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Society for Endocrinology guidelines for the treatment of male hypogonadism

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Summary

Male hypogonadism (MH) is a common endocrine disorder. However, uncertainties and variations in its diagnosis and management exist. There are several current guidelines on testosterone replacement therapy (TRT) which have been driven predominantly by single disciplines. The Society for Endocrinology commissioned this new guideline to provide all care providers with a multidisciplinary approach to treating patients with MH. This guideline has been compiled using expertise from endocrine (medical and nursing), primary care, clinical biochemistry, urology & reproductive medicine practices. These guidelines also provide a patient perspective to help clinicians best manage MH.

Key Words

Hypogonadism, testosterone, libido, erectile dysfunction, guideline

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MAIN TEXT

Key points

1. Testicular defects cause hypergonadotrophic hypogonadism or PH, identified by elevated serum gonadotrophin and low T concentrations. There is rarely a need for repeated venepuncture under optimal conditions to confirm the diagnosis.

2. The biochemical features of central hypogonadism may be indistinguishable from systemic disease (i.e. non-gonadal illness - NGI), sleep-deprivation, or even afternoon or post-prandial venepuncture. Contextual clinical ascertainment, appropriate conditions for blood sampling, and repeated measurements are required for diagnostic rigour.

3. Weight loss is a highly effective way for obese men with NGI to simultaneously reduce their cardio-metabolic risk and overall well-being, while increasing their testosterone levels.

4. Most patients with MH require long-term testosterone treatment. Effective self-management and optimising therapy is needed to achieve desired treatment outcomes, improve patient well-being and quality of life, and to minimise adverse effects of testosterone treatment over- or under- replacement. Clinicians should consider individual needs and preferences when discussing testosterone initiation. Clinicians should develop a tailored treatment plan in partnership with their patients considering the benefits and disadvantages of available testosterone treatment formulations individualised for each patient.

5. All patients should be provided with education about their condition and treatment aiming to improve adherence and optimisation of testosterone treatment. Clinicians should

consider individual needs and preferences when discussing testosterone treatment initiation.

6. Regardless of the aetiology of hypogonadism, sexual dysfunction and infertility can severely impact quality of life, including psychological, relationship and interpersonal issues.

1. Introduction and Methods

Male Hypogonadism (MH) is defined by deficient testosterone production and impaired spermatogenesis by the testes. MH can manifest at any point in life, from puberty, adult life and through to old age, and is characterised biochemically by low circulating serum testosterone levels and clinically by a wide range of signs and symptoms of T deficiency (Table 1) [1]. MH has consequences for health and well-being beyond sexual function and contributes to male infertility. The actual prevalence of MH is uncertain, depending on whether estimates are based upon the diagnosis of a hypogonadism-related disease (e.g. Klinefelter syndrome), or based solely on a defined biochemical cut-off (e.g. serum testosterone <10 nmol/L), giving rise to conflicting narratives. Cross-sectional and longitudinal epidemiologic data have identified an age-related decline in serum testosterone, particularly the circulating free fraction, and yet much of this results from accumulating co-morbidities, such as obesity, chronic disease, medications and frailty, rather than from primary disorders of the hypothalamo-pituitary-gonadal axis, or even from ageing *per se* [1,2]. Nevertheless, although hypogonadism-associated conditions may be individually rare, the large number and diversity of these conditions results in a cumulatively significant mass of patients. This is likely to increase with more cancer survivors, gonadectomised female-to-male gender transitions, primary care opiate scripts, and

greater numbers of diagnosed Klinefelter cases. In the UK healthcare environment, these men largely depend on Endocrinologists for an accurate diagnosis and long-term management plans. The Society for Endocrinology (SfE) is a professional and scientific body dedicated to the advancement of knowledge and promotion of good practice in the field. Although based in the United Kingdom, it is not a narrowly national body and, indeed, a significant number of committee members and officers practice in the Republic of Ireland. The SfE's Clinical Committee commissioned this Guideline and appointed CNJ and RQ as co-chairs. The Clinical Committee and co-chairs nominated a working-group to represent multiple disciplines relevant to the guideline. A patient member was also nominated to attend all meetings, and approve decisions with other working group members. Meetings (face-to-face and remote) were held between 2019 and 2020 to assign specific areas of the guideline scope to members of the working group to perform narrative reviews of the literature and provide reports on their topic. Individual reports were peer-reviewed by other members of the working group. Where consensus could not be reached on specific points, the co-chairs made decisions on content. An advanced draft of this guideline was revised following peer review by the SfE Clinical Committee, prior to submission for publication.

2. Aetiology of male hypogonadism

Making a clear distinction between Primary Hypogonadism (PH) and Central Hypogonadism (CH) through measurement of serum LH and FSH levels, as opposed to making a non-specific diagnosis of "testosterone deficiency" or "low testosterone", is a mandatory clinical requirement under all circumstances, because the outcome of this analysis determines:

1. The available first-line options for inducing/restoring fertility, which differ fundamentally: gonadotrophin therapy to induce spermatogenesis in CH *versus* mTESE, donor sperm or adoption, as potential options to becoming a parent.

2. The palette of potential differential diagnoses, which can in turn signpost specific disease management strategies beyond testosterone therapy, *e.g.* mitigation of the risks of developing type 2 diabetes (T2DM), cancer, or venous thromboembolism in men with Klinefelter syndrome; screening for the presence of hyperprolactinaemia, iron overload, wider pituitary dysfunction, or parasellar mass lesion in CH.
3. The nature of any confirmatory or second line investigations required, such as pituitary biochemical profiling and imaging in CH, *versus* karyotype/copy number variation in PH.
4. Confirmation of the diagnosis of MH through further contextual clinical ascertainment. For instance, the diagnosis is invariably secure when basal biochemistry indicates PH, but further contextual clinical ascertainment is required to properly distinguish CH (for which testosterone treatment is first line therapy) from NGI, for which first-line interventions are instead directed at lifestyle-coaching, disease-management, or addressing general health needs.

It is crucial to identifying the aetiology of CH is ruling out potential causes and confounders, which demands contextual clinical history, physical examination, medication review and biochemical assessment under controlled conditions, usually on more than one occasion.

2.1. Primary Hypogonadism

Primary Hypogonadism (PH) is characterized by elevated serum gonadotrophin levels in the setting of low testosterone levels due to Leydig cell dysfunction (whether impaired cellular function, or reduced cell mass). It may be accompanied by impaired or absent spermatogenesis. Some testicular disorders underlying hypogonadism are exceedingly rare, such as congenital anorchia (*i.e.* vanishing testes), Leydig cell hypoplasia secondary to inactivating mutations of the LH receptor [3], *dystrophia myotonica* and Kennedy syndrome, but much more common are cryptorchidism, trauma, orchitis, Klinefelter syndrome, post radiotherapy or chemotherapy

184 damage, and male ageing. An under-reported feature of PH is a 3-fold greater prevalence of
185 MetS and T2DM, albeit the direction of causation is unclear [4-6].
186
187 *2.2. Cryptorchidism*
188 The lower temperature of the scrotum (compared to the abdomen) is critical for Sertoli and
189 germ cell function and survival. Approximately 1-2% of males are born with cryptorchidism
190 that persists beyond 3-4 months postnatal and 80-90% of cases are unilateral [7]. Testes that
191 remain in the inguinal canal (or abdomen) beyond the first year of life have significantly
192 reduced function and it is recommended that surgical correction of undescended testes is
193 performed in the first year of life, usually after six months when anaesthetic risks diminish [8].
194 Even in unilateral cryptorchidism, the contralateral testis is not completely normal suggesting
195 that cryptorchidism is a bilateral disease [9]. There are concerns that endocrine disruptors
196 (chemicals in the environment – air, soil, or water supply – food sources, personal care
197 products and manufactured products that interfere with the normal function of the endocrine
198 system) may be contributing to a rising incidence [10].
199
200 *2.3. Klinefelter syndrome*
201 Klinefelter syndrome (KS) with a 47XXY or 48XXXY karyotype is the most common
202 chromosomal aneuploidy and the most common form of PH in males, occurring in
203 approximately 1:660 males [11]. The gonadal phenotype comprises seminiferous tubule atrophy,
204 disrupted spermatogenesis and small testes, but with Leydig cell function preserved in the
205 initial life stages. Gynaecomastia is prominent, along with behavioural and neurocognitive
206 problems, and tall stature resulting from 3 copies of the SHOX gene. Only 10% of patients
207 with KS are diagnosed before puberty and approximately 25% are never diagnosed [11]. This

likely reflects a combination of poor medical training in reproductive medicine and mosaic forms of KS having a milder clinical phenotype with non-specific symptomatology.

Serum LH, FSH and inhibin B (InB) levels are typically normal until puberty, at which point seminiferous tubules degenerate, losing germ cell, then Sertoli cells and eventually hyalinise and testicular function progressively declines, with testicular volume rarely exceeding 5-6 mL [11]. Testosterone therapy becomes mandatory when serum T concentrations become hypogonadal, or when clinical features develop. However, there is a view that testosterone treatment should also be considered from the point at which serum gonadotrophins begin to rise in early puberty, so as to ensure full development of secondary sexual characteristics and optimise bone health [11].

Reports have identified increased risk for mediastinal tumours, autoimmune disorders, vascular disease, thromboembolism and cancer in cohorts of patients with KS, some of which may relate to poorer lifestyle. As with other forms of PH, there is an approximately tripled risk for metabolic complications including obesity, MetS and T2DM. Accordingly, lifestyle coaching should be part of regular consultations along with ongoing monitoring of bone health with densitometry and regular assessment of adherence to testosterone therapy. In addition to these health problems and the physical stigmata of KS, affected boys often have poor motor skills, behavioural problems and may exhibit neurocognitive deficits [12]. While highly variable, many patients with KS have problems with cognition and language acquisition such as dyslexia, learning disabilities and difficulties with executive function. These difficulties often require speech and language therapy, special education programmes and/or psychological counselling. The combination of cognitive behavioural problems and hypogonadism can negatively affect quality of life and prevent effective adaptation to living with KS [13]. Impulsivity and anger-management issues may be inherent to the condition but are unlikely to be caused or exacerbated by physiological testosterone therapy. A multi-disciplinary approach including

medical, nursing, psychological and social care can assure assessment of psychosocial concerns, discussing these aspects with patients and families, identifying educational or employment and social resources, and making appropriate inter-professional referrals as needed. With increasing age, the diagnostic yield from screening for KS among men presenting with PH progressively falls and its clinical utility becomes less apparent.

2.4. Acquired primary hypogonadism

Acquired PH in men may result from trauma, infection, or inflammation (*i.e.* mumps orchitis), medical / surgical interventions, systemic disease, or chronological ageing (**Table 1**), albeit an underlying cause frequently cannot be identified. Unlike in women, there does not appear to be a syndrome of primary, autoimmune testicular insufficiency. Orchitis may occur secondary to viral infection and develops in around 25% of mumps infections among post-pubertal men [14]. Unilateral inflammation occurs in approximately two-thirds of patients and can lead to loss of testicular volume, but fertility is maintained in 75% of cases. Bilateral orchitis is less common, but spermatogenesis recovers in only a third of men [14] and an unknown proportion develop PH. The European Male Ageing Study (EMAS) found that 1–2% of older men had PH and another 10% had compensated primary hypogonadism (CPH), which were associated in equal measure with burden of comorbidities and chronological age [15]; the SPECT-China study showed similar findings were very similar [6]. Unlike the menopause in females, the majority of older men in the general population maintain adequate gonadal function, while the small minority of men who develop hypogonadism usually have poor health with multiple co-morbidities and/or obesity.

Insert Table 1 here

2.5. Hypothalamic and pituitary disorders – Central hypogonadism (CH)

Testosterone secretion is contingent upon adequate LH stimulation of the Leydig cells. Hypogonadism resulting from inadequate gonadotrophin stimulation is biochemically evident in low (or inappropriately normal) serum gonadotrophin levels. CH can be congenital or acquired (**Table 1**) and results from either defects at the level of the hypothalamus (*i.e.* isolated GnRH deficiency), pituitary defects causing inadequate gonadotrophin release, genetic mutations resulting in inadequate action of GnRH or gonadotrophins, or functional suppression of the hypothalamo-pituitary-gonadal (HPG) axis [16]. However, certain conditions can lead to a false-positive biochemical "diagnosis" of CH, which include venepuncture performed in the non-fasted state, in the afternoon, during intercurrent illness, sleep-deprivation or from taking undeclared medicinal or recreational drugs. This emphasises the importance of a comprehensive history that accounts for contextual clinical correlation factors and venepuncture under standardised conditions (8-10 am, fasted and well-rested).

2.6. Congenital hypogonadotrophic hypogonadism

Congenital hypogonadotrophic hypogonadism (CHH) is a rare disorder (1/4,000–10,000 males) caused by isolated GnRH deficiency and clinically characterized by absent or incomplete puberty and infertility [16]. When CHH occurs with anosmia (lack of sense of smell), it is termed Kallmann syndrome. While sense of smell and reproduction may appear to be unrelated functions, the embryonic origins of GnRH neurons in the olfactory placode provide the development link. More than 30 genes have been identified as underlying CHH and Kallmann syndrome either alone or in combination [16-18]. Some gene mutations disrupt GnRH neuron development and migration manifesting as Kallmann syndrome; others may disrupt GnRH homeostasis and secretion and clinically present as cases of normosmic CHH [16]. In some cases, mutations in the gene encoding the GnRH receptor (*GNRHR*) result in decreased GnRH action and CHH ensues (described below). CHH may occur with other associated phenotypes

such as cryptorchidism with or without micropenis, renal agenesis, hearing loss, midline defects (cleft lip/palate) and skeletal anomalies. CHH can be difficult to distinguish from other causes of pubertal delay and, consequently, many patients are diagnosed late with significant psychosocial impact [19]. These patients need of psychological support and may benefit from peer-to-peer support. Effective treatments are available for inducing secondary sexual characteristics and fertility in most men with CHH [16,20]. Spontaneous fertility has been reported; on rare occasions associated with "fertile eunuch" or Pasqualini syndrome, but more commonly with the hormonal reversal of CHH that is observed in about 10-15% of cases following treatment, but may not be sustained and thus warrants ongoing monitoring [21].

2.7. Other syndromic forms of congenital central hypogonadism

Developmental defects can result in hypothalamic-pituitary dysfunction CH. Many problems present with a constellation of features and thus are referred to as syndromic forms. These cases are typically identified during childhood, as anterior hormone deficiency, adrenal failure, obesity, or neurologic aspects command attention well before absent puberty manifests [22]. Given the complexity of these cases patients and families need purposeful planned transitional care to ensure continuity and ongoing support.

2.8. Combined pituitary hormone deficiency (CPHD) and septo-optic dysplasia (SOD)

Patients with combined pituitary hormone deficiency (CPHD) are often diagnosed early in childhood and treated for the respective pituitary hormone deficiencies, yet gonadotrophin deficiency may not become apparent until the failure of puberty to commence spontaneously. Importantly, these patients are responsive to treatment inducing secondary sexual characteristics and fertility [23]. A number of genes have been identified to underlie this condition yet the majority of cases remain without an identified genetic cause [24]. Septo-optic

dysplasia (SOD) is a developmental brain malformation that can present with pituitary hormone deficiencies, severe visual impairment, neurocognitive disability and developmental disorders on the autism spectrum [25]. Notably, genetic overlap has been reported between SOD, CPHD, CHH and CHARGE syndrome [18,26].

2.9. CHARGE, Bardet-Biedl and Prader Willi Syndromes

The constellation of coloboma (ocular malformation of the lens, iris, or retina), congenital heart defects, choanal atresia (abnormal formation of the nasal cavity), retardation of growth and development, genital hypoplasia, and ear anomalies associated with deafness define CHARGE syndrome [27]. In addition to immunologic problems, patients with CHARGE syndrome may exhibit hypogonadotrophic hypogonadism necessitating treatment. Approximately two-thirds of cases are explained by mutation Chromodomain-helicase-DNA-binding protein 7 (*CHD7*) [27] a gene also involved in CHH and Kallmann syndrome [16]. Bardet-Biedl syndrome (BBS) is a recessive genetic disorder of the cellular cilia that may present with a wide range of clinical features (obesity, mental retardation, renal anomalies, polydactyly, retinal degeneration, as well as cardiovascular, hepatic and metabolic problems[28]. In addition to being clinically heterogeneous, BBS is genetically diverse with 19 identified loci and complex genetics (i.e. digenicity, oligogenicity) [28] akin to CHH and Kallmann syndrome [16]. Although traditionally associated with CH, a recent clinical study found no evidence for hypogonadism among males with BBS when this was screened for systematically [29]. Prader Willi syndrome (PWS) is a rare genetic disorder (1/10'000-25'000) on chromosome 15 that causes physical, mental and social disability. During infancy, PWS is characterized by hypotonia and poor feeding (failure to thrive). Subsequently, additional features such as developmental delays, cognitive disability, short stature, hyperphagia, obesity, and behavioural problems (i.e. obsessive food seeking)

emerge [30]. Multiple endocrine deficiencies are common with patients typically needing growth hormone and testosterone therapy [31].

