EAU GUIDELINES ON MALE HYPOGONADISM

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G.R. Dohle (Chair), S. Arver, C. Bettocchi, T.H. Jones, S. Kliesch

Introduction

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

Aetiology and classification

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

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

Table 1: Most common forms of primary hypogonadism

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

Table 2: Most common forms of secondary hypogonadism

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

Kallmann'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, haemo-chromatosis and vascular insufficiency or congenital
Pituitary adenomas	Hormone-secreting adenomas; hormone-inactive pituitary adenomas; metastases to the pituitary or pituitary stalk

Recommendation	LE	GR
Differentiate the two forms of hypogonadism (primary and secondary 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.	1b	B

Diagnostic evaluation

Table 3: 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

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

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

Hot flushes
Loss of vigour

Recommendations for diagnosis evaluation	**LE**	**GR**
Restrict the diagnosis of testosterone deficiency to men with persistent symptoms suggesting hypogonadism (Tables 3 and 4).	3	C
Measure testosterone in the morning before 11.00 hours, preferably 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: - 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: - 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.	2	B
Analyse LH serum levels to differentiate between primary and secondary forms of hypogonadism.	2	A

Recommendations for screening men with adult-onset hypogonadism	**LE**	**GR**
Screen for testosterone deficiency only in adult men with consistent and multiple signs and symptoms listed in Table 4.	3	C
Young men with testicular dysfunction and men older than 50 years of age with low testosterone should additionally be screened for osteoporosis.	2	B

Disease management

Table 5: Indications for testosterone treatment

Delayed puberty (constitutional or congenital forms (hypogonadotropic hypogonadism, Kallmann's 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 dysfunctions and hypogonadism
Type 2 diabetes mellitus with hypogonadism

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

Table 7: Testosterone preparations for replacement therapy

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

Transdermal testosterone	Gel; daily application	Steady-state testosterone level without fluctuation.	Risk of interpersonal transfer.
Subdermal depots	Subdermal implant every five to seven months	Long duration and constant serum testosterone level.	Risk of infection and extrusion of the implants.

Recommendations for testosterone replacement therapy	**LE**	**GR**
Fully inform the patient about expected benefits and side-effects of the treatment option. Select the preparation with a joint decision by an informed patient and the physician.	3	A
Use short-acting preparations rather than long-acting depot administration when starting the initial treatment, so that therapy can be adjusted or stopped in case of adverse side-effects.	3	B
Do not use testosterone therapy in patients with male infertility and active child wish since it may suppress spermatogenesis.	1b	A
Only use human chorionic gonadotropin treatment for hypogonadotrophic hypogonadal patients with simultaneous fertility treatment.	1b	B
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.	2	A

Recommendations on risks factors in testosterone treatment	LE	GR
Perform haematological, cardiovascular, breast and prostatic assessment before the start of treatment.	1a	A
Monitor testosterone, haematocrit, haemoglobin and prostate-specific antigen (PSA) during testosterone treatment.	3	A
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.	3	B
Assess for cardiovascular risk factors before commencing testosterone treatment 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 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.	1b	A

Recommendations for follow-up	LE	GR
Assess the response to testosterone treatment at three, six and twelve months after the onset of treatment, and thereafter annually.	4	C
Monitor testosterone, 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 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.	4	C
Assess men with cardiovascular diseases for cardiovascular symptoms before testosterone treatment is initiated and continue close clinical assessment during treatment.	1b	A

This short booklet text is based on the more comprehensive EAU Guidelines (978-90-79754-91-5), available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines.