlled trials concluded that the data did not support a causal role between TRT and adverse cardiovascular events [58]. There are however no long-term studies or randomised controlled trials (RCT's) that provide a definitive answer. Observational studies have reported that TRT improves survival when compared to men who were not treated [56, 110]. These findings are supported by a large retrospective analysis of 6,355 men treated with TRT compared to 19,065 non-users which did not demonstrate any increased risk of myocardial infarction with TRT [111].

Caution should however be used in men with pre-existing cardiovascular disease. Firstly, hypogonadism must be carefully diagnosed beyond reasonable doubt. Secondly, if TRT is prescribed then testosterone levels should not exceed the mid-normal range and the haematocrit should not exceed 0.54. 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 value of > 54 is based on the increased risk of cardiovascular mortality from the Framingham Heart Study [112] which was recently confirmed in another study [113]. This value is also supported by the known increased risk of thrombosis in the congenital condition of idiopathic erythropoiesis [114]. The majority of patients with cardiovascular disease will be receiving anti-platelet therapy. An electrocardiogram prior to TRT in the assessment of hypogonadism could be considered.

Venous thromboembolism in one study of men on TRT reported 42 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. High endogenous levels of testosterone and/or estradiol are not associated with an increased risk of venous thromboembolism [115]. TRT 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 12 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 [48, 116, 117]. 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 hematocrit measurements, on a regular basis.

5.6.4 **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 [118].

5.7 **Summary of evidence and recommendations on risk factors in testosterone replacement treatment (TRT)**

Summary of evidence	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
Recent studies indicate that testosterone therapy 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 TRT and obstructive sleep apnoea.	3
There is no substantive evidence that TRT, when replaced to the normal physiological range, is related to the development of major adverse cardiovascular events.	1a
In hypogonadal men TRT has been demonstrated to have a positive impact on cardiovascular risks [58].	1b

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

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

6. FOLLOW-UP

6.1 **Monitoring of patients receiving testosterone replacement therapy**

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 three weeks of treatment, and reach a plateau at six weeks [49]. Changes in erectile function and ejaculation may require up to six months [49]. Effects on QoL, and also on depressive mood, may become detectable within one month, but the maximum effect may take longer [49].

6.2 **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. It is

of importance to evaluate symptom regression and lack of response prompts termination of treatment and eventual reassessment of the diagnosis.

6.3 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 six months of TRT and may continue for three more years [49].

6.4 Haematocrit

It is important to use only minimal or no venous occlusion when taking a blood sample for haematocrit measurements [114]. 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 [115]. The effect of erythropoiesis may become evident at three months and peaks at twelve months [49].

6.5 Prostate safety

TRT results in a marginal increase in PSA and prostate volume, plateauing at 12 months [49]. Previous fears that TRT might increase the risk of prostate cancer have been contradicted by a number of meta-analyses [70, 88, 89, 91]. However, there are insufficient long-term data available to conclude that there is safety from prostate cancer with TRT. 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 TRT can result in fluid retention and an exacerbation of the condition [116, 117]. 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 hematocrit measurements, on a regular basis.

6.7 Recommendations for follow-up

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

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

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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>. 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.