2.10. Adrenal hypoplasia congenita

A rare form of hypogonadotrophic hypogonadism occurs in the setting of adrenal hypoplasia congenital. Mutations in Nuclear receptor subfamily 0, group B, member 1 (*NR0B1*, formerly *DAX1*) result in early adrenal failure, and subsequently absent/incomplete puberty is the initial sign of CH [32].

2.11. Acquired central hypogonadism (CH)

In this situation, CH develops in adult life following prior full pubertal development and can result from trauma (*e.g.* skull fracture, pituitary stalk dissection and, particularly, military blast trauma), vascular events (*e.g.* pituitary apoplexy), infiltrative or metabolic disorders (*e.g.* iron overload, or hypophysitis), parasellar tumours, surgery, radiotherapy, hyperprolactinaemia, energy-deficit, or illicit drug use (*i.e.* marijuana, opiates or androgens) [14].

Anabolic androgens: Anabolic androgens are testosterone-like substances exerting powerful effects on the muscle, bone, reproductive health, cardiovascular system, brain, and behaviour [33]. Most men taking anabolic androgens, do so for cosmetic rather reasons rather than for athletic performance. The supra-physiological androgen levels suppress the HPG axis, resulting in testicular atrophy and infertility which can be reversible. In addition, affected men may develop psychiatric disturbances including mania, depression and anxiety, together with psychical and psychological dependency. However, as androgens are typically abused in very high doses and as some products have an extended half-life, recovery of HPG axis function can take from several months to a year or longer [33-34], with fertility taking up to 3 years to fully recover [34]. Significantly, levels of Insulin-like Factor 3 (INSL3) remain low for at least 3 years

following cessation of androgen abuse, independently of testosterone, suggesting a persistent impairment of Leydig cell function [35].

In adult-onset isolated GnRH deficiency, men who previously completed puberty present in adulthood with CH secondary to profound HPG axis suppression and complete loss of LH pulsatility [36]. These men have no other apparent underlying cause of their hypogonadism and defect is identified as hypothalamic as they respond to physiologic pulsatile GnRH therapy. Long-term follow up studies suggest that the neuroendocrine defect is permanent as these men do not subsequently regain HPG axis function [37].

2.12. Parasellar tumours causing central hypogonadism

Craniopharyngiomas, Rathke's cleft cysts, pituitary adenomas, gliomas, germinomas, and meningiomas can cause CH. As space-occupying lesions, compression and destruction of the hypothalamic-pituitary region can impair GnRH-induced gonadotrophin secretion. In adults, prolactin-secreting pituitary adenomas (prolactinomas) are the most frequently encountered and can cause functional HPG axis suppression in addition to CH from mass-effect [14].

2.13. Iatrogenic central hypogonadism

Common causes include surgery, chemotherapy, radiation treatment, long-term high-dose glucocorticoid treatment, or opiates used for chronic pain management or narcotic addiction [38], along with androgen deprivation therapy (ADT) for prostate cancer, for which the achievement of CH is the goal of treatment. Finally, transgender males also require testosterone therapy, which is generally sufficient to suppress hypothalamo-pituitary-ovarian function pending oophorectomy, but in the interim may be combined with a GnRH analogue or progestogen (systemic or intrauterine) should amenorrhoea not be achieved by testosterone alone.

2.14. Functional central hypogonadism

CH can also result from physiological causes and this is better known in females, where physical, emotional, or nutritional stressors can result in suppression of menses (functional hypothalamic amenorrhea) [39], albeit there may also be a genetic propensity [40,41]. However, males appear more resistant to hypothalamic suppression from either excessive exercise or energy deficits, as only small series have been reported to date and, moreover, genetic influences have not been identified [42]. Typically, such cases are restricted to patients with eating disorders (*i.e.* anorexia nervosa) or endurance athletes on very low-fat diets. A much more common form of functional hypogonadism results from hyperprolactinaemia suppressing hypothalamic GnRH secretion. Elevated serum prolactin levels may result from physiologic causes (*e.g.* stress, illness, sleep deprivation), pathophysiologic (*i.e.* prolactinoma) or iatrogenic causes (*i.e.* dopamine antagonist drugs) [43]. Notably, dopamine negatively regulates prolactin secretion while serotonin has a stimulatory role. Thus, both dopamine-antagonist antipsychotic drugs and serotonergic anti-depressants can cause elevated prolactin levels and may induce hypogonadism [43]. Opiates (see *2.13*) are another common cause of functional central hypogonadism. Importantly, the HPG axis recovers once the underlying stimulus to energy-deficit or hyperprolactinaemia (or the opiate drug itself) is removed, and the evidence for benefit of testosterone treatment is patchy, particularly in respect of opiates, wherein many adverse impacts on health arise independently of hypogonadism. Nevertheless, as the clinical features of these forms of functional hypogonadism (sexual dysfunction, fatigue, anaemia, osteoporosis, sarcopaenia, gynaecomastia and infertility) are so strikingly congruent with those of permanent forms of MH, testosterone treatment should generally be prescribed unless resolution or removal of the stimulus to MH is anticipated within a reasonable timeframe.

2.15. Systemic disease – non-gonadal illness (NGI)

Stress from acute illness, including surgery, burn injuries, myocardial infarction, stroke and sepsis have all been noted to suppress the HPG axis [44] and, when stress becomes prolonged as per any chronic illness, suppression of GnRH-induced gonadotrophin secretion becomes entrenched [45]. NGI is also observed in relation to ageing and obesity (see below). Importantly, this effect is reversible upon recovery from or remission of the underlying disease process. The evidence basis for testosterone treatment of NGI arising from these conditions is slim.

2.16. Ageing and central hypogonadism

Four key epidemiologic studies, as summarised by Dean et al, examined testosterone deficiency in ageing Western men: 1) the Massachusetts Men's Aging Study (n >1,600, aged 40-70 years), 2) Boston Area Community Health Survey (n >1,400, aged 30-79 years), 3) Hypogonadism in men (n >2,100, aged >45 years), and 4) the European Male Ageing Study (EMAS) (n>3,000, aged 40-79 years) [46]. These studies point to a progressive decline in serum T with age and alterations in sex hormone binding globulin (SHBG). The Survey on Prevalence in East China for Metabolic Diseases and Risk Factors (SPECT-China study) found a similar fall in testosterone levels to EMAS up to and including middle age, whereas older men who had maintained traditional non-Western diet and largely avoided weight-gain did not exhibit lower testosterone levels than younger Chinese men [6]. Historically, several terms were used to describe the age-related fall in serum testosterone, including male menopause, andropause, and androgen deficiency syndrome of the aging male. The EMAS multicentre European cohort study provided much-needed clarity and defined "late-onset hypogonadism" (LOH) as at least three sexual symptoms (decreased sexual interest, morning erections and erectile dysfunction [ED]) in the setting of a total serum testosterone level <11 nmol/L and calculated free testosterone <220 pmol/L [47]. Importantly, low serum T levels combined with potentially attributable sexual symptoms only occur in a small minority of ageing men (2-6%) and can be

largely attributed to comorbidities causing gonadotrophin suppression (*i.e.* NGI), and in particular obesity. Therefore the priority is to address or treat comorbidities as far as possible, with the evidence for benefit of testosterone treatment being slim. In contrast, as outlined in section *2.4*, both EMAS and SPECT-China crucially identified a small subset of older men (1-2%) having acquired *primary* hypogonadism that was equally associated with chronologic age and comorbidities [46].

