

# Male hypogonadism: pathogenesis, diagnosis, and management

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Organic male hypogonadism due to irreversible hypothalamic–pituitary–testicular (HPT) pathology is easily diagnosed and treated with testosterone-replacement therapy. However, controversy surrounds the global practice of prescribing testosterone to symptomatic men with low testosterone and non-gonadal factors reducing health status, such as obesity, type 2 diabetes, and ageing (ie, functional hypogonadism), but without identifiable HPT axis pathology. Health optimisation remains the gold-standard management strategy. Nevertheless, in the last decade large clinical trials and an individual patient data meta-analysis of smaller clinical trials confirmed that testosterone therapy induces modest, yet statistically significant, improvements in sexual function without increasing short-term to medium-term cardiovascular or prostate cancer risks in men with functional hypogonadism. Although testosterone improves bone mineral density and insulin sensitivity in these men, trials from the last decade suggest insufficient evidence to determine the safety and effectiveness of use of this hormone for the prevention of fractures or type 2 diabetes. This Review discusses the pathogenesis and diagnosis of male hypogonadism and appraises the evidence underpinning the management of this condition.

## Introduction

The hypothalamic–pituitary–testicular (HPT) axis orchestrates the testicular synthesis of testosterone and spermatogenesis in men.<sup>1</sup> Defects in any component of the HPT axis can impair testicular function. Male hypogonadism is a clinical syndrome of impaired androgen production from the testes that is usually associated with impaired spermatogenesis and subfertility. Male hypogonadism caused by an intrinsic and often irreversible HPT pathology is called organic (also termed classical) hypogonadism. Organic hypogonadism has a straightforward, established diagnostic and treatment pathway.

Testosterone prescriptions have increased globally without a clear increase in the number of men with organic hypogonadism due to a possible rise in testosterone treatment in men with functional hypogonadism.<sup>2,3</sup> Functional hypogonadism is defined as the co-existence of clinical features consistent with androgen deficiency and reduced serum testosterone concentration in the absence of an identifiable HPT axis pathology.<sup>4,5</sup> Functional hypogonadism can be reversed when the external factors (eg, non-specific HPT axis suppression due to chronic disease, such as obesity) are corrected, leading some clinicians to question the validity of the condition's existence. Although the safety and efficacy of testosterone treatment in men with organic hypogonadism is undisputed, controversy has long surrounded the benefits and safety of testosterone treatment in men with functional hypogonadism, which is reflected in US Food and Drug Administration (FDA) guidance.<sup>6</sup> Over the last 2 years, evidence has emerged directly addressing the benefits and risks of testosterone treatment in men with functional hypogonadism, at least in the medium term. This Review draws upon authors' experience from diverse health-care settings, to summarise our understanding of pathophysiology, presentation, diagnostic criteria, and management of male hypogonadism. Furthermore, a dedicated section

on diagnostic and management controversies aims to highlight areas of uncertainty and provides a balanced approach for clinicians to support affected men.

## Physiology of HPT axis

Hypothalamic co-secreting kisspeptin, neurokinin B, and dynorphin A (KNDy) neurons stimulate pulsatile gonadotropin-releasing hormone (GnRH) release from the median eminence to stimulate pituitary secretion of luteinising hormone (LH) and follicle-stimulating hormone (FSH; figure 1).<sup>7</sup> Circulating sex hormone concentrations, environmental factors, and metabolic cues (including leptin) directly or indirectly regulate hypothalamic GnRH secretion.<sup>8</sup>

FSH stimulates testicular Sertoli cell function. These cells promote spermatogenesis, with each cell able to support the maturation of 2–4 germ cells on average.<sup>9</sup> Sertoli cells also secrete peptide hormones: anti-Müllerian hormone (AMH; predominating from immature Sertoli cells) and inhibin B (from mature cells), with the latter suppressing FSH secretion by pituitary gonadotroph cells.<sup>10</sup> LH primarily acts to stimulate Leydig cell steroidogenesis, principally testosterone production.<sup>11</sup> Leydig cells also secrete insulin-like peptide 3 (INSL3) in a gonadotropin-independent manner.<sup>12</sup> Intratesticular concentrations of testosterone are 25-times to 125-times higher than in the peripheral circulation.<sup>13</sup> Within the circulation, only 2% of the released endocrine testosterone is entirely free (non-protein bound). However, testosterone binds to albumin with low affinity whereas it binds to sex-hormone binding globulin (SHBG) with high affinity and therefore, all non-SHBG-bound testosterone (free and albumin-bound) might be bioactive.<sup>8</sup>

Approximately 5–10% of testosterone is converted by the 5- $\alpha$  reductase enzyme to dihydrotestosterone (DHT).<sup>14</sup> Testosterone and DHT bind to a single androgen receptor (AR) that is expressed in numerous sites including

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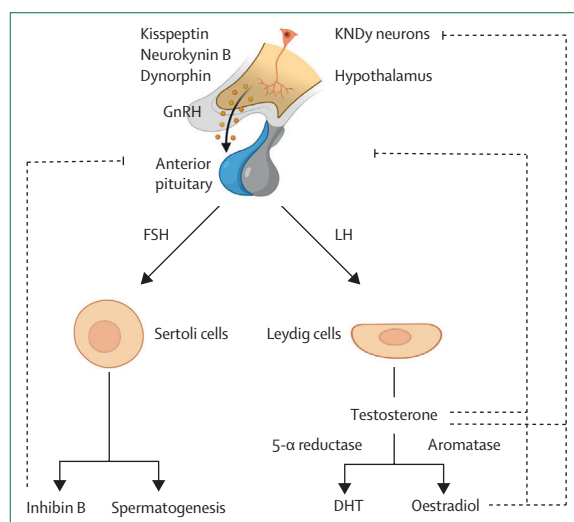
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**Figure 1: Hypothalamic-pituitary-testicular axis**

DHT= dihydrotestosterone. FSH=follicle-stimulating hormone. GnRH=gonadotropin-releasing hormone. KNDy=kisspeptin, neurokinin B, and dynorphin A. LH=luteinising hormone. ---=inhibition. Figure created with BioRender.com.

the reproductive system, bones, muscles, haemopoietic system, and the brain, but DHT binds more avidly and disassociates slower from the receptor than testosterone does.<sup>15</sup> Expression of 5 $\alpha$ -reductase is highest in the prostate gland, skin, and liver. Local DHT production is crucial for prostate growth. About 0.1% of circulating testosterone is converted to oestradiol by aromatase enzyme in many sites<sup>14</sup> including adipose tissue, testes, muscle, bone, and the brain. Although the systemic concentration is low, local tissue concentrations in those sites could be high. Androgens and oestradiol inhibit pituitary LH secretion both directly and upstream via central hypothalamic regulators, such as kisspeptin neurons.<sup>16</sup>

Regulation of the HPT axis and effects of androgens vary during different stages of life. In early foetal life, androgens stimulate the development of the male internal and external genitalia.<sup>17</sup> Placental human chorionic gonadotropin stimulates the testes in early foetal life. Later in gestation, testicular androgen production is also driven by the foetal hypothalamic-pituitary unit. Along with INSL3 and AMH, androgens are responsible for the final (inguinoscrotal) phase of testicular descent and the growth of the penis.<sup>17,18</sup> Gonadotropin and androgen concentrations increase in the first postnatal week for a duration of 3–6 months, which is called mini puberty and might play a key role in programming fertility potential for adult life by driving the proliferation of the Sertoli cells and elongation of the seminiferous tubules that constitute more than 80% of the testicular volume. However, there are few germ cells and Leydig cells in the neonatal seminiferous tubules as the AR is not yet expressed in the testes. This neonatal proliferation of Sertoli cells is clinically important because there is a tight correlation between the number of Sertoli cells and germ cells (and thus

spermatogenesis) in the adult man.<sup>19</sup> Indeed, the peak testosterone concentration reached in mini puberty correlates closely with the sperm count reached two decades later in young adult life.<sup>20</sup> Studies have shown that Neonatal blockade of mini puberty in juvenile macaques is associated with reduced testicular volume and sperm count in adults.<sup>21</sup> Thereafter, the HPT axis enters a quiescent period until puberty, although Sertoli cells continue to secrete inhibin B and AMH.

Puberty is initiated by the reactivation of the HPT axis with the onset of pulsatile release of GnRH triggered by hypothalamic KNDy neuronal activation.<sup>22</sup> The onset of puberty is manifested by testicular enlargement due to a second proliferation of Sertoli cells and increased seminiferous tubule diameter and volume.<sup>23,24</sup> Further testicular enlargement occurs with the proliferation and differentiation of germ cells. This stage is followed by testicular androgen production resulting in the development of secondary sexual characteristics that include deepening of voice, male-type facial and body hair growth, masculine body habitus, prostatic growth, and growth spurt. A relative excess of oestrogens compared with androgens can occur during puberty resulting in physiological gynaecomastia that is usually transient and self-limiting.<sup>25</sup> In adult life, the continued function of the HPT axis is necessary for the maintenance of spermatogenesis and androgen production. Spermatogenesis is an intricate process, which depends on multiple stimuli acting on Sertoli cells. Testosterone binds to androgen receptors on Sertoli cells facilitated by high intra-testicular paracrine testosterone concentration.<sup>13</sup>

Testosterone promotes male sexual function and is required for normal sexual desire and spontaneous erections. Androgens increase bone density and strength (directly on cortical bone and indirectly via oestrogen on trabecular bone), increase lean mass and muscle growth, and reduce fat mass.<sup>26</sup> Testosterone also promotes erythropoiesis.<sup>27</sup> Additionally, androgens have complex effects on cardiovascular health. For example, testosterone predominantly has acute non-genomic vasodilatory effects in the short term, but chronic genomic androgen action causes vasoconstriction.<sup>28</sup> Testosterone might also have anti-arrhythmic properties via shortening the QT interval,<sup>29</sup> and might protect the myocardium from ischaemic injury.<sup>30</sup> Some of the effects of testosterone in men are indirect through aromatisation to oestradiol. For example, epiphyseal fusion and anabolic effects on the bone are predominantly through oestradiol, which also plays a major supporting role in regulating male sexual function, fat mass, glucose metabolism, and HPT axis negative feedback.<sup>26,31</sup>

## Pathophysiology and classification of male hypogonadism

### Organic hypogonadism

Hypogonadism due to testicular pathology (primary hypogonadism) is characterised by gonadotropin

concentration elevation due to reduced or absent negative feedback inhibition on the hypothalamus and pituitary. Klinefelter's syndrome, treatment for testicular cancer, systemic chemotherapy, and cryptorchidism are common causes of primary hypogonadism (table 1).

Impaired testicular function due to deficient gonadotropin stimulation, either caused by a defect in the anterior pituitary or reduced GnRH secretion from the hypothalamus, is called hypogonadotropic, central, or secondary hypogonadism.<sup>17</sup> Gonadotropin concentrations are either low or inappropriately normal in the presence of reduced testicular function.<sup>1</sup> Congenital hypogonadotropic hypogonadism might be associated with other phenotypic defects, most commonly anosmia (Kallmann's syndrome), or with wider congenital hypopituitarism (ie, combined pituitary hormone deficiency; table 1). Acquired causes of organic hypogonadotropic hypogonadism include pituitary macroadenomas, cranial irradiation and surgery, hyperprolactinaemia, and traumatic brain injury.

### Functional hypogonadism and late-onset hypogonadism

Functional hypogonadism is sometimes referred to as eugonadal sick syndrome.<sup>4,5</sup> When functional hypogonadism occurs in older men it is also referred to as late-onset hypogonadism, which has an age-dependent increase in prevalence due to the accumulation of age-related comorbidities causing functional hypogonadism in older men.<sup>32</sup> However, functional hypogonadism can be seen even in adolescents and young men with a wide variety of conditions with obesity being the most common (table 1).<sup>33</sup> The other extreme of energy balance (ie, severe energy deficit, such as relative energy deficiency in sports) can also cause functional hypogonadism.<sup>34,35</sup> Long-term exposure to opioids, androgen abuse, and severe illness are other possibly reversible causes of hypogonadotropic hypogonadism that might be viewed as functional.

Following COVID-19, some men are reported to have low testosterone improving over several months with low or normal gonadotropin concentration suggesting functional hypogonadism<sup>36</sup> in addition to GnRH neuronal death.<sup>37</sup> Primary testicular involvement is seen in some patients.<sup>38</sup> However, temporary suppression of the HPT axis is quite common after any severe illness and whether post-COVID-19 male hypogonadism is a specific entity remains unproven.

Several population studies have observed a decline in total testosterone with ageing.<sup>39–42</sup> Harmonised data from large population studies reported that the 2.5th centile of total testosterone concentration decreases with ageing.<sup>43</sup> For most men, this decline did not result in testosterone concentrations lower than the lower limit of normal for young healthy men that is used for the diagnosis of male hypogonadism.<sup>43</sup> SHBG increases with age, so in middle-aged and older men the decline of free testosterone with age is steeper than the decline of total testosterone.<sup>39–42</sup> For example, a cross-sectional analysis of the European Male Ageing Study<sup>39</sup> showed an 8.6% (1.5 nmol/L) drop in total testosterone across four decades (0.4% annual decline). In contrast, the free testosterone drop was 33.1% (116 pmol/L, a 1.3% decrease per annum). In addition, there is evidence of Leydig cell dysfunction with increased LH and decreased testosterone being more noticeable in the 8th and 9th decades of life.<sup>44</sup> Attenuation of LH pulse amplitude has also been observed in older men.<sup>45</sup> In most of the older men who experience some Leydig cell dysfunction, testosterone is maintained by the stimulation of elevated LH suggesting a compensated primary hypogonadism.<sup>46</sup>

Obesity and co-morbidities seem to account for much of the decreasing serum testosterone in older men.<sup>39,41,47</sup> Low total testosterone in men with obesity is sometimes

	Hypogonadotropic hypogonadism	Hypergonadotropic hypogonadism	Mixed aetiology
Congenital	Kallmann syndrome; normosmic congenital hypogonadotropic hypogonadism; syndromes associated with congenital hypogonadotropic hypogonadism (CHARGE syndrome, Waardenburg syndrome, congenital adrenal hypoplasia, Hartsfield syndrome, and 4H syndrome); and congenital combined pituitary hormone deficiency including septo-optic dysplasia	Klinefelter's syndrome and its variants; Down syndrome; Y-chromosome microdeletion; myotonic dystrophy; androgen synthetic defects; bilateral cryptorchidism; and bilateral congenital anorchia (vanishing testes syndrome)	Congenital adrenal hyperplasia; Prader-Willi syndrome
Acquired (organic)	Sellar masses (pituitary adenomas, craniopharyngiomas, meningiomas, gliomas, and pituitary metastases); traumatic brain injury; iatrogenic (surgery and radiotherapy); hyperprolactinaemia; glucocorticoid excess; inflammatory (primary lymphocytic hypophysitis, IgG-4-mediated hypophysitis, and immune check-point therapy associated hypophysitis); iron deposition (eg, hereditary haemochromatosis, transfusion-dependent); infiltrative lesions (sarcoidosis, Langerhans cell histiocytosis); and pituitary apoplexy	Viral orchitis (eg, mumps orchitis, COVID-19); bilateral orchidectomy; testicular radiation; systemic chemotherapy (alkylating agents); and bilateral testicular torsion or trauma	NA
Acquired (functional)	Obesity; type 2 diabetes; opioid use; exogenous sex steroids including androgen abuse; severe calorie restriction; excessive exercise; and androgen deprivation therapy (eg, GnRH agonists or antagonists)	Age-related or medications (eg, ketoconazole or abariterone)	Chronic illnesses (eg, HIV infection, inflammatory bowel disease, coeliac disease, sickle cell disease, and post-COVID-19 condition); organ failure (chronic kidney disease, cirrhosis, heart failure, and respiratory failure); and excessive alcohol use

GnRH=Gonadotropin-releasing hormone. H4=hypomyelination, hypodontia, and hypogonadotropic hypogonadism.

**Table 1: Aetiological classification of male hypogonadism**

attributable to an obesity-induced decrease in SHBG.<sup>39</sup> Men with low total testosterone solely due to low SHBG are eugonadal, and their free serum testosterone concentration is normal— a scenario referred to as pseudo-hypogonadism.<sup>5</sup> However, studies have confirmed the association of low free testosterone concentration with class 3 obesity (BMI >40 kg/m<sup>2</sup>).<sup>48</sup> Gonadotropin concentrations remain low or inappropriately normal, suggesting suppression.<sup>48</sup> The exact mechanism of this hypothalamic–pituitary suppression is not fully identified. Central resistance to leptin and suppression of kisspeptin production from the KNDy neurons in the arcuate nucleus of the hypothalamus due to dysregulation of insulin, adiponectin, and gut hormone signalling are the postulated mechanisms for this suppression.<sup>32,48</sup> The effect of increased pro-inflammatory cytokines, such as tumour necrosis factor- $\alpha$ , interleukin (IL)-6, and IL-1 $\beta$  on the hypothalamus is another potential mechanism. The postulated excess oestradiol production from adipose tissue causing negative feedback on the HPT axis seems unrelated owing to the evidence that serum oestradiol is not higher in men with obesity.<sup>49</sup>

#### Association of male hypogonadism with cardiovascular risk factors and outcomes

Men older than 40 years with low testosterone have a higher prevalence of metabolic syndrome,<sup>50</sup> type 2 diabetes,<sup>51</sup> and dyslipidaemia<sup>52</sup> possibly through a bi-directional association. An individual participant data meta-analysis published in 2024, reported increased all-cause mortality and cardiovascular mortality in men with low testosterone in an age-adjusted analysis.<sup>53</sup> However, the association lost significance in a fully adjusted model except for testosterone concentration of less than 7.4 nmol/L for all-cause mortality and concentration of less than 5.3 nmol/L for cardiovascular mortality.<sup>53</sup> This study did not observe an association between cardiovascular events and low testosterone. The authors reported that LH of more than 10 IU/L was independently associated with all-cause mortality.

Adverse metabolic profiles including metabolic syndrome, insulin resistance, and atherogenic lipid profile have been reported in men with organic hypogonadism, such as Klinefelter's syndrome<sup>54,55</sup> and congenital hypogonadotropic hypogonadism.<sup>56</sup> Men with Klinefelter's syndrome have an increased risk of arterial and venous thrombosis and death due to thrombosis,<sup>57</sup> which is possibly related to excess X-linked gene dosage. There is insufficient evidence on cardiovascular morbidity and mortality in organic hypogonadism of other aetiologies.

#### Epidemiology

Defining the prevalence of male hypogonadism is challenging and an overall estimation of organic causes of male hypogonadism is unavailable in existing literature. Klinefelter's syndrome is the most common cause of primary hypogonadism and is reported in 1:660 male

births according to data from newborn screening.<sup>58</sup> All other non-iatrogenic causes of primary hypogonadism have a prevalence that is possibly less than 1:5000 population and are considered rare.<sup>59</sup> Old age, treatment for testicular cancer, and systemic chemotherapy are common causes of primary hypogonadism.<sup>59</sup> Primary hypogonadism has a rising prevalence (up to 5–10%) in men aged 65–70 years and older due to age-related Leydig cell dysfunction and these men having persistent compensated hypogonadism.<sup>39,41</sup>

Isolated and syndromic forms of congenital hypogonadotropic hypogonadism are also rare, with an approximate incidence of 1:30000 of male births, based on information derived from a search of Finnish secondary care databases.<sup>60</sup> Out of the acquired causes of hypogonadotropic hypogonadism, the estimated prevalence of hypogonadism due to non-functioning sellar masses including pituitary adenoma is 1:10000. The incidence of hypogonadism due to traumatic brain injury is estimated at 7:10000 patient-years, with approximately 10% of men developing hypogonadism after mild traumatic brain injury and 70% of men developing hypogonadism after moderate-severe traumatic brain injury, especially with military blast trauma.<sup>59</sup> Androgen deprivation therapy for prostate cancer might cause intentional secondary or primary hypogonadism depending on the agent used (GnRH analogues or testosterone synthesis inhibitors) and might affect as much as 2% of older men.

Androgen abuse and chronic opioid use are growing causes of reversible male hypogonadism worldwide. The lifetime prevalence of androgen abuse has been reported as 5% among men.<sup>61</sup> Literature from the last 5 years suggest that eugonadism returns between 3 and 12 months after cessation of androgen abuse in most men, but the upper time limit for recovery has not been determined.<sup>62–64</sup> There is wide heterogeneity in the reported prevalence of hypogonadism in men with chronic opioid use (28–86%) due to variations in the drug used, dose, duration, and patient factors.<sup>65</sup>

Population studies have reported highly variable rates of hypogonadism in older men, based entirely upon serum testosterone concentrations, and have not differentiated between organic and functional forms. Prevalence of low testosterone concentration (relative to reference ranges derived from healthy young men) among men aged 70–80 years is as high as 70%, according to some studies.<sup>40</sup> However, the prevalence of the combination of low testosterone with clinical features of androgen deficiency is much lower. For example, in European Male Ageing Study (EMAS), low serum testosterone was observed in 17% of men older than 40 years, but only 2% of all men had symptoms of androgen deficiency and low serum testosterone.<sup>66</sup> The overall prevalence of symptomatic, functional hypogonadism in men aged between 40 and 79 years was 5.3% in a Chinese nationwide study.<sup>67</sup> In a large

Clinical features	
Foetal life	
Early	Disorders or differences of sexual differentiation (eg, female external genitalia, atypical genitalia, bifid scrotum, and hypospadias)
Late	Micropenis; cryptorchidism; and features mentioned under pre-pubertal and post-pubertal
Pre-pubertal	Delayed puberty (no secondary sexual characteristics or virilisation); high-pitched voice; small testicular volume; eunuchoid body habitus (longer limbs, upper body or lower body ratio of less than 1, and arm span exceeding height by 6 cm or more); and features mentioned under post-pubertal
Post-pubertal	
Specific or suggestive of hypogonadism	Deficient male-type body hair (in severe hypogonadism); low libido and loss of morning erections; hot flushes; gynaecomastia; infertility due to azoospermia, oligospermia or poor semen quality; height loss of more than 6 cm or minimal trauma fractures; and unexplained anaemia
Non-specific	Erectile dysfunction; lower muscle mass; gynaecoid fat distribution; fatigue, reduced energy; and depressive mood

**Table 2: Clinical features depending on the onset of male hypogonadism**

cross-sectional study, the prevalence of low free testosterone was 50% among men with obesity and type 2 diabetes and 40% among men with obesity but no diabetes, whereas it was only 26% in men without diabetes or obesity.<sup>68</sup> In EMAS, obesity and the presence of two or more co-morbidities were associated with a 13-times and 9-times increase in the risk of functional hypogonadism, compared with normal-weight men and those without co-morbidities, respectively.<sup>66</sup>

## Diagnosis

The diagnosis of male hypogonadism is made based on clinical androgen deficiency and confirmation with biochemical testing. Routine screening in the population or health-care settings in the absence of suggestive clinical features is not recommended.

## Clinical assessment

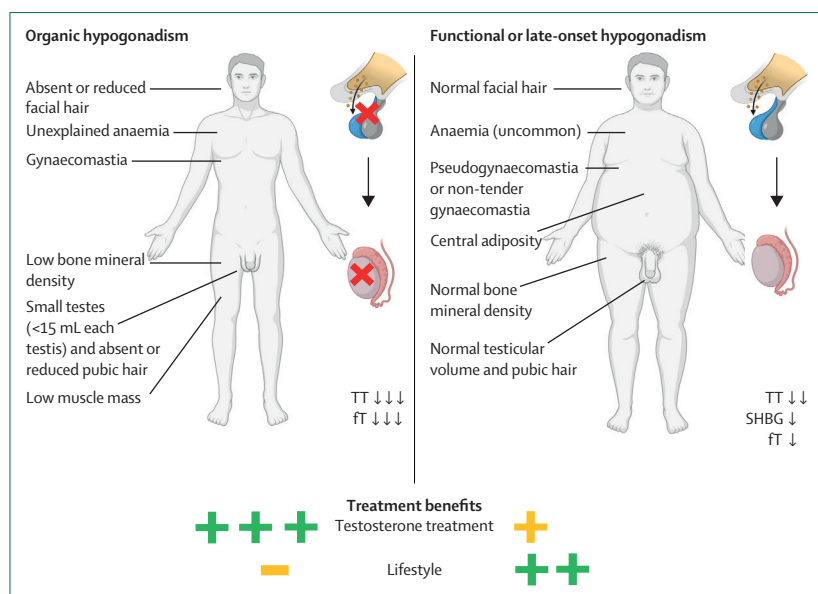
Clinical assessment comprises patient's medical history review and physical examination focusing on clinical features of hypogonadism, diagnostic studies providing collateral evidence of androgen deficiency (eg, haematocrit and bone densitometry), evidence for the aetiology of hypogonadism, and the characterisation of systemic conditions that can affect the clinical presentation.

Androgen effects at different stages of life determine the presentation of male hypogonadism according to the time of onset (table 2). Children with defects in testicular function in very early foetal life present with disorders of sexual differentiation, such as female external genitalia and hypospadias.<sup>17</sup> In contrast, children with congenital hypogonadotropic hypogonadism develop male external genitalia since the testes in early foetal life respond to maternal human chorionic gonadotropin but have a high prevalence of cryptorchidism or micropenis; hypospadias is very unusual.

Boys with severe prepubertal onset of hypogonadism present with delayed puberty including no secondary sexual characteristics (table 2).<sup>69</sup> Some men with congenital hypogonadotropic hypogonadism can experience partial or stalled puberty,<sup>70</sup> while the great majority of adolescents with Klinefelter's syndrome enter puberty before Leydig

cell failure is complete.<sup>71</sup> When the onset of hypogonadism is after puberty, secondary sexual characteristics have already developed and spermatogenesis had been reached.<sup>17</sup> However, some men with long-standing, severe adult-onset hypogonadism might experience body hair loss, small testicular volume, and infertility.<sup>69</sup> Because seminiferous tubules (and Sertoli cells) encompass 80–90% of testicular volume and Leydig cells contribute little volume, the testicular volume does not distinguish mild from severe androgen deficiency. Men with severe post-pubertal androgen deficiency can have normal combined testicular volume, whereas some men with Klinefelter's syndrome, infertility, and small testes can have clinically insignificant androgen deficiency. Gynaecomastia can develop due to an imbalance of androgen and oestradiol action on breast tissue and is more prevalent in primary hypogonadism.<sup>25</sup> Although physical symptoms including inability to engage in vigorous activity and psychological symptoms, such as loss of energy, low mood, and fatigue were associated with low testosterone in observational studies, sexual symptoms showed the strongest syndromic association in large population studies<sup>66</sup> and the greatest chance of improvement with testosterone treatment.<sup>72</sup> Hence, these non-sexual symptoms have a low specificity to aid the diagnosis of hypogonadism. Differences in the clinical presentation of organic and functional male hypogonadism are summarised in figure 2.

Some testicular disorders selectively impair spermatogenesis and infertility, while sparing Leydig function and testosterone production. For example, Y chromosome microdeletions result in small testes, oligospermia, or azoospermia with elevated FSH,<sup>17</sup> but normal testosterone and LH concentrations. Similarly, men with a history of post-pubertal mumps orchitis or chemotherapy-induced primary hypogonadism often have defective spermatogenesis with preserved androgen production since Leydig cells are affected to a lesser degree by these factors. On the other hand, a small group of men with congenital hypogonadotropic hypogonadism have post-pubertal testicular volumes and some degree of spermatogenesis, but low serum testosterone concentrations (Pasqualini syndrome).<sup>69</sup>



**Figure 2: Comparison between organic and functional hypogonadism**

Clinical presentation, pathophysiology, biochemistry and treatment approach in men with organic and functional hypogonadism are summarised. FT=free testosterone. SHBG=sex hormone-binding globulin. TT=total testosterone. --=no effect. Figure created with Biorender.com.

In the presence of features suggestive of hypogonadism, medical history review further helps to narrow down the aetiology of the condition. For example, a history of testicular trauma, surgery, or a history of mumps or testicular pain during puberty or adult life suggests primary hypogonadism. Any case of unexplained primary hypogonadism in a young man should raise clinical suspicion for Klinefelter's syndrome.<sup>58,70</sup> Anosmia is seen in about 50% of men with congenital hypogonadotropic hypogonadism (Kallmann's syndrome). Some affected individuals have synkinesis (mirror movements), deafness, renal agenesis, syndactyly, and midline defects including cleft lip and palate that are red flags, which can help make the diagnosis and thus shorten the diagnostic process.<sup>69</sup> Family history analysis with a pedigree chart will support the diagnosis and prediction of potential genetic mutations when combined with phenotypic characteristics. For example, X-linked recessive inheritance strongly suggests *ANOS1* mutation.<sup>73</sup> When acquired secondary hypogonadism is clinically possible, attention should be paid to features suggestive of other pituitary hormone deficiencies and the mass effects of sellar lesions, such as headache and visual field defects. A thorough medication and substance history is crucial since drug-induced hyperprolactinaemia, glucocorticoids, and opioids can cause functional hypogonadism. The growing epidemic of androgen abuse raises the importance of, in the appropriate clinical context (eg, muscular physique and very low concentrations of SHBG and HDL-cholesterol), interviewing patients for prior exposure to androgens. Patients might have been unintentionally exposed to undeclared androgens from non-hormonal nutritional supplements.<sup>74</sup>

The possibility of systemic illness, severe malnutrition, and obesity should be assessed since these conditions can all cause reversible suppression of the HPT axis.

### Laboratory testing and imaging

Total serum testosterone, the principal diagnostic test to confirm clinical suspicion of male hypogonadism, should be measured by a high-quality assay in the morning (7–10 am), in the fasting state, and in the absence of any acute illness.<sup>75–77</sup> Testosterone concentration is highest in the morning after sleep, so its measurement later in the day might cause underestimation of the testosterone concentration.<sup>78</sup> Similarly, testosterone concentration reduces after meals<sup>79,80</sup> and during acute illness.<sup>81</sup> Sleep deprivation can affect testosterone concentration and therefore the patient should be tested after an adequate night's sleep.<sup>82</sup> Testosterone concentrations have clinically significant day-to-day variation within an individual,<sup>83</sup> so repeat testing of a low reading is recommended unless LH and FSH concentrations are already known to be elevated or the patient is clearly pre-pubertal in appearance. Once the diagnosis of male hypogonadism is confirmed, gonadotropins should be measured to distinguish primary from secondary hypogonadism.<sup>75</sup> Elevated FSH and LH suggest primary hypogonadism. The value of sellar imaging with MRI is more controversial since routine imaging of all men with secondary hypogonadism for sellar masses has low yield,<sup>84</sup> but is clearly indicated in the presence of features of mass effects, such as visual field defects, other pituitary hormone deficiencies, any degree of hyperprolactinaemia, and very low testosterone concentration (<150 ng/dL/ 5.2 nmol/L).<sup>75</sup> Genetic testing for congenital hypogonadotropic hypogonadism is becoming widely available, with mutations in about 60 genes identified so far; however, mutations are not identified in approximately half of affected men.<sup>85</sup> Identifying specific genetic mutations can guide further evaluation for syndromic features and counselling on prognosis. For example, men with the *ANOS1* mutation might have unilateral renal agenesis and less favourable fertility outcomes.<sup>73</sup>

Haematocrit must be measured when querying the diagnosis of male hypogonadism, since anaemia is common in male hypogonadism and testosterone treatment increases haematocrit.<sup>86</sup> Infertility is a hallmark of organic hypogonadism.<sup>69</sup> Semen abnormalities are also associated with functional hypogonadism.<sup>87</sup> However, it is unclear whether these abnormalities are directly caused by hypogonadism or associated comorbidities. Semen analysis might be useful to assess baseline reproductive potential before commencing testosterone treatment in men wanting future fertility and possibly to reassure men who are unduly concerned that they might be hypogonadal.

Measurement or estimation of free testosterone concentration has no diagnostic value for male hypogonadism when serum SHBG lies within the reference range. However, elevated or low SHBG concentrations might be

associated with discordant total and free testosterone concentrations. For example, a eugonadal man with low SHBG might have low total testosterone and normal free testosterone concentrations.<sup>75</sup> SHBG is low in men with obesity, uncontrolled type 2 diabetes, glucocorticoid use, exogenous androgen exposure, nephrotic syndrome, untreated hypothyroidism, severe cirrhosis with synthetic dysfunction, and untreated acromegaly. SHBG increases with age, hepatopathy, or compensated cirrhosis, untreated HIV infection, untreated hyperthyroidism, severe energy deficit, substantial chronic alcohol consumption without hepatopathy, and use of enzyme-inducing anticonvulsants (carbamazepine, phenytoin, and phenobarbital)<sup>88</sup> and oestrogens. Additionally, some genetic variants cause higher or lower SHBG concentrations. Studies suggest that free testosterone is more closely associated with symptoms of hypogonadism, bone mineral density, and haematopoiesis compared with total testosterone.<sup>89-91</sup> Therefore, free testosterone concentration should be assessed in men with conditions that alter SHBG or have a borderline low serum total testosterone concentration. Measuring free testosterone is ideally done with the use of equilibrium dialysis as direct immunoassays are not accurate. Calculating free testosterone based on the measured total testosterone, SHBG, and albumin is a reasonable alternative when equilibrium dialysis is unavailable. This calculation can be done with the use of different formulae or calculators. The Vermeulen formula is one such widely used formula that has satisfactory performance at upper and lower ranges of SHBG.<sup>92,93</sup> A commonly used diagnostic threshold for free testosterone is 220 pmol/L based on the EMAS study.<sup>66</sup>

Routine testicular ultrasound is not recommended unless the testes are impalpable or other palpable masses are evident on testicular examination. Organic hypogonadism in young men has been consistently associated with low bone mineral density, while there is inconsistent evidence regarding the association of bone mass in older men with functional hypogonadism.<sup>94</sup> Hence, baseline bone densitometry should be considered in men with organic hypogonadism. It is also prudent to consider the overall fracture risk and regional and national standards of care for osteoporosis in older men with functional hypogonadism.

### Diagnostic challenges

In contrast to organic hypogonadism, the diagnosis of functional hypogonadism is challenging and controversial since most clinical features are non-specific and might be attributed to comorbidities, such as type 2 diabetes or sleep apnoea. Moreover, such comorbidities can lead to non-specific suppression of the HPT axis (ie, eugonadal sick syndrome).<sup>5</sup> The absence of highly specific symptoms in functional hypogonadism places increased importance on the diagnostic cut-off for total testosterone concentration. Reference ranges provided by commercial assay kits are often derived from random, non-fasted blood samples

and therefore have little diagnostic value.<sup>76</sup> A harmonised reference range has been developed with large population-based cohort studies of healthy men without obesity in Europe and the USA with a Centre for Disease Control and Prevention (CDC) reference method,<sup>43</sup> where 2.5th centile for healthy men without obesity aged between 19 and 39 years was 264 ng/dL (9.2 nmol/L). This concentration is endorsed by the US Endocrine Society as the lower limit of the reference range.<sup>75</sup> Two large randomised controlled trials (RCTs), the Testosterone Trials<sup>95</sup> and Testosterone Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE),<sup>96</sup> support the validity of the harmonised reference range based on the observations of the benefits of testosterone therapy on clinical features of hypogonadism in men with similar serum testosterone concentrations (<9.54 and 10.2 nmol/L, respectively). The fact that the Testosterone Trials<sup>95</sup> and TRAVERSE<sup>96</sup> benefitted from using CDC-certified serum total testosterone assays with tight inter-assay variability should be acknowledged; however, most world regions do not have similar assays, so measured testosterone concentrations within the same sample might vary by 20% when measured in different laboratories.<sup>76</sup> This variability might explain why clinical guidelines in some geographical regions have needed to apply a more pragmatic approach with total testosterone concentration of less than 8 nmol/L (230 ng/dL) and more than 12 nmol/L (346 ng/dL) deemed secure thresholds for hypogonadism and eugonadism, respectively.<sup>76</sup> Efforts to reduce inter-assay variability among serum total testosterone concentration assays are crucial to minimise incorrect classification of symptomatic men without classical hypogonadism. In summary, a serum total testosterone threshold of approximately 300 ng/dL (10.4 nmol/L) has large placebo-controlled RCT evidence showing the efficacy and safety of testosterone for reducing sexual symptoms in symptomatic men with functional hypogonadism.<sup>96</sup> However, when using total testosterone assays that are not CDC-certified, modified thresholds might be considered to avoid misclassification of symptomatic men.

### Management

The cornerstone of managing organic male hypogonadism is testosterone therapy. Testosterone was first extracted from bull testes by Laqueur and his group in Amsterdam in 1935.<sup>97</sup> In the same year, the method of chemical synthesis of testosterone was published by two independent groups: Butenandt and Hanish,<sup>98</sup> and Ruzicka and Wettstein.<sup>99</sup> Fertility management, which is another crucial aspect in the management of male hypogonadism, is not discussed in this Review.

Testosterone is available in different formulations, such as injectable esters, pellets, transdermal, nasal, and oral preparations. Testosterone is associated with several adverse effects that can be either drug-related or formulation-specific (table 3). The decision about which

	Dose, delivery method, and monitoring	Pros	Cons
Testosterone undecanoate (Nebido [Grünenthal, Germany])	1000 mg every 10–14 weeks (UK regimen); 750 mg IM, followed by 750 mg at 4 weeks, and 750 mg every 10 weeks (US regimen). Injected slowly deep into the gluteal muscle; monitor trough T concentration aiming for the lower end of the normal reference range.	Infrequent administration.	Requires IM injection. Pain and discomfort associated with IM injection. Coughing episode immediately after administration (uncommon).
Combination of testosterone esters (propionate 30 mg, phenylpropionate 60 mg, isocaproate 60 mg, and decanoate 100 mg)-Sustanon (Aspen, Ireland)	250 mg/mL every 3–4 weeks IM; monitor mid-interval T concentration aiming for mid-normal of the reference range.	Inexpensive relative to other treatment options.	Requires IM injection. Pain and discomfort associated with IM injection. Possible fluctuations in symptoms resulting from peaks and valleys in concentrations. Contraindicated if history of severe peanut allergy.
Testosterone enanthate or cypionate	150–200 mg IM every 2 weeks. 50–100 mg IM or SC weekly. Monitor mid-interval T concentration aiming for mid-normal of the reference range.	Inexpensive relative to other treatment options.	Requires IM injection (no data on SC injections unless using proprietary autoinjectors). Pain and discomfort associated with IM injection. Possible fluctuations in symptoms resulting from peaks and troughs in concentrations.
Transdermal (gel, testosterone solution, and T patches)	Once a day. 1% Testogel (Androgel [Besins Healthcare, Belgium]): 50–100 mg. Testogel pump 16.2 mg/g: 20–25–81 mg. 2% Tostran (Advanz, UK; Tostrex [Ferring Pharmaceuticals, Switzerland], Fortesta [Endo Pharmaceuticals, Pennsylvania, USA]): 40–70 mg. Testavan (Simple Pharma, UK): 23–46 mg. Monitor T concentration 2–6 h after gel application, 2–3 weeks after initiation; aim for mid-normal reference range; 60 mg of solution applied in the axillae OD (not available in the UK); and 1 or 2 patches deliver 2–4 mg of T over 24 h OD.	Ease of application; less erythrocytosis than injectable T.	Skin irritation, possibility of transfer by direct skin-to-skin contact to a partner or a child. T concentrations might be variable from application to application.
Nasal gel Natesto (Acerus Pharmaceuticals Corporation, Ontario, Canada)	2 pump actuations, one per nostril, applied intranasally two to three times daily (one pump actuation delivers 5.5 mg of testosterone).	Ease of application on the go.	Headache, rhinorrhoea, epistaxis, nasal discomfort, nasopharyngitis, bronchitis, upper respiratory tract infection, sinusitis, and nasal scab.
Bio-adhesive buccal testosterone tablets	30 mg controlled-release tablets applied to the upper gum BD (not available in the UK).	Easy and fast to apply; steady levels, avoiding peaks and troughs.	Gum-related adverse events in 16% of treated men. Possible risk of detachment when eating. Detailed patient education required.
Oral testosterone undecanoate capsules; SEDDS testosterone undecanoate	40–120 mg BD or TDS. Absorption is better when taken with a fatty meal. JATENZO (Clarus Therapeutics, IL, USA). 158 mg, 198 mg, 237 mg, 316 mg, or 296 mg BD. Monitor serum T 7 days after initiation, 6 h after morning dose. TLANDO (Antares Pharma, NJ, USA), 225 mg BD. Monitor serum T 3–4 weeks after initiation, 8 h after morning dose. Kyzatrex (Marius Pharmaceuticals, NC, USA) 100 mg, 150 mg, or 200 mg BD; monitor serum T 7 days after initiation, and 3–5 h after morning dose.	Ease of administration; newer T formulations based on SEDDS overcome the need for high-fat meal contents.	Low bioavailability. High inter-individual and intra-individual variability absorption. Needs to be taken with high-fat content meals, nausea, vomiting, heartburn, headache, and increase in BP.
Subcutaneous testosterone implants	Pellets 100 or 200 mg. Total dose 600–1200 mg. Effective for 3–6 months, depending on formulation.	Infrequent administration.	Requires surgical incision for insertion. Local haematoma, infection. Pellet extrusion through the skin.

BD=twice daily. IM=intramuscular. OD=once daily. SC=subcutaneous. SEDDS=self-emulsifying drug delivery system. T=testosterone. TDS=three times per day.

Table 3: Testosterone formulations and their characteristics

testosterone formulation to use depends on what is available in each health-care system and on patient's preference. Short-acting intramuscular injectable esters (testosterone enanthate; testosterone cypionate; testosterone propionate; combined esters, eg, Sustanon [Aspen, Ireland]) are the most commonly used preparations worldwide. These preparations are generally administered every 2–3 weeks; but fluctuations in circulating testosterone might lead to escape from symptom control before the next injection.<sup>100</sup> Once-daily transdermal testosterone gel is a popular alternative for men who do not want testosterone injections. Injectable testosterone undecanoate has a longer half-life (34 days) so is less prone to supratherapeutic peaks in serum testosterone compared with short-acting testosterone esters.<sup>101</sup> In the USA, testosterone

undecanoate is approved as a single injection of 750 mg that is repeated 4 weeks later, and then every 10 weeks. In the European Union and the UK, a single dose of 1000 mg testosterone undecanoate in castor oil (4 mL vial) injected every 10–14 weeks has been approved, although longer intervals between injections might be required to avoid erythrocytosis. Testosterone nasal gel (Natesto [Acerus pharmaceuticals, Ontario, Canada]) has been marketed in the USA since 2014, but requires administration 2–3 times per day. In the last decade, the FDA approved the use of oral testosterone undecanoate formulated in a distinctive self-emulsifying drug delivery system bypassing the need for concurrent high-fat content meal consumption.

The treatment goal is to restore serum testosterone to normal reference range. The specific timing and target

serum testosterone concentrations vary by formulation.<sup>75,77,102–104</sup> An initial follow-up after an appropriate interval (depending on formulation) to evaluate haematocrit, serum testosterone concentration, symptom control, and any possible side-effects needs to take place. Thereafter, haematocrit and serum testosterone concentration typically should be measured every 6–12 months during treatment. In men taking testosterone undecanoate, measuring trough serum testosterone concentration, aiming for a concentration of 10–15 nmol/L. Mid-interval testosterone concentration targeting the middle of the reference range is recommended in men using short-acting injections due to differences in pharmacokinetics.<sup>75</sup> Serum testosterone might be measured 2–6 h after application of testosterone gel. The risk of erythrocytosis with testosterone treatment has been clearly described in a large meta-analysis,<sup>105</sup> with a highest risk determined in older men receiving injectable formulations.<sup>106</sup> Haematocrit monitoring is an essential long-term biomarker of testosterone status during testosterone treatment. This monitoring detects erythrocytosis as a sign that testosterone dose (or dose interval) usually requires adjustment to reduce testosterone exposure in a patient even when serum concentrations appear to be on target, although smoking-cessation, weight loss, hypertension control, or review of SGLT-2 inhibitor treatment (concomitant use reported to cause erythrocytosis)<sup>107</sup> might also be required in parallel.

Prostate-related adverse effects of testosterone including prostate-specific antigen concentration of more than 4 ng/mL, increase of at least 1.5 ng/mL, or undergoing prostate biopsies have been described in literature.<sup>108</sup> Results from RCTs up to 36 months duration do not support any causative association between short-to-medium term testosterone administration and prostate cancer.<sup>109</sup> The TRAVERSE RCT<sup>110</sup> and other large studies<sup>111,112</sup> have reported no difference in prostate cancer or other prostate events between testosterone and placebo-treated hypogonadal men. However, these studies were only up to 5 years and mean treatment exposure was only 1–2 years. Given the absence of long-term safety data, some guidelines advocate for prostate cancer monitoring with the use of prostate specific antigen evaluation and digital rectal examination starting at the age of 40 years for hypogonadal men who are classed as having a high risk of prostate cancer (eg, African Americans, individuals with positive family history for prostate cancer) or at the age of 55 years and up to 69 years for hypogonadal men who are not at high risk of prostate cancer.<sup>75</sup>

Testosterone is contraindicated in cases of advanced prostate malignancy but might be considered in carefully selected men with untreated prostate cancer on active surveillance or at low risk of recurrence if biochemical and imaging evidence suggests no disease progression.<sup>113–115</sup> Patients should be fully counselled that the long-term effects of testosterone in this setting are still unknown and require further investigation. The decision to initiate

testosterone treatment remains individualised by balancing risks and benefits. Close monitoring and joint management with a urologist and oncologist are needed. Other contraindications to testosterone include breast malignancy, fertility seeking in the near-term<sup>75,106,116</sup> due to the suppressive effect of exogenous testosterone on endogenous gonadotropins, baseline erythrocytosis (HCT >0.50), and uncontrolled heart failure or sleep apnoea.<sup>75</sup>

Concerns about a potential causal link between testosterone treatment and cardiovascular events have been well documented. In 2015, the FDA issued a caution<sup>6</sup> for the use of testosterone in men with low testosterone concentration due to ageing, as testosterone might increase risks for heart attacks and strokes as evident in retrospective studies and a meta-analysis of RCTs<sup>117–119</sup> that were taken into consideration in the 2014 review panel. The European Medicines Agency did not endorse this warning.<sup>120</sup> Since then, several RCTs observed that testosterone treatment increasing serum testosterone concentration to the reference range did not increase cardiovascular risk, although these studies were underpowered for cardiovascular event detection<sup>95,121–123</sup> The FDA acknowledging the limitations of robust evidence, urged for the need of a “well-designed clinical trial to more clearly address the question of whether an increased risk of heart attack or stroke exists among users of testosterone products”.<sup>6</sup> Two studies published since 2022, the NIHR Testosterone and Efficacy and Safety (TestES), a meta-analysis of 35 studies including individual participant datasets for half of those studies from the UK,<sup>111</sup> and the TRAVERSE RCT of transdermal testosterone in hypogonadal men (serum testosterone concentration <300 ng/dL [10.4 nmol/L]) aged 45–80 years, at high cardiovascular risk from the USA,<sup>96</sup> observed that testosterone did not increase major adverse cardiac events in men with hypogonadism in the short-to-medium term (up to 2 years).

### Efficacy of testosterone

Testosterone has obvious and undisputed efficacy in alleviating hypogonadal symptoms in men with organic hypogonadism, thus precluding placebo-controlled RCTs for ethical reasons. Additionally, testosterone is used to induce the development of secondary sexual characteristics in men who have not undergone or completed puberty.<sup>75,77</sup>

However, the efficacy of testosterone to improve health in older men with functional hypogonadism has been elucidated within the last decade. The NIH Testosterone Trials,<sup>95</sup> a coordinated set of seven placebo-controlled double-blinded trials involving 788 men aged more than 65 years with a serum testosterone of less than 275 ng/dL (9.5 nmol/L), have assisted clinicians in informing decisions on the role of testosterone and its effect on older men. The trials showed improvements in sexual function, anaemia, walking distance, volumetric bone mineral density and estimated bone strength, mood, and depressive symptoms.<sup>86,95,124</sup> However, testosterone had no effect

on cognitive function or vitality.<sup>125</sup> Testosterone Trials efficacy data on sexual function were criticised due to an apparent reduction in treatment effect by the end of the one-year study period; however, the later TRAVERSE trial addressed this criticism since effects of testosterone on sexual function were maintained in men with functional hypogonadism.<sup>126</sup> The TestES consortium concluded that short to medium-term testosterone improved erectile dysfunction to a similar degree regardless of age, BMI, and diabetes status;<sup>111</sup> however, older men and men with obesity were less likely to reach adequate sexual function on testosterone due to more severe baseline symptoms.

### Controversies on testosterone

Most men seeking evaluation for low testosterone concentration are aged more than 40 years and have obesity or diabetes. There is evidence to support an association between low testosterone and inability to perform vigorous activity, fatigue and depression<sup>66</sup> as well as an association with metabolic syndrome,<sup>127,128</sup> reduced bone mineral density<sup>129</sup> and higher cardiovascular risk.<sup>130</sup> However, low testosterone due to functional hypogonadism is possibly reversible. Gold-standard treatment for these patients therefore consists of lifestyle modifications through diet and exercise to lower BMI<sup>49</sup> and waist circumference (in men with BMI >40 kg/m<sup>2</sup> and/or waist circumference >102 cm) and treatment of comorbidities.<sup>5</sup> Weight reduction results in the resolution of functional hypogonadism in a substantial percentage of men.<sup>131</sup>

The TRAVERSE trial surprisingly observed that the incidence of clinical fractures was higher in the testosterone group compared with placebo, although these were generally not classical fragility fractures.<sup>132</sup> This result is in contrast with the widely reported positive effect of testosterone on bone structure and quality.<sup>133–136</sup> The TRAVERSE trial did not use bone mineral density or other markers of bone quality, and the fracture incidence increased within months of commencing treatment, signifying potential behavioural change that could have led to more fractures. Therefore, the results should be interpreted with caution. However, older men with osteoporosis or at high risk of fragility fracture should receive bone-specific drug therapy proven to reduce major osteoporotic fractures, irrespective of any consideration for testosterone therapy.

Another area of ambiguity is the potential for testosterone to improve glycaemic indices in men. The Testosterone Treatment And Lifestyle Program For Type 2 Diabetes RCT observed that testosterone undecanoate (albeit causing erythrocytosis in 25% of participants)<sup>122</sup> reduced the prevalence of type 2 diabetes in middle-aged men with total testosterone of less than 14 nmol/L and impaired glucose tolerance or newly diagnosed type 2 diabetes, who were also receiving intensive lifestyle treatment; some other RCTs<sup>137,138</sup> and registry studies have yielded similar results.<sup>139,140</sup> In contrast, the TRAVERSE sub-study found

no difference in progression from prediabetes to diabetes between testosterone and placebo in middle-aged and older men mostly with functional hypogonadism.<sup>141</sup> Additionally, several RCTs<sup>142,143</sup> and a meta-analysis<sup>144</sup> did not observe improvements in insulin resistance and HbA<sub>1c</sub> with testosterone. It is therefore possible that physiological testosterone treatment has no significant benefit on glycaemic indices in contrast to supraphysiological treatment. In summary, the ability of testosterone to reduce type 2 diabetes risk is controversial, and it should not be solely offered for the treatment of type 2 diabetes or prediabetes in men.

Studies report inconsistent effects of testosterone on lipid parameters in men with hypogonadism. Some RCTs have reported no change in LDL cholesterol, HDL cholesterol, or triglycerides with testosterone treatment.<sup>145,146</sup> In the Testosterone Trials, there was a decrease in total and HDL cholesterol.<sup>147</sup> The TestES meta-analysis reported slightly lower HDL cholesterol (1.15, SD 0.33 vs 1.21, SD 0.39 mg/dL) and triglycerides (1.73, SD 1.3 vs 1.89, SD 1.51 mg/dL) in men treated with testosterone compared with men treated with placebo.<sup>111</sup> Overall, testosterone is unlikely to produce a clinically significant change in the lipid parameters in middle-aged and older men with hypogonadism.

The TestES<sup>111</sup> and TRAVERSE<sup>96</sup> studies provide reassurance that short-to-medium-term testosterone does not increase the risk of major adverse cardiovascular events in men with symptomatic low testosterone. However, TRAVERSE reported no difference in deep venous thromboses, but a higher incidence of pulmonary embolism (0.9% vs 0.5%) in the testosterone arm compared with placebo though the absolute numbers were very small. Unexpectedly, non-fatal arrhythmias warranting intervention (5.2% vs 3.3%), atrial fibrillation (3.5% vs 2.4%), and acute kidney injury (2.3% vs 1.5%) were also higher in the testosterone arm compared with placebo.<sup>96</sup> Previous studies have reported conflicting evidence regarding the risk of venous thromboembolism from testosterone.<sup>111,148</sup> In summary, we cannot exclude that testosterone increases risks of thrombosis or arrhythmias, though the reported risk of major adverse cardiovascular events is not increased compared with placebo.

The extent to which men with functional hypogonadism overall benefit from testosterone is widely debated due to conflicting evidence and differences among international guidelines. The European Menopause and Andropause Society<sup>149</sup> recommends that testosterone is only offered to men with a diagnosis of late-onset hypogonadism based on its specific criteria focused on sexual symptoms in men with low testosterone (only 2% of men aged more than 40 years fulfil these criteria).<sup>66</sup> However, some have advocated for broader treatment of middle-aged and older men to mitigate bone demineralisation, depressive symptoms, poor quality of life, and metabolic disorders, such as type 2 diabetes and obesity. There is still insufficient

### Search strategy and selection criteria

We searched PubMed and Google Scholar on March 5, 2024, from inception to March 2024 for publications in English with search terms, 'male hypogonadism' and 'testosterone'. We selected original articles, systematic reviews and meta-analyses, narrative reviews and clinical guidelines relevant to the topic from the search results.

evidence comparing testosterone to established therapies including lifestyle intervention, metabolic interventions (eg, GLP-1 receptor agonists), and treatment of mood disorders. We would currently advise only using testosterone to treat sexual symptoms in men with functional hypogonadism for whom health optimisation is not possible.

### Conclusions

Male hypogonadism encompasses a diverse group of congenital and acquired conditions either due to intrinsic pathology in the HPT axis or reversible suppression. Clinical presentation depends on the time of onset. Absence of secondary sexual characteristics is the hallmark of prepubertal male hypogonadism. Diagnosis of organic male hypogonadism should be mostly straightforward due to convincing clinical presentation and biochemistry, but even so, very few older men with primary testicular failure are being identified and treated considering the anticipated prevalence of this condition. Management with testosterone also does not pose any controversies. The increasing number of men presenting with functional hypogonadism poses diagnostic challenges due to subtle clinical features and controversies in diagnostic serum testosterone cut-offs. Similarly, treating the underlying risk factors such as obesity supersedes testosterone use, though the evidence suggests medium-term cardiovascular safety and modest symptomatic benefits of testosterone treatment in this group of men. For these men, lifestyle change represents a more holistic and globally effective treatment across multiple parameters.

### Contributors

NDS and NP reviewed the literature and drafted the initial manuscript. LA, MG, RQ, BDA and CNJ revised the manuscript. All authors read and agreed on the final manuscript.

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MG has received research funding from Bayer and Otsuka; and speaker's honoraria from Besins, Health Care, and Novartis. LA participated in advisory boards for Androlabs, Merck, and Galapagos; and receives a senior clinical research fellowship from Research foundation Flanders (1800923N). RQ participated in an advisory board for Roche Diagnostics. CNJ received investigator-led grants from Logixx Pharma; and received a National Institute for Health and Care Research post-doctoral fellowship. All other authors declare no competing interests.

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