

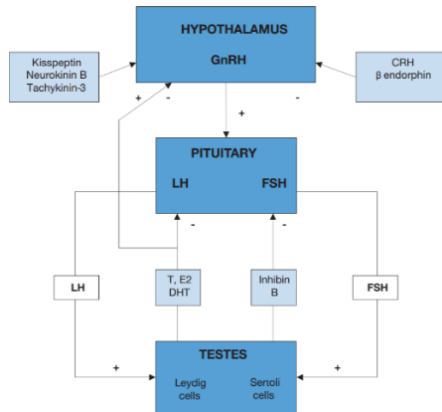
EPIDEMIOLOGY and PREVALENCE:

Male hypogonadism is characterized by decreased production of androgens and/or impaired sperm production caused by poor testicular function or as a result of inadequate stimulation of the testes by the hypothalamic-pituitary axis.

The prevalence increases with age and the major causes are central obesity, co-morbidity and overall poor health.

Hypogonadism may adversely affect multiple organ functions and quality of life (QoL).

PHYSIOLOGY OF TESTOSTERONE PRODUCTION:



In healthy men, 60-70% of circulating testosterone is bound to the high-affinity sex-hormone-binding globulin (SHBG). The remaining circulating testosterone ('bioavailable' testosterone) binds lower affinity, high-capacity binding protein sites, and only 1-2% of testosterone remains nonprotein bound.

Many factors are associated with an increase or reduction of SHBG circulating levels.

GnRH = gonadotropin releasing hormone; LH = luteinising hormone; FSH = follicle-stimulating hormone; T = testosterone; E2 = 7-β-estradiol; DHT = dehydroepiandrosterone; CRH = corticotrophin releasing hormone.

LATE-ONSET HYPOGONADISM (LOH)

Clinical condition in ageing men (usually > 40 years) frequently diagnosed in the absence of an identifiable classical causes and often associated with co-morbidities.

DIAGNOSTIC EVALUATION

Recommendations	Strength rating
Screen for late onset hypogonadism (LOH) (including in T2DM) only in symptomatic men.	Strong
Do not use structured interviews and self-reported questionnaires for systematic screening for LOH as they have low specificity.	Strong

SPECIFIC SYMPTOMS ASSOCIATED WITH LOH:

	Sexual symptoms	Physical symptoms	Psychological symptoms
More specific	- Reduced libido - Erectile dysfunction - Decreased spontaneous/morning erections	- Decreased vigorous activity - Difficulty walking >1 km - Decreased bending	- Low mood/mood deflection - Decreased motivation - Fatigue
Less specific	- Reduced frequency of sexual intercourse - Reduced frequency of masturbation - Delayed ejaculation	- Hot flushes - Decreased energy - Decreased physical strength/function/activity	- Concentration or mnemonic difficulties - Sleep disturbances

TREATMENT:

Patients with symptomatic hypogonadism without specific contraindications suitable candidates to receive testosterone therapy.

Absolute contraindications: Locally advanced or metastatic prostate cancer, male breast cancer, Men with an active desire to have children, Haematocrit > 54%, Uncontrolled congestive heart failure.

Summary of evidence
Testosterone therapy can improve milder forms of ED and libido in hypogonadal men.
Testosterone therapy can improve other sexual symptoms, including intercourse frequency, orgasm and overall satisfaction.
Testosterone therapy can similarly increase lean mass, and reduce fat mass, and improves insulin resistance.
Testosterone therapy may improve weight, waist circumference and lipid profile, but findings are not unique.
Testosterone therapy can improve milder depressive symptoms in hypogonadal men.
Testosterone therapy can improve bone mineral density, but information related to fracture risk is lacking.

CHOICE OF TREATMENT:

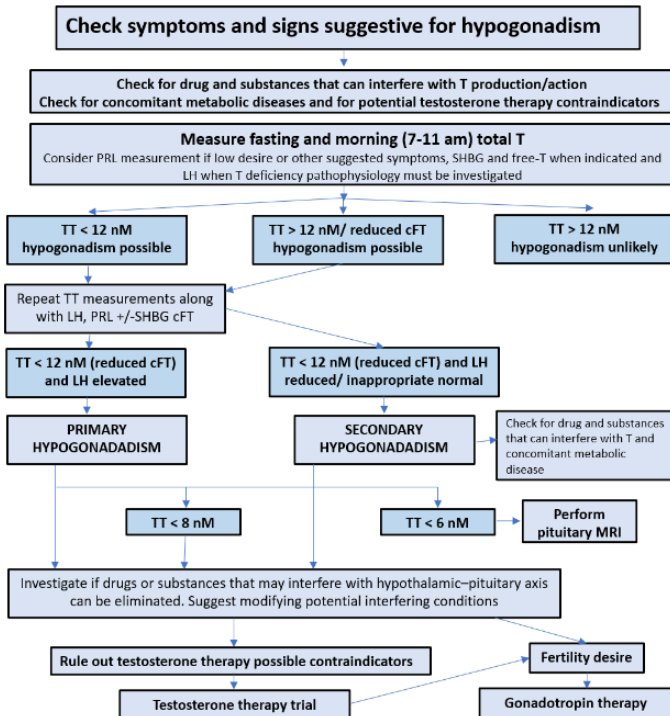
Summary of evidence
Weight loss obtained through a low-calorie diet and regular physical activity result in a small improvement in testosterone levels.
Testosterone gels and long-acting injectable TU represent T preparations with the best safety profile.
Gonadotropins treatment can be used to restore fertility in men with secondary hypogonadism.

Recommendations	Strength rating
Treat, when indicated, organic causes of hypogonadism (e.g., pituitary masses, hyperprolactinemia, etc).	Strong
Improve lifestyle and reduce weight (e.g., obesity); withdraw, when possible, concomitant drugs that can impair testosterone production; treat co-morbidity before starting testosterone therapy.	Weak
Fully inform patients about expected benefits and adverse effects of any treatment option. Select the testosterone preparation in a joint decision process, only with fully informed patients.	Strong
The aim of testosterone therapy is to restore serum testosterone concentration to the average normal range for young men.	Weak
Use testosterone gels rather than long-acting depot administration when starting initial treatment, so that therapy can be adjusted or stopped in the case of treatment-related adverse effects.	Weak

SAFETY AND FOLLOW UP IN HYPOGONADISM MANAGEMENT:

Parameters	Year 1 of treatment			After year 1 of treatment	
	Baseline	3 months	6/12 months	Annually	18-24 months
Clinical					
Symptoms	X	X	X	X	
Body Mass Index					
Waist circumference	X	X	X	X	
Digital rectal examination	X	X	X	X	
Blood pressure	X	X	X	X	
Biochemistry					
PSA (ng/mL)	X	X	X	X	
Haematocrit (%)	X	X	X	X	
Testosterone	X	X	X	X	
Lipid and glycaemic profile	X	X	X	X	
Instrumental					
DEXA	X				X

Recommendations	Strength rating
Fully counsel symptomatic hypogonadal men who have been surgically treated for localised prostate cancer (PCa) and who are currently without evidence of active disease considering testosterone therapy, emphasising the benefits and lack of sufficient safety data on long-term follow-up.	Weak
Restrict treatment to patients with a low risk for recurrent PCa (i.e., pre-operative PSA < 10 ng/mL; Gleason score < 7 (International Society for Urological Pathology grade 1); cT1-2a) and treatment should start after at least 1 year follow-up with PSA level < 0.01 ng/mL.	Weak
Safety data on the use of testosterone therapy in men treated for breast cancer are unknown.	Strong
Assess for cardiovascular risk factors before commencing testosterone therapy.	Strong
Assess men with known cardiovascular disease (CVD) for cardiovascular symptoms before testosterone therapy and with close clinical assessment and evaluation during treatment.	Strong
Treat men with hypogonadism and pre-existing CVD, venous-thromboembolism or chronic cardiac failure, who require testosterone therapy with caution, by careful clinical monitoring and regular measurement of haematocrit (not exceeding 54%) and testosterone levels.	Weak
Exclude a family history of venous-thromboembolism before starting testosterone therapy.	Strong
Monitor testosterone, haematocrit at 3, 6 and 12 months after testosterone therapy initiation, and thereafter annually. A haematocrit > 54% should require testosterone therapy withdrawal and phlebotomy. Re-introduce testosterone therapy at a lower dose once the haematocrit has normalised and consider switching to topical testosterone preparations.	Strong



TT = total testosterone; cFT = calculated free testosterone; PRL = prolactin; SHBG = sex hormone-binding globulin; LH = luteinising hormone; MRI = Magnetic resonance imaging.