

MORE THAN ONE REASON TO TAKE ANOTHER LOOK AT PHYSIOLOGICAL TESTOSTERONE



Testosterone is much more than a mediator of androgenesis and physiology in males. Testosterone interacts with a variety of body systems and a normal physiological level of testosterone plays a role in maintenance of the skeletal, nervous, cardiovascular and genitourinary systems.^{1,2} Increasing age is associated with a relatively constant decline in serum testosterone, at a rate of 1% to 2% per year.^{3,4} For some the age-related decline in testosterone is associated with a cluster of signs and symptoms that resembles those observed in men with classical hypogonadism.² So let's explore why men need physiological levels of testosterone and where low testosterone may be hiding in your practice.



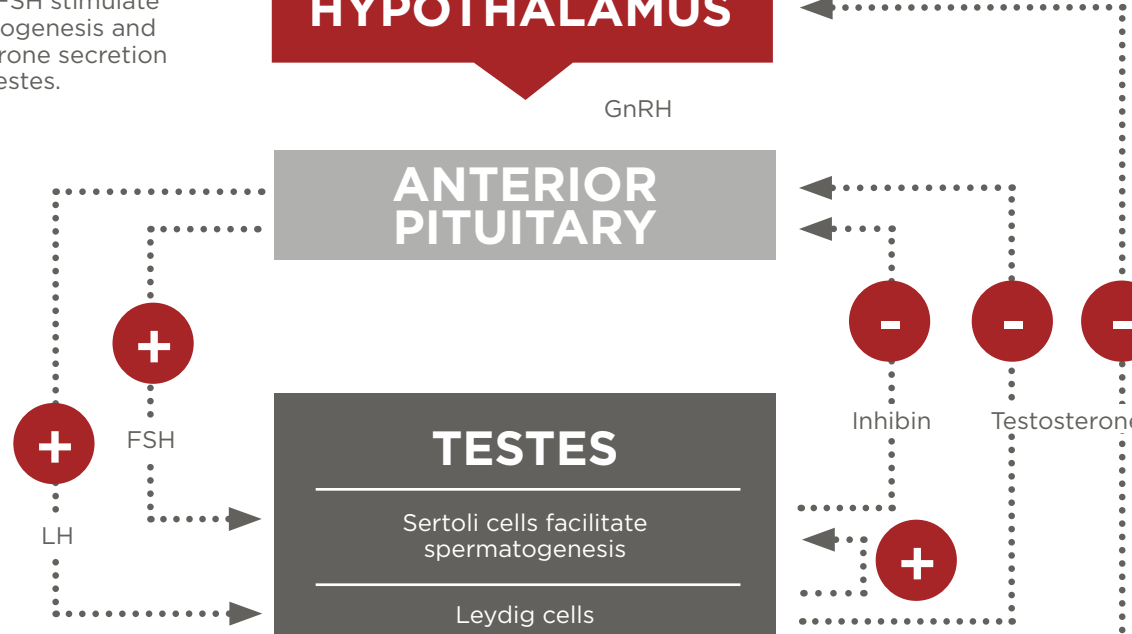
Recapping the basics

In males, testosterone is produced mostly in the testes.¹ Androgen synthesis is regulated by gonadotrophin-releasing hormone (GnRH) secretion from the hypothalamus which stimulates luteinising hormone (LH) secretion from the anterior pituitary. LH stimulates the testicular Leydig cells to produce testosterone.⁵ Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), although a lesser fraction is albumin-bound and a small proportion exists as free testosterone. With age, serum free testosterone decreases to a greater extent than total testosterone because SHBG concentrations are higher in older men than younger men.⁶

The interaction of testosterone with other body systems is wide-ranging and complex. Testosterone not only interacts with androgen receptors in end organs such as the bones, brain, muscles, testes and prostate, but through its conversion to oestradiol, it may influence systems that interact with estrogen receptors as well.⁷

Pituitary hormone effects:

LH and FSH stimulate spermatogenesis and testosterone secretion by the testes.



Testes hormone effects:

Testosterone and inhibin inhibit the secretion of GnRH by the hypothalamus and LH and FSH by the pituitary.

Testosterone has multifaceted physiological functions and therefore low testosterone (low T) can adversely affect the function of multiple organ systems.⁸ Testosterone deficiency (TD) is characterised by a reduced production of testosterone and signs and symptoms associated with unequivocally low testosterone levels.⁸ Patients with TD present with a wide variety of distressing symptoms, which are associated with poor quality of life.⁸

A clinical diagnosis of TD requires the measurement of low testosterone blood levels and signs and symptoms of TD.⁹ Generally, the most easily recognised clinical signs of TD in older men are decreased muscle mass and strength, osteoporosis and an increase in central adiposity. The sexual symptoms that best predict low testosterone are erectile dysfunction (ED), loss of morning erections and low libido.¹⁰

International guidelines advocate a wide variety of populations where testosterone screening may be warranted. The US Endocrine Society and British Society for Sexual Medicine recommend that men should be considered at high-risk of TD if diagnosed with any of the following conditions:⁹

- ED, loss of spontaneous erections or loss of sexual desire
- Type 2 diabetes mellitus (T2DM)
- Metabolic syndrome (MetS)
- Osteoporosis
- Long-term opioid use.