2.17. Obesity and male hypogonadism

There are consistent data showing a negative correlation between obesity and testosterone, irrespective of age [15,48]. Obese men often exhibit low-normal serum gonadotropins with slightly low testosterone, but this is reversible and studies of lifestyle modification (i.e. diet and exercise) or bariatric surgery show that the rise in serum testosterone is proportional to the amount of weight lost [48,49]. The relationship between testosterone and fat (obesity) appears to be bi-directional, with several underlying mechanisms underpinning this. Lower serum testosterone levels result in decreased lean muscle mass and increased fat mass, which in turn promotes adipocyte-aromatase-mediated conversion of testosterone to oestradiol, thereby directly decreasing circulating testosterone, as well as doing so indirectly via oestradiol-mediated suppression of GnRH secretion, creating thus a vicious cycle. Other contributing factors include the dysregulated signalling of leptin, adiponectin and gut hormones (ghrelin, peptide YY), the effects of pro-inflammatory adipocytokines (*e.g.* tumour necrosis factor alpha, interleukin [50] and physiologic stressors accompanying obesity (e.g. chronic diseases such metabolic syndrome, sleep apnoea and arthritis), overall constituting non-gonadal illness (NGI) [48]. However, due to the inhibitory effect of hyperinsulinaemia on hepatic SHBG secretion, obese men tend to run low SHBG levels, such that measurement of total testosterone may at first sight appear to indicate a CH (or NGI) biochemical picture, whereas in fact free T is likely

to be normal. These men are not usually anaemic, osteopaenic, or infertile and thus the mainstays of management are lifestyle change, weight loss and the identification and treatment of other obesity-associated comorbidities, such as sleep apnoea. Although testosterone treatment may improve lean body mass and surrogate markers of cardio-metabolic metabolic health in these men, the erythrocytosis that is frequently induced thereby makes the overall balance of benefits versus risks far less clear.

3. Diagnosing male hypogonadism

The diagnosis of MH requires a combination of characteristic clinical features and corroborative biochemistry. Lacking any relevant clinical features or risk factors on medical history, there would usually be no justification for initiating a biochemical workup. The diagnosis of MH may be obvious due to strong risk factors including pubertal delay [51] prior cancer alkylating therapy, radiotherapy or orchidectomy, and known Klinefelter syndrome. However, the diagnosis of MH may be challenging because some clinical features may be non-specific. Clinical features suggestive of MH comprise the sexual (reduced libido and sexual activity, erectile dysfunction and reduced spontaneous erections), skeletal (loss of height, low trauma fractures and low bone density), reproductive (cryptorchidism, infertility or low sperm count), vasomotor (hot flushes and sweats), haematological (reduced haemoglobin or haematocrit in the absence of other identifiable cause) and tender glandular gynaecomastia. By contrast, symptoms such as disturbances of mood, sleep, or neurocognitive function, reduced muscle mass and strength and increased body fat appear to be less specific to MH [1] and, indeed, are much less likely to improve with testosterone treatment [52]. A targeted medical history is required identify confounding factors that might affect the interpretation of the biochemical profile, such as non-gonadal illness, energy deficit or excess, and drugs particularly androgens,

opioids, glucocorticoids and cannabinoids. Examination should note if voice tone is pre- or post-pubertal, male pattern hair development, gynaecomastia, testicular volume, and evidence of cryptorchidism or orchidopexy.

A variety of criteria have been proposed for the diagnosis of MH as discussed in two recent reviews comparing current guidelines [53,54]. A harmonised reference range for serum total testosterone has been calculated in over 9,000 healthy non-obese young men from Europe and North America using the Centers for Disease Control and Prevention (CDC) reference method; the 2.5th and 97.5th percentile were reported as 9.2nmol/L and 31.8nmol/L, respectively [55,56]. However, the diagnosis of MH also needs to take into account the presence of clinical features likely caused by low testosterone. The EMAS study observed that in approximately 3,400 men aged 40-79 years, the odds of experiencing sexual symptoms increased with either a total testosterone <8nmol/L (regardless of calculated free testosterone) or total testosterone <11nmol/L (with cFT<220pmol/L) [47]; men with levels of testosterone above these threshold were no more likely to experience symptoms related to hypogonadism than the background population. The presence of specific risk factors described above and diagnostic features such as anaemia and low bone mineral density can help make the diagnosis where results are equivocal.

It is also important to consider the potential clinical benefits of testosterone treatment for men with MH. Results from a systematic review and meta-analysis demonstrated that testosterone treatment improves sexual symptoms in men with serum testosterone <8 nmol/L unrelated to non-gonadal illness [57]. However, there is a paucity of published evidence investigating the clinical effects of testosterone treatment in men whose baseline serum total testosterone is >12nmol/L. Although the clinical effects of testosterone treatment in men *without* hypogonadism represent an interesting area of research, there is currently insufficient evidence to be able to translate this into clinical practice and testosterone treatment is not licenced in

men without MH [58]. In summary, a multi-method approach is necessary to establish the diagnosis of MH, though it is evident that the higher the serum testosterone threshold is set, the greater the risk of making an incorrect diagnosis of MH. This emphasises the importance of contextualising clinical and laboratory information when making a differential diagnosis.

4. Analytical performance of serum testosterone assays for men

The UK National External Quality Assurance Scheme (NEQAS) for Steroid Hormones monitors laboratory performance in the measurement of serum testosterone, SHBG and the derived analyte Free Testosterone. Most laboratories use either commercial diagnostic kits using an immunoassay principle or a Mass Spectrometry method. Overall, the performance of these tests is generally acceptable compared to other hormone analytes. The UK NEQAS for Steroid Hormones has trend data covering many years allowing to gauge the current state-of-the-art. Method bias, when compared to the reference value, does shift over time within any laboratory and an assay which is unbiased today could nevertheless drift into having a 5% bias over a period of years. Although mass spectrometry (MS) performance for testosterone levels in the female range is superior to that of immunoassays (many of which display a concentration-dependent bias with a negative bias at lower concentrations), the performance of some immunoassays outperforms MS methods in the male range. The between-laboratory agreement for some immunoassays can be as good as 4% CV, whereas MS users vary by up to ±10%, which could be considered a desirable performance limit. Therefore, MS is by no means the gold standard that was previously supposed and, at present, ±15% is used as the definition of out-of-consensus performance. The recovery of added testosterone for most methods is not quantitative and can be as high as 130% and as low as 90% for some of the major methods [59].

4.1. Free testosterone

Testosterone circulates bound to plasma proteins, predominantly albumin and, particularly, sex hormone binding globulin (SHBG). However, levels of testosterone and its binding proteins can vary considerably between and within individuals due to physiological and pathological causes. Concentrations of SHBG can vary depending on variables such as diet, body mass index (BMI), insulin, thyroid and sex steroid hormone concentrations, and age [60-69]. In these situations, measurement or calculation of free testosterone should provide added confidence in the differentiation between mild hypogonadism and eugonadism [70,71].

There are four approaches to estimating free testosterone, comprising direct measurements of free testosterone by 1. equilibrium dialysis, 2. ultra-centrifugation, or 3. gel filtration, and 4. calculation of the free testosterone fraction by mass action formula based on the binding characteristics of SHBG and albumin. It is generally accepted that all three methods of direct measurement are technically demanding, are not available to routine clinical laboratories and, crucially, lack much in the way of clinical correlation to established measures of androgen action, such as sexual function, bone mineral density and haemopoiesis. The commonly used alternative is to calculate the free fraction, for which there are several available formulae, though they all give different results possibly due to SHBG and albumin having inconstant binding characteristics (Heinrich-Balard et al 2015; Goldman et 2017). CFT using the Vermeulen formula has been increasingly used in clinical practice over the past 20 years and the calculated free testosterone results have shown clinical validity in many studies [62,72-81]. The original Vermeulen equation was validated using assays for testosterone and SHBG that are no longer available but has recently been re-validated using current state-of-the-art methods [61].

Calculated free testosterone has been increasingly used in clinical practice over the past 20 years. However, the implementation is challenged by the variability of analytical methods for testosterone and SHBG used in routine clinical laboratories. These variations as well as the various equations to calculate free testosterone have a significant impact on the results reported

by clinical laboratories. The most recent data from UKNEQAS show that there are seven methods for testosterone and six methods for SHBG in common use [59] which creates a myriad of combinations and calculated free testosterone results [60,61,63,66-68]. It is essential, therefore, that each combination of assays has its own specific reference ranges and decision limits for free testosterone, and this requires close collaboration between clinical and laboratory specialists. Clinicians and laboratories should avoid using generic or extraneous reference ranges, in order to safeguard against misclassification of patients [1,82]. It is important to highlight that the accuracy and clinical utility of free testosterone quantification is limited in the absence of these precautions; future efforts to resolve these issues would reduce risks of misdiagnosing men with symptoms suggestive of hypogonadism.

In summary, total testosterone is the unchallenged first-line investigation for suspected hypogonadism. Calculated free testosterone is used only as a second-line test in conditions associated with deranged SHBG concentrations, or when total testosterone is in the borderline range for patients with clinical features suggestive of androgen deficiency. However, the use of free testosterone is still controversial [64] and it is impossible to derive accurate free testosterone estimations without tightly regulated testosterone and SHBG assay performance.

5. Testosterone therapy

MH is associated with several physical, psychological, and social symptoms and, with rare exceptions, patients require long-term testosterone treatment and older age or disability should be no barrier for initiating testosterone treatment. Current treatment formulations and modalities for testosterone treatment, though not yet perfected, can offer an individualized treatment regime if accompanied by appropriate patient education and shared decision making. Given the complexity of testosterone treatment, it is crucial that patients understand and engage

with their treatment planning, and are supported to self-monitor testosterone treatment in order to recognise and manage potential adverse effects [83].

Currently available testosterone formulations, dosage, administration and benefits and disadvantages of each formulation are presented in **Table 2** [1,83,84]. The clinician should support the patient to identify a suitable testosterone formulation through a structured needs assessment and by providing patients with a rationale of benefits and disadvantages of each testosterone treatment formulation [83]. The most used formulations in the UK are transdermal gels and intramuscular injections.

Insert Table 2 here

5.1. Testosterone transdermal gel

This is a clear alcohol gel applied once a day, preferably in the morning, to dry, clean, unbroken and healthy skin, excluding the genital area. The gel is absorbed rapidly through the skin within 5–10 min and testosterone level elevate to the reference range within 2–4 h after application. Dose titration, aiming for mid-normal reference range for total testosterone, is based on blood test taken approximately 2-6 hours post-gel application, avoiding the gel application site [85,86]. Full absorption of the gel may take up to six hours and, therefore, showering or swimming within that time should be avoided. It is important to advise patients on the potential risk of direct skin-to-skin transfer of testosterone. Transfer of testosterone gel to pregnant women may cause abnormalities or harm to the unborn baby. To minimise risk of transfer, patients are advised to: wash hands thoroughly immediately after applying the gel; cover the application site (shoulders, upper arms, abdomen) with clothing once the gel has dried; shower before any situation involving close skin-to-skin contact within 6 hours after applying the gel.

606 Testosterone gel is well tolerated; however, occasional irritation or dryness may occur which
607 patients can treat with unscented moisturising topical creams.
608
609 *5.2. Testosterone intramuscular injections*
610 These injections are administered intramuscularly (IM) into the gluteal muscle or upper thigh,
611 although improved pharmacokinetics and potentially greater tolerability have been reported
612 with off label subcutaneously (SC) injection [87]. They are oily preparations (such as castor oil)
613 which allow slow release over a long period after being injected. Most patients have their
614 injection given by their GP or practice nurse, which often causes restrictions in lifestyle.
615 Testosterone injections provide high levels of testosterone (peaks) shortly after the injection,
616 which tend to drop below the reference range (troughs) towards the end of the injection interval.
617 This results in some patients experiencing symptoms related to high and low testosterone levels
618 between the injections, such as mood swings, difference in energy levels and sexual drive
619 which can be more prominent with the short acting IM injections.
620 Testosterone injections (**Table 2**) may be either of the following:
621 1. *Short acting* administered IM every 2-4 weeks or SC once a week depending on formulation
622 and patient response. Administration of testosterone cypionate and enanthate by SC injection
623 at 50-100 mg once a week has comparable pharmacokinetics, safety and tolerability to IM
624 administration and a steady state concentration of serum testosterone between dose intervals
625 [87,88]. This can also support patient self-management as self-administration is more feasible than
626 IM injections. Education is important to consult patients and their families on how to monitor
627 improvement in well-being and response to treatment and any potential side effects as well as
628 peak and trough levels between injections [83].
629 2. *Long-acting* testosterone undecanoate 1 g/4 mL IM injections, typically every 10–14 weeks
630 although much longer intervals may be needed. This should be warmed and injected very

631 slowly deep into the gluteal muscle, to minimise injection-related pain and risk of micro-
632 embolism. The first and second injections are given 6–8 weeks apart as a loading dose, with
633 the third injection given 12 weeks later. However, for the graded induction of puberty in men
634 and older teenagers, the 6–8 week loading dose should be omitted [89,90]. A testosterone level
635 and full blood count measured just prior to the third injection will then determine the frequency
636 of future injection intervals. Other things being equal, the interval between injections is set to
637 achieve a trough testosterone at the lower end of the normal reference range [91,92], but other
638 factors such as adverse effects, haematocrit, bone density and clinical well-being also need to
639 be factored-in [54]. Once steady-state has been achieved, trough bloods should be measured every
640 3–5 injections or annually, depending on the final injection interval; it is not usually necessary
641 do draw blood with each injection.
642
643 *5.3. Benefits of testosterone treatment and side effects*
644 The objective of testosterone treatment is to reverse or prevent the symptoms and long-term
645 effects of MH and to maintain general well-being [1]. Optimised testosterone treatment can:
646 • Induce or complete secondary sexual development
647 • Improve sex drive, libido and sexual function
648 • Improve mood and well-being
649 • Improve muscle mass and strength
650 • Restore or maintain masculine characteristics such as facial and body hair
651 • Maintain bone strength and prevent osteoporosis
652 • Maintain red cell production and prevent anaemia.
653 testosterone treatment suppresses gonadotrophin secretion and is therefore unsuitable for men
654 during conception (see section on “fertility considerations”). It is important to consult the
655 patient on what to expect from testosterone treatment and the estimated time periods when he

will experience the benefits of testosterone treatment. Setting realistic expectations and supporting the patient to recognise and manage potential testosterone treatment side effects effectively has a significant impact on treatment adherence [83]. Effects of testosterone treatment on sexual and quality of life parameters can appear within 3-6 weeks, such as improvement in sexual interest, depressive symptoms and energy levels, but changes in physical parameters, such as erythropoiesis, lipids, fat mass, lean body mass, glycaemic control, muscle strength and bone density may require 6-12 months to become apparent [93].

The suitability of each treatment option and any formulations-specific side effect as outlined in **Table 2** should be assessed and addressed at each consultation. Potential side effects described with testosterone treatment include acne, headache, irritability, aggressiveness, mood swings, depression, weight gain, oedema, prolonged painful or frequent erections, gynaecomastia, increased haematocrit and male pattern baldness [1]. However, these side effects can be significantly minimised with optimised testosterone treatment; noting also that symptoms such as mood swings, depression, gynaecomastia and irritability are also prominent in undertreated hypogonadism. The patient should be advised to monitor and discuss any of these side effects with their endocrine team to review and adjust their treatment regime. A symptoms diary is often very helpful which can be cross-checked against the biochemistry results and testosterone treatment formulation.

6. Post-finasteride syndrome and anabolic androgens

Finasteride is a 5α-reductase enzyme inhibitor used in the treatment of benign prostatic hypertrophy and male androgenetic alopecia (AGA). Patient self-reported studies show that finasteride causes adverse drug-related reactions with sexual impairment (decreased libido, erectile dysfunction, ejaculation problems), depression, anxiety, and physical symptoms that persist after treatment discontinuation and can be permanent for some patients, though their

long-term impact and precise mechanism have not been clarified [94,95]. A recent study of 55 men treated with finasteride for AGA found no significant difference in all sperm parameters, serum, FSF, LH, testosterone, prolactin and oestradiol level at treatment initiation (T0), a year after treatment (T12) and a year post-treatment discontinuation (T24) [96]. Current evidence does not support indication of testosterone treatment in the treatment of post-finasteride syndrome [97,98]. Men on finasteride should be counselled about the possibility of these adverse effects and warned that unwanted symptoms can persist after treatment discontinuation, the origin of which remains unclear. Patients should be referred to psychology services for relevant therapeutic interventions [99].

Some retrospective series have explored the potential of hormone therapy including hCG and selective oestrogen receptor modulators (SERM) to aid withdrawal from anabolic steroids[33]. However, there are currently no randomised control studies suggesting whether such treatment can ameliorate symptoms of anabolic androgen withdrawal, or improve the prognosis of successful withdrawal.

7. Patient education to support self-management

All patients should be provided with education about their condition and treatment aiming to improve adherence and optimisation of testosterone treatment. Clinicians should consider the patient's needs and individual preferences when discussing testosterone treatment initiation. Except perhaps in the context of compensated PH, we do not subscribe to the concept of a time-limited "individual therapeutic trial" of testosterone treatment and would expect and encourage any man having a verified diagnosis of hypogonadism to continue treatment lifelong. Non-adherence to testosterone treatment can compromise patients' quality of life, physical and cognitive performance and bone density [19,100,101]. Nevertheless, treatment gaps of more than a year and high discontinuation rates after six months post-testosterone treatment initiation were

706 reported by 37% [19,102] and 65% [103] of patients, respectively. Similar high discontinuation rates
707 post-testosterone treatment initiation were also reported by Donatucci et al; 52% of patients
708 on daily transdermal testosterone treatment discontinued treatment after 3 months compared to
709 31% of patients on short-acting testosterone treatment injections, though it should be noted that
710 the latter group did not include patients on long-acting testosterone undecanoate injections and
711 it is not clear if patients who discontinued testosterone treatment switched to another
712 testosterone treatment formulation [104]. The gap between stopping and restarting testosterone
713 treatment tended to decrease over time, suggesting that patients who experienced a benefit from
714 testosterone treatment remained on treatment [104]. Dissatisfaction with the information received
715 about treatment, perceived impaired communication with clinicians, and lack of continuity of
716 care were also reported by patients as significant barriers to treatment non-adherence.[19].
717 However, one should anticipate high drop-out rates among men without accurately verified
718 hypogonadism started empirical on testosterone treatment for non-specific symptoms and,
719 predictably, achieving little benefit. Individual patient needs will often guide the treatment
720 option for testosterone treatment; factors that influence this are ease of use, ability to raise
721 testosterone levels, improvement in symptoms, convenience, cost, and the patient's preferred
722 route of administration such as topical versus injections [105,106]. Beyond the well-known effects
723 of testosterone treatment on sexual function (which may or may not be relevant to older men),
724 it is important to make them aware of the other long-term health benefits of testosterone
725 treatment, such as on bone and muscle strength [54,83].
726 Patient Advocacy Groups (PAG) play an important role in supporting patients with MH. The
727 patient member of The Guideline Committee leads a UK-based PAG and made a significant
728 contribution to these guidelines. His feedback which is summarised in **Box 1**, is based on the
729 shared experiences of PAG members which he is coordinating.
730 **Insert Box 1 here**

8. Cardiovascular and cerebrovascular risk during testosterone therapy

Androgens have an array of reported biological actions including systemic and coronary vasodilation [107], increase in haematocrit by stimulating erythropoiesis [108], promotion of platelet aggregation [109], positively inotrophic effects on cardiomyocytes [110] and shortened QT interval on electrocardiogram [111]. Androgens and testosterone treatment are therefore likely to have complex actions on cardiovascular and cerebrovascular risk.

Older men with untreated hypogonadism have increased mortality compared with eugonadal men, even after adjusting for age, study centre, body mass index (BMI), current smoking, and poor general health [112,113], There is ongoing controversy regarding the effects of testosterone treatment on cardiovascular risk. Indeed, a large multicentre randomised controlled trial (RCT) was stopped early due to an increased rate of adverse cardiovascular events in men aged >65 years taking testosterone treatment [114]; notably many subjects had significant co-morbidities and target serum testosterone levels were set in the top half of the reference range, which may have attributed to the risk of adverse events in this patient group. Other RCTs reported either no effect, or even a reduction in markers of cardiovascular disease [115,116]. testosterone treatment has been reported to increase noncalcified plaque volume and total plaque volume vs. placebo [117], and is associated with small reductions in LDL, HDL, VLDL cholesterol and fasting insulin [118]. Several systematic reviews have reported on different outcomes using several cardiovascular endpoints in varying patient subgroups [119-122]. Unsurprisingly, their varied conclusions underline the current lack of consensus regarding the clinical effectiveness and safety of testosterone treatment in symptomatic men with low testosterone. The NIH testosterone (T) trials provided the largest RCT data of testosterone treatment in men with MH [52]. A highly selected group of 790 men, 65 years of age or older, with a serum testosterone concentration ≤ 275 ng/dL (9.535 nmol/L), excluding men with PH, and symptoms suggesting

hypogonadism were randomly assigned to receive either testosterone gel or placebo gel for 1 year [52]. Though not powered to investigate the safety of testosterone treatment, the NIH T trials reported that a total of 14 men had myocardial infarction, stroke, or death from cardiovascular causes; 7/14 (50%) of these men received placebo [52]. The US Federal Drugs Administration (FDA) recommends that men on testosterone treatment be advised of the potential cardiovascular risks [123], whereas the European Medicines Agency (EMA) considers that there is insufficient evidence to link testosterone treatment with increased cardiovascular risk [124].

Two ongoing projects may help to elucidate the safety of testosterone treatment. Firstly, the NIHR Testosterone and Efficacy & Safety (TestES) consortium is an individual patient data (IPD) meta-analysis pooling patient level adverse event data from individual RCTs [125]. Secondly, the US-led TRAVERSE trial is currently enrolling 6000 men aged 45–80 years with serum testosterone levels<300ng/dL and high cardiovascular risk to random allocation of testosterone gel or placebo for five years [126]. Additionally, published data from studies involving transgender men and women clearly show an increased risk of cardiovascular disease with oestrogen treatment in transwomen, but not from testosterone treatment in transmen, although these individuals were young and therefore at low background risk [127,128].

A recent observational study suggested that in men with or without hypogonadism, testosterone treatment was associated with increased risk of venous thrombo-embolism (VTE) (age-adjusted odds ratios 2.32 and 2.02, respectively) when compared with men not taking testosterone treatment [129]. Men with obesity, for whom lifestyle change likely represented a better intervention anyway, were at higher risk of VTE in this study, and the highest overall risk was observed during the first six months of treatment. Clinicians should therefore counsel men that testosterone treatment can increase the risk of thrombosis, although the absolute risk is low and can probably be mitigated by ensuring that haematocrit remains physiological. When haematocrit is elevated >0.5, testosterone treatment should be adjusted according to the

781 treatment formulation, by either lowering the dose of the daily transdermal testosterone
782 treatment, by extending the interval periods between testosterone injections, or by switching to
783 transdermal testosterone treatment which may have a lower risk of erythrocytosis compared to
784 with injectable testosterone treatment [130]. Secondary causes of elevated haematocrit should also
785 be investigated and, when haematocrit remains markedly elevated, testosterone treatment
786 should be stopped and haematological advice urgently sought.
787 In summary, the available RCT and observational data fail to reveal any consistent association
788 (positive or negative) between testosterone treatment and cardiovascular and cerebrovascular
789 events. Therefore, we conclude that testosterone treatment has uncertain effects on
790 cardiovascular and cerebrovascular risk. However, further data are likely to become available
791 soon, which will provide a more secure evidence base in respect of cardiovascular risk or safety
792 for clinicians prescribing testosterone treatment to men with hypogonadism. Meanwhile,
793 clinicians are advised to consider cardiovascular risk in men before initiating testosterone
794 treatment; in men with high cardiovascular risk, we recommend counselling them that the
795 cardiovascular safety of testosterone therapy remains uncertain
796
797 **9. Effects on bone mineral density**
798 Hypogonadism causes reductions in bone mineral density (BMD), while testosterone treatment
799 increases both vertebral and femoral BMD [131]. Currently, there are no data from which to
800 determine whether testosterone treatment reduces fracture risk in men with hypogonadism,
801 although this is assumed to be likely. In men with hypogonadism and reduced BMD, consider
802 repeating BMD assessment at an appropriate interval after commencement of testosterone
803 therapy. testosterone treatment is not indicated for treatment of osteoporosis in the absence of
804 MH. For older men with MH having established osteoporosis and already at high risk of
805 fracture, bone-specific drugs should be considered in addition to testosterone treatment.

However, for younger men with MH, it is more logical to defer consideration of bone-specific drugs until testosterone treatment-induced improvements in BMD have plateaued. At that point, if osteoporosis is still present, then bone-specific drugs can be added to testosterone treatment. However, hard data are lacking.

10. Screening for prostate cancer in men during testosterone therapy

Prostate cancer is the most common non-dermatological cancer and the second leading cause of cancer death in men in Europe and North America [132]. Prostate cancer primarily affects older men. It is therefore not surprising that many older men are at risk of both male hypogonadism and prostate cancer. Androgen hormones are trophic to prostate tissue, and androgen deprivation therapy is routinely used for the treatment of prostate cancer.

10.1. Testosterone therapy in men without prostate cancer

Circulating levels of testosterone are correlated with serum PSA in hypogonadism; however, there is no statistical relationship with PSA in eugonadal men (*the saturation hypothesis*) [133]. A systematic review suggested that testosterone treatment does not increase the subsequent risk of prostate cancer in men without prior disease [134]. Furthermore, a Canadian study on 12,779 men with new hypogonadism found that during 58,224 person-years of follow-up, use of testosterone treatment was not associated with an overall increased risk of prostate cancer (hazard ratio 0.97; 95%CI 0.71-1.32) [135]. For these reasons, it is generally accepted that testosterone treatment does not increase the risk of developing new prostate cancer. However, these is a physiological restoration of prostate size after initiation of testosterone treatment in men with MH which may unmask *incidental* problems. It is important to ask men with MH about the occurrence of urinary symptoms within the first few months following testosterone treatment initiation; those symptoms should be investigated according to routine practice.

Historically, prostate cancer screening has been conducted during testosterone treatment, in the form of serum PSA measurement and digital rectal examination (DRE) (since 1% of prostate cancers are non-PSA-secreting). However, endocrinologists generally have no experience recognising the features of prostate cancer during DRE, which makes this practice likely to be ineffective and potentially harmful. Major risk factors for prostate cancer are increased age, black ethnicity and family history, and all men (regardless of testosterone treatment) should undergo screening according to local practice. Theoretically, prostate screening might exclude a pre-existing tumour during testosterone treatment, but there is insufficient evidence to support the efficacy or safety of such an approach. In the absence of robust evidence, we do not recommend that mandatory screening for prostate cancer be performed during testosterone treatment.

10.2. Testosterone therapy in men with prostate cancer

A recent systematic review of 36 studies including 2,459 testosterone-treated patients found that testosterone treatment is not associated with increased risk of disease progression in prostate cancer [136]. The quality of studies included was poor though, with no level 1 evidence. Also, this review suggested that testosterone treatment might be harmful in men with metastatic prostate cancer (progression rate: 38.5%-100.0%), those undergoing active surveillance for low-risk localised prostate cancer (15.4-57.1%), and those with high-risk prostate cancer who were successfully treated (0.0%-50.0%). Joint management with a urologist is mandatory in men with known prostate cancer (treated or untreated), to monitor PSA and where necessary, conduct imaging with MRI, PSMA-PET, or CT/bone scan based on PSA kinetics and the clinical state of the patient. For those men with untreated prostate cancer (for example those for conservative management / surveillance) monitoring will be more intense and a multi-disciplinary decision between patient, urologist/uro-oncologist, and endocrinologist should be

made regarding risks *versus* benefit for testosterone treatment. Any changes on surveillance MRI imaging, PSA kinetics, or development of prostate cancer-associated symptoms will usually be an indication to cease testosterone treatment.

It is important to note that these recommendations are expert opinion based on the best available evidence, and that there remains significant uncertainty about screening for prostate cancer in the general population, albeit even more so in men on testosterone treatment. Our recommendations thus offer a pragmatic solution to a problem whose precise dimensions are unknown. It is hoped that these recommendations can be tailored in future based on RCTs examining prostate cancer risk in men on testosterone treatment and especially those with risk factors based on age, family history, and ethnicity.

11. Fertility considerations for testosterone therapy

11.1. Fertility in men with MH

Fertility is initiated at puberty, secondary to the rise in GnRH/gonadotrophin secretion and increasing testosterone production by the testis. It is well established that optimal normal spermatogenesis requires both FSH and testosterone, but there is a lack of a clear dose-dependency for both these trophic factors. Testosterone concentrations in the testis are approx. 100-fold higher than in the circulation and this is essential for the paracrine action of testosterone on Sertoli cells to support spermatogenesis. Thus, intratesticular or paracrine testosterone deficiency sufficient to impact on spermatogenesis is not a consideration where there is ongoing LH secretion and functional Leydig cells. However, classical hypogonadal pathologies are important causes of infertility, e.g. Klinefelter syndrome, Kallmann syndrome, hypopituitarism. Where the pathology is in the hypothalamus or pituitary causing CH, there is the potential for successful endocrine treatment. Obesity is also associated with CH [137]. Although spermatogenesis is dependent on LH and FSH, there are no accurate cut-off levels

for either parameter in CHH that usefully predict male infertility or disordered spermatogenesis, so a semen analysis should be obtained whenever fertility needs to be assessed. Men with normal or elevated gonadotrophin levels (or an isolated elevation of FSH) do not benefit from gonadotrophin therapy, or indeed any other medical therapy, to stimulate spermatogenesis or improve fertility and assisted reproduction will often be required.

11.2. Impact of testosterone therapy on fertility

Exogenous testosterone will suppress gonadotrophin secretion and thus spermatogenesis, and indeed this is the basis for the development of hormonal male contraception. Conversely it cannot be assumed that testosterone treatment will cause infertility, and contraception should always be discussed and advised where appropriate. Fertility intentions should be explicitly discussed with the patient whenever testosterone treatment is being considered, and the likely time needed for induction of spermatogenesis (see below). Patients with CH can, however, be reassured that testosterone treatment does not negatively impact the chances of success from subsequent gonadotrophin therapy [20].

11.3. Treatment of subfertility in men with MH

Subfertility should be investigated with physical examination for signs of hypogonadism, semen analysis (with a second sample if the first is abnormal), complemented with measurement of LH, FSH and testosterone prior to initiating testosterone treatment. Fertility may benefit from lifestyle factors such as balanced diet and smoking cessation. In the situation of a heterosexual relationship, it is always essential to consider the fertility status and age of the female partner in order to establish the prospects for successful conception (whether natural or assisted) and pregnancy prior to starting treatment for the male partner. In men with CH, the considerations are starting human chorionic gonadotrophin (hCG), FSH, or both. Pulsatile

GnRH therapy might be used in men with normal pituitary function but is not widely available. hCG can be considered an LH-mimetic, with very high potency and long half-life compared to LH. Administration is with the aim of stimulating the Leydig cells of the testis and thus stimulating endogenous testosterone production: it is therefore only of value when there is clear-cut LH and testosterone deficiency. Very low doses of hCG (125 IU) will restore intratesticular testosterone concentration [138], while higher doses are required to normalise circulating testosterone concentrations. A conventional starting dose is 1000-1500 IU sc twice a week, with a check of FBC, testosterone and oestradiol levels after 4 weeks. The dose can be increased to 2,500 IU twice or thrice-weekly, with higher doses rarely required or being effective; a high serum oestradiol level signposting risk of gynaecomastia may suggest reduction of the hCG dose. Unfortunately, there are currently no hCG products with marketing authorisation in the UK, so the choice lies between one having UK and European marketing authorisation for women only, or one that has marketing authorisation for use in males in certain European countries, but not yet in the UK. One possibility is to use Ovitrelle®, which is a prefilled pen-type injector containing 10,000 IU recombinant hCG marketed for IVF in women. The dose is adjustable according to the number of 'clicks' on twisting the barrel, but there are no marked gradations. **Table 3** indicates the dose according to the number of clicks, but it is important to recognise that this is empirical. We do not endorse combination therapy with both hCG and testosterone in men with MH

Insert Table 3 here

hCG alone may be enough to restore spermatogenesis in men with CH of post-pubertal onset, e.g. after pituitary surgery [139]. This may reflect some remaining FSH secretion, albeit at low levels. Post-pubertal stimulation of spermatogenesis can be successfully achieved more often than where there has not been pubertal development (84% vs 68%), and with higher sperm

concentrations achieved [20]. Similarly, a second course of gonadotrophin therapy will stimulate spermatogenesis faster than the first course. Regarding FSH administration, the issues are whether it is required, and when to initiate it. As described above, men with adult-onset CH may not require it. It is however almost invariably required in men with congenital/prepubertal CH, in whom both FSH and hCG therapy should be initiated simultaneously at the outset. The historic approach was to add FSH after 6 months treatment with hCG if the man remained azoospermic, but in fact men with congenital/prepubertal hypogonadotrophism hardly ever achieve meaningful spermatogenesis with hCG monotherapy, even when prolonged for up to 10 years [140] and so this hCG-first regimen is logically reserved for men with CH acquired post-pubertally. A dose of 75-300 IU sc three times per week is used, thus the patient also receiving hCG will require to self-inject 5 times per week, potentially for many months. FSH levels can be measured on treatment and a physiological target range 4 to 8 IU/L is advisable [141]. The long-acting FSH analogue corifollitrophin alpha requires administration every 2 weeks, and while there is evidence of efficacy in this indication [142], it is not widely used.

It has been postulated that in men with the most severe form of congenital CH (testicular volume < 4 ml), pre-treatment with FSH for several months before adding hCG may improve subsequent spermatogenesis, but the evidence is limited albeit the scientific basis appears sound [141]. Moreover, FSH monotherapy necessarily prolongs untreated hypogonadism unless exogenous testosterone is also given. Prior administration of androgens has been shown in a meta-analysis and subsequent RCT not to result in a slower response to gonadotrophin therapy [20,143].

Repeat semen analysis should be performed 3 months after initiating treatment, and at 3-month intervals thereafter. Baseline testicular volume, pubertal status and a history of cryptorchidism are indicators of time to respond, but fertility may be achieved even with a history of bilateral testicular maldescent [144-146]. Patients should be clearly counselled at the start about the likely

prolonged duration of treatment; however, it is important to recognise that fertility may be achieved with very low sperm concentrations, and conventionally normal sperm concentrations will not be achieved in many men. A meta-analysis indicated that a mean sperm concentration of 5.2 million/ml (95%CI 4.7-7.1) was achieved by gonadotrophin therapy [20], with a median time to achieve sperm in the ejaculate of 7.1 months (95% CI 6.3-10.1) and to conception of 28.2 months (21.6-38.5) [145]. The need for protracted treatment and the anticipated production of low numbers of sperm (but seemingly of high quality) should be carefully considered to prevent premature recourse to assisted reproduction, but conversely the age of the female partner may also be a factor in when that becomes appropriate. *i.e.* when the female partner is in her late 30s, prompt recourse to assisted reproductive technology (ART) would be wise from the moment that sperm appear in the ejaculate.

Once pregnancy is established, there are the following options:

- Revert to or initiate testosterone therapy;
- If the couple are considering a second child, it is possible to stop FSH and continue with hCG alone. This will maintain testosterone production and continue to support some degree of spermatogenesis: at the time a further pregnancy is desired, FSH may be restarted if indicated by repeat semen analysis;
- If there is concern over testicular function (e.g. if only a very low sperm concentration has been achieved, and ICSI was required) embryo (where available) and sperm cryopreservation should be considered.

977 **Box 1:** Patient feedback on testosterone treatment and self-management support

- In the UK, patients generally have good access to testosterone treatment
- A wide variation exists in the follow-up testing of patients, including the availability of bone densitometry
- Improved awareness of the different needs of various patients on testosterone treatment is required
- For some patients, blood testing is not done in a timely manner, *e.g.* at the end of a long acting testosterone IM injection, which can result in weeks of low testosterone before the patient received their next injection.

Patients on long term therapy have symptomatic awareness of abnormalities in their testosterone levels, which can be very useful to monitor and can be used as a guide even in the absence of blood test results. Active communication between the patient and health care provider is crucial to optimising testosterone treatment and avoid over- or under-replacement. Engaging with the patient is particularly important in the rarer forms of male hypogonadism where different treatment protocols may be more appropriate.

Some patients may be hesitant about starting or continuing testosterone treatment as they are unaware of all the treatment benefits and may be concerned about side effects, which can have a negative impact on adherence to treatment. Clinicians are advised to make patients aware of all possible testosterone treatments and differences in approach regarding monitoring and to support them to select the most suitable treatment for their needs.

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979 **Table 1: Aetiology of male hypogonadism**

Congenital disorders	**Acquired diseases**
Primary Gonadal Insufficiency	
Klinefelter syndrome	Gonadectomy - bilateral
uncorrected bilateral Cryptorchidism	Trauma or Torsion - bilateral
Testicular regression (vanishing testes)	Orchitis - bilateral
Partial Androgen Insensitivity syndrome	Chemotherapy - alkylating
inactivating LHCG receptor mutations	Radiotherapy - pelvic
Congenital adrenal hyperplasia	Ageing and age-associated co-morbidities
	Heavy Tobacco smoking
	Chronic alcohol abuse
	Systemic diseases: - HIV infection - Sickle cell disease - Coeliac disease - Uraemia
Central Hypogonadism	
Isolated GnRH deficiency - Kallmann syndrome - normosmic Congenital HH	Parasellar tumours, especially prolactinoma Inflammatory/Infiltrative diseases - sarcoidosis - histiocytosis - Iron overload, *e.g.* genetic Haemochromatosis
Syndromic forms of GnRH deficiency : - Combined Pituitary Hormone deficiency - Septo-Optic Dysplasia - CHARGE syndrome - Bardet-Biedl syndrome? - Prader-Willli syndrome - *Adrenohypoplasia Congenita* (*NROB1*) - leptin deficiency / leptin resistance	Trauma / Vascular / Radiation - military blast trauma - pituitary Apoplexy or Stalk transection - cranial Surgery & Irradiation
	Drug-induced - Opioids & Narcotics - high-dose Glucocorticoids - Androgen Deprivation Therapy - Anti-dopaminergic Antipsychotics - Cannabinoids - Androgenic anabolic steroids - Estrogens
	-

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981 **Table 2: Testosterone therapy formulations and their characteristics.** T – Testosterone.

Formulation and *dose*	Administration & monitoring	Advantages	Disadvantages
Transdermal topical T gels and axillary solution *50–100 mg of 1% Testogel®, 40–70 mg of 2% Tostran®, 23-46 mg of Testavan® or 20.25–81 mg of 16.2mg/g (Testogel® pump) transdermal gel once daily* *60 mg of T solution applied in the axillae once daily (not available in the UK)*	Clear alcohol gel available in sachets, tubes and pumps containing, applied dry, clean skin on shoulders, abdomen, upper arms or thighs (avoid genital area). Monitor total T 2-6 hours post-gel application, 2-3 weeks post-treatment initiation or dose adjustment, aiming for mid-normal reference range total T.	Convenient, flexible and easy application; good skin tolerability. Effective, provides T levels within normal range for 24 h. Steady physiological levels of serum T with no "peak & troughs" between applications. Dose easily adjustable to individual needs. No pain of injections.	May cause skin dryness and irritation for some patients. Takes time to apply. Potential of transfer to a female partner or child by direct skin-to-skin contact. Fear of transfer may inhibit intimacy; patient education minimises potential of transfer. Increased DHT levels due to presence of 5α-reductase in the skin. Considerable inter- and intra-individual T levels require close dose titration.
Long-acting T undecanoate IM injections *1000 mg in 4 mL (Nebido®) ampoule of oily preparation every 10-14 weeks*	Injected slowly deep into the gluteal muscle. The second injection (loading dose) is given at 6 weeks, and the third dose 12-weeks after the second. Injection interval is adjusted based on trough total T level just before the third injection, aiming for lower end of normal reference range level. Monitor trough total T and FBC every 3–5 injections or annually.	Effective, maintains physiological serum T levels for 3 months or longer. Smoother serum T profile compared to short-acting T injections, with less noticeable "peak and trough" symptoms. Convenient, 3-monthly administration without the side effects seen with T implants.	Pain, discomfort and adverse reaction at injection site. Requires large muscle bulk for injection. Lifestyle restrictions as it cannot be self-administered. Not recommended as first-line treatment option due to inability of withdrawal in case of adverse events (AE). Rare AE of pulmonary micro-embolism presenting with severe coughing episode during injection.
Short-acting T injections 1. *Combination of testosterone esters 250 mg/mL (Sustanon®) IM every 3–4 weeks (propionate 30 mg, phenylpropionate 60 mg, isocaproate 60 mg, decanoate 100 mg);* 2. *Testosterone enanthate or cypionate 150–200 mg IM every 2 weeks or 50–100 mg IM or SC once a week*	Oily preparation (1 mL) injected slowly into the gluteal muscle or upper thigh. Adjust injection interval based on trough total T level at the end of the injection aiming for lower end of normