GUIDELINES ON MALE HYPOGONADISM

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Introduction

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

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

Aetiology and forms

Male hypogonadism can be classified in 4 forms:

1. Primary forms caused by testicular insufficiency.
2. Secondary forms caused by hypothalamic-pituitary dysfunction.

3. Late onset hypogonadism.
4. Male hypogonadism due to androgen receptor insensitivity.

The main causes of these different forms of hypogonadism are highlighted in Table 1.

The type of hypogonadism has to be differentiated, as this has implications for patient evaluation and treatment and enables identification of patients with associated health problems.

Table 1: Different forms of male hypogonadism and main causes

Primary forms (testicular insufficiency)	**Main causes**
Congenital forms	Klinefelter syndrome
	Testicular dysgenesis (cryptorchidism)
	Congenital anorchia
Acquired forms	Testicular malignancy
	Orchitis
	Medications (chemotherapy)
	Systemic diseases
	Acquired anorchia
Secondary forms (hypothalamic-pituitary dysfunctions)	**Main causes**
Congenital forms	Kallmann syndrome
	Idiopathic hypogonadotrophic hypogonadism (IHH)

Acquired forms	Pituitary tumour (prolactinoma)
	Drugs
	Systemic disease (renal failure, haemochromatosis, hypothyroidism, trauma, infections)
	Abuse of anabolic steroids
	Morbid obesity
	Radiotherapy
Late onset hypogonadism	Ageing
(Combined testicular and hypothalamic pituitary insufficiency)	Obesity
	Chronic diseases
	Poor health status
Androgen receptor insensitivity	Partial androgen insensitivity syndrome (PAIS)

Diagnosis

The diagnosis of male hypogonadism is based on clinical symptoms and signs of androgen deficiency (Tables 2 and 3), together with consistently low serum testosterone levels.

Table 2: Signs and symptoms suggesting prepubertal-onset hypogonadism
Small testes
Cryptorchidism
Gynaecomastia
High voice
Unclosed epiphyses
Linear growth into adulthood
Eunuchoid habitus
Sparse body/facial hair
Infertility
Low bone mass
Sarcopenia
Reduced sexual desire/activity

Table 3: Signs and symptoms associated with late-onset hypogonadism
Loss of libido
Erectile dysfunction
Sarcopenia
Low bone mass
Depressive thoughts
Changes in mood, fatigue and anger
Sleep disturbances
Loss of body hair
Hot flushes
Loss of vigour
Insulin resistance
Metabolic syndrome
Visceral obesity
Gynaecomastia

Diminished cognitive functions

Routine screening for testosterone deficiency is not indicated. However, testosterone assessment should be done in men with:

- Pituitary mass, following radiation involving the sellar region and other diseases in the hypothalamic and sellar region.
- End-stage renal disease receiving haemodialysis.
- Treatment with medications that cause suppression of testosterone levels e.g. corticosteroids and opiates;
- Moderate to severe chronic obstructive lung disease;
- Infertility.
- Osteoporosis or low-trauma fractures.
- Human immunodeficiency virus (HIV) infection with sarcopenia.
- Type 2 diabetes.

Acquired hypogonadotropic hypogonadism (secondary forms) can be caused by some drugs, hormones, anabolic steroids and by tumours of the pituitary gland. Imaging (CT or MRI) of the sellar region and complete endocrine work-up is requested when a pituitary tumour is suspected.

Recommendations for screening	**GR**
Screening for testosterone deficiency is only recommended in adult men with consistent and preferably multiple signs and symptoms, listed in Tables 2 and 3.	C
Adult men with established severe hypogonadism should be screened for concomitant osteoporosis.	B
Total testosterone assessment should be repeated at least on two occasions with a reliable method.	A

- In men with total testosterone levels close to the lower normal range (8-12 nmol/l), the free testosterone level should be measured to strengthen the laboratory assessment. - In men with suspected or known abnormal sex hormone-binding globulin (SHBG) levels, free testosterone should also be included.	

Treatment

The aim of treatment is to restore testosterone levels to the physiological range and thereby improve the patient's quality of life. Indications and contraindications are listed in Tables 4 and 5.

Table 4: Indications for testosterone treatment
Adult men with consistent and preferably multiple signs and symptoms of hypogonadism (listed in Tables 2 and 3) and low testosterone
Delayed puberty (idiopathic, Kallmann syndrome)
Klinefelter syndrome with hypogonadism
Sexual dysfunction and low testosterone
Low muscle strength and bone mass in hypogonadism
Hypopituitarism
Testicular insufficiency and symptomatic hypogonadism

Table 5: Contraindications against testosterone treatment
Prostate cancer
Prostate-specific antigen (PSA) > 4 ng/mL
Male breast cancer
Severe sleep apnoea
Male infertility
Haematocrit > 50%
Severe lower urinary tract symptoms due to benign prostatic enlargement

Choice of treatment

Testosterone replacement therapy (TRT) is safe and effective and the agents are available as oral preparations, intramuscular injections, and transdermal gel or patches (Table 6).

Table 6: Testosterone preparations for replacement therapy

Formulation	Administration	Advantages	Disadvantages
Testosterone undecanoate	Oral; 2-6 cps every 6 h	Absorbed through the lymphatic system, with consequent reduction of liver involvement	Variable levels of testosterone above and below the mid-range. Need for several doses per day with intake of fatty food

Testosterone cypionate	Intramuscular; one injection every 2-3 weeks	Short-acting preparation that allows drug withdrawal in case of onset of side effects	Possible fluctuation of testosterone levels
Testosterone enanthate	Intramuscular; one injection every 2-3 weeks	Short-acting preparation that allows drug withdrawal in case of onset of side effects	Possible fluctuation of testosterone levels
Testosterone undecanoate	Intramuscular; one injection every 10-14 weeks	Steady-state testosterone levels without fluctuation	Long-acting preparation that cannot allow drug withdrawal in case of onset of side effects
Transdermal testosterone	Gel or skin patches; daily application	Steady-state testosterone level without fluctuation	Skin irritation at the site of application and risk of interpersonal transfer

Sublingual testosterone	Sublingual; daily doses	Rapid absorption and achievement of physiological serum level of testosterone	Local irritation
Buccal testosterone	Buccal tablet; two doses per day	Rapid absorption and achievement of physiological serum level of testosterone	Irritation and pain at the site of application
Subdermal depots	Subdermal implant every 5-7 months	Long duration and constant serum testosterone level	Risk of infection and extrusion of the implants

In patients with secondary hypogonadism, anti-oestrogens or hormonal stimulation with hCG and FSH or alternatively GnRH can restore testosterone production.

Recommendations	**GR**
The patient should be fully informed about expected benefits and side effects of each treatment option. The selection of the preparation should be a joint decision by an informed patient and the physician.	A
Short-acting preparations may initially be preferred to long-acting depot administration when starting treatment. Patients can switch to a long-acting depot if preferred and side effects are absent or minimal.	B

Human chorionic gonadotrophin (hCG) treatment can only be recommended for hypogonadal patients who are receiving simultaneous fertility treatment.	B

Risk factors in testosterone treatment

- 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.
- Randomised controlled trials support the hypothesis that TRT does not result in changes in prostatic histology. However, there are not yet data available that show long-term prostatic safety of TRT.
- Testosterone therapy is not related to the development of de novo cardiovascular events. However, patients with severe cardiovascular diseases should be screened first by a cardiologist before TRT is initiated.

Recommendations for initiation of treatment	**GR**
Haematological, cardiovascular, breast and prostatic assessment should be performed before the start of treatment.	A
Men with severe cardiovascular co-morbidity should be assessed by a cardiologist before TRT is initiated and there should be close cardiovascular monitoring during TRT.	C
Prostate health should be assessed by digital rectal examination (DRE) and PSA before the start of TRT.	A
In patients treated for localised prostate cancer and without signs of prostate cancer recurrence, testosterone therapy should not start before at least 1 year of follow-up.	C

Recommendations for monitoring	GR
The response to treatment (symptoms and testosterone serum levels) should be assessed 3, 6 and 12 months after the onset of treatment, and thereafter annually.	C
In men with an abnormal bone mineral density (BMD), BMD measurements should be repeated 6 and 12 months after the start of TRT and thereafter annually.	C
Haematocrit should be monitored at 3, 6 and 12 months and thereafter annually. The testosterone dosage should be decreased, or therapy discontinued if the haematocrit increases above normal levels.	C
Prostate health should be monitored by PSA testing at 3, 6 and 12 months and thereafter annually.	C
Routine screening of potential cardiovascular side effects is not indicated in men receiving TRT.	A

This short booklet text is based on the more comprehensive EAU guidelines (978-90-79754-83-0), available to all members of the European Association of Urology at their website, http://www.uroweb.org.

Hypogonadism in male patients defined as testosterone level decrease in serum associated with specific symptoms and/or signs (see the detailed description below) can be observed in case of abnormal changes in testes and/or pituitary such as Klinefelter syndrome, Kallmann syndrome and also in male patients with idiopathic, metabolic or iatrogenic disorders resulting in androgen deficiency. The Guidelines does not review all disorders conditioning development of testosterone deficiency (hypogonadism), but focusing on the options of the clinical conditions of hypogonadism generally observed in male patients. Definition: male hypogonadism is a clinical syndrome caused by androgen deficiency which may adversely affect multiple organ functions and quality of life (1). Androgens play a crucial role in the development and maintenance of male reproductive and sexual functions.Â This document presents the European Association of Urology (EAU) guidelines on the diagnosis and treatment of male hypogonadism. These guidelines aim to provide practical recommendations on how to deal with primary low testosterone and ageing-related decline in testosterone in male patients, as well as the treatment of testosterone disruption and deficiencies caused by other illnesses. 1.1 Reference 1. Nieschlag E, Behre HM (eds). remains in force. TUE Physician Guidelines Male Hypogonadism. 2. Organic secondary hypogonadism may be due to: a. Genetic abnormalities of pituitary and hypothalamus b. Pituitary or hypothalamic tumors c. Other anatomical (structural), destructive and infiltrative disorders of the pituitary.Â 2. Varicocele is not a cause of organic hypogonadism and not an acceptable diagnosis for TUE for testosterone treatment. 3. Andropause is not an acceptable diagnosis for TUE for hypogonadism. Â© WADA â€“ World Anti-Doping Program TUE Physician Guidelines â€“ Male Hypogonadism - Version 6.2 â€“ May 2019. Page 2 of 13. TUE Physician Guidelines Male Hypogonadism. TUE should only be approved for hypogonadism that has an organic etiology. 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.Â 3.4.1Male hypogonadism of testicular origin (primary hypogonadism). 3.4.4Male hypogonadism due to defects of androgen target organs. 4.DIAGNOSTIC EVALUATION. 4.1Clinical symptoms and laboratory testing. Background: Evidence regarding functional hypogonadism, previously referred to as 'late-onset' hypogonadism, has increased substantially during the last 10 year. Objective: To update the European Academy of Andrology (EAA) guidelines on functional hypogonadism. Methods: Expert group of academicians appointed by the EAA generated a series of consensus recommendations according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system. Results: The diagnosis of functional hypogonadism should be based on both the presence of clinical symptoms supported by repeatedly low morning fasting serum total testosterone (T) measured with a well-validated assay, after exclusion of organic causes of hypogonadism.