Let's take a look at why some of these conditions are on their radar.



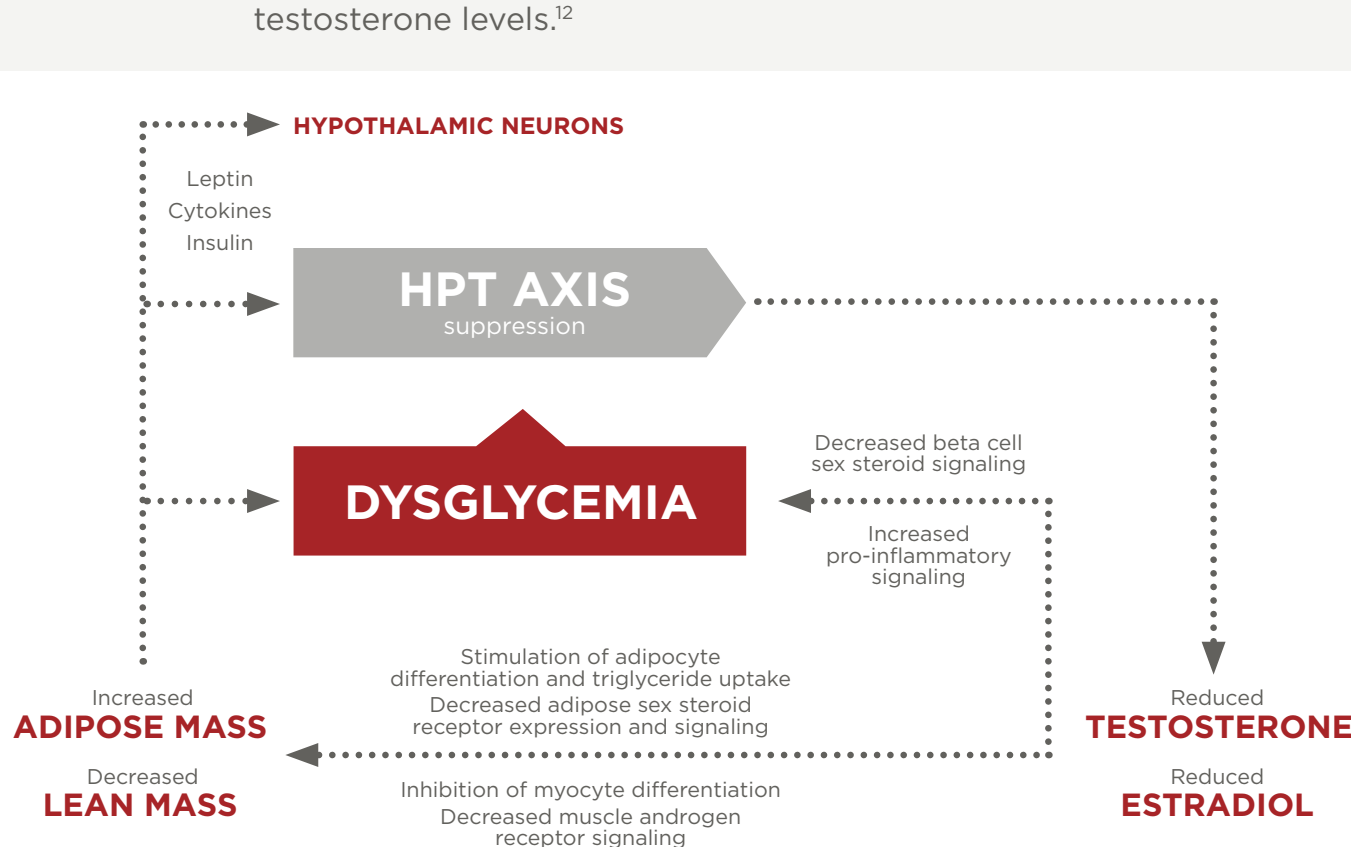
Testosterone and sexual health

There is a well-established, inverse relationship between sexual symptoms and testosterone level. Specifically, poor morning erection, low sexual desire and ED are associated with testosterone levels lower than physiological normal levels.¹⁰ In fact, it is a patient's desire to maintain a satisfactory sexual response that is a major driver for hypogonadal patients to seek medical advice.⁸

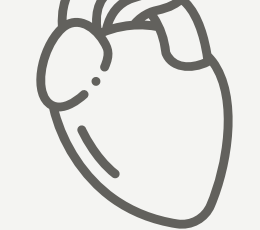


Testosterone and fat and lean muscle mass

Obesity is the most important risk factor for TD.^{11,12} Obesity is associated with reduced free testosterone due to adiposity-associated gonadal axis suppression while TD promotes adipose accumulation and decreased myogenesis.¹¹ Testosterone is required for the maintenance of lean muscle mass and size and strength, while estradiol (also influenced by testosterone levels)⁷ is required to prevent increases in fat mass.¹³ Obese men with sub-physiological testosterone lose both fat and lean mass during diet.¹¹ However, testosterone treatment to normalise testosterone levels in these obese men has been shown to decrease total fat mass and adipose tissue while retaining total and appendicular lean mass.¹¹ Testosterone treatment induced a shift to almost exclusive fat mass loss in these patients.¹¹ Where obesity and dysglycaemia co-exist (diabesity), a bidirectional model is proposed where diabesity may accelerate age-related decline in testosterone, associated with increased adipose mass and decreased lean mass.¹² Dysglycaemia in turn, suppresses the HPT axis, reducing testosterone levels.¹²



Adapted from Grossman M, et al. 2019.¹²



Testosterone and cardiovascular (CV) health

Physiologic levels of testosterone are beneficial to the CV system and guidelines are recognising the potential cardioprotective role of testosterone.^{3,8,13} Low testosterone is now considered a risk factor for CV disease and TD is associated with an increased in CV disease events, such as myocardial infarction and mortality.^{3,8,14,15}

Data from observational and epidemiological studies demonstrate an association between low testosterone and increased risk for CV disease, including atherosclerosis, coronary artery disease, and other major adverse cardiovascular events.¹⁶

A longitudinal analysis from the population-based Health in Men study, in a cohort of older Western Australian men, provided the first evidence to suggest that levels of circulating testosterone outside of the normal physiologic range is associated with all-cause mortality and that higher levels of dihydrotestosterone (DHT) lowers CV risk.¹⁵ The risk of stroke was approximately two times greater for men with testosterone or DHT in the lowest quartile compared with men with highest quartile levels, independent of age, conventional CV risk factors and the presence of concurrent comorbidities.¹⁵

Low testosterone is also associated with an unfavourable metabolic profile, and in turn, CV risk.³ A cross-sectional and longitudinal community-based study of 1,500 older men found that lower testosterone was associated with key risk factors for cardiovascular disease, including higher body mass index, greater waist circumference, the presence of diabetes mellitus and hypertension, and lower high-density lipoprotein cholesterol.¹⁷

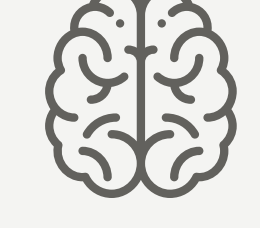


Testosterone and bone health

Testosterone exerts its most important effects on bone through its aromatisation to estradiol.¹ Low levels of testosterone and estradiol are associated with increased bone loss and risk of fractures in elderly men.¹⁸

Androgen receptors are found in chondrocytes in the growth plates of bones and osteoblasts and osteocytes, and testosterone has been shown to decrease bone resorption and increase bone mineral density and may interact with vitamin D.¹ Because of this osteopenia, osteoporosis and fracture prevalence rates are all higher in men with TD.¹⁹

Data from the Testosterone Trials showed one year of testosterone treatment, in older men with low testosterone, elevated testosterone to mid-normal levels, and in doing so, increased bone mineral density and estimates of bone strength in the spine and hip.²⁰



Testosterone and mental health

Testosterone is a neuroactive steroid that can influence mood, with normal testosterone levels associated with positive markers of mood, including energy and wellbeing compared with low testosterone levels.¹ Meta-analysis of 27 RCTs shows testosterone treatment improves symptoms of depression in men independent of initial testosterone level, age, and depression status.²¹

In a self-reported survey of men aged 21 to 66 years with perceived low testosterone, the most frequently reported benefit of taking prescription testosterone was improved energy levels related to both fatigue and social drive/motivation.²²

Internationally, endocrinological associations are considering the impact of testosterone beyond patients presenting only with sexual dysfunction and low energy⁵

The American Association for Clinical Endocrinologists, the American College of Endocrinology and the British Society for Sexual Medicine recommend testosterone measurement in all men with type 2 diabetes, a total body mass index >30 kg/m² or a waist circumference >102 cm.^{5,8}

So, testosterone is a multifaceted hormone that, at normal physiological levels, supports many functions of the body, and any deviation from these normal levels can manifest in a wide range of health issues.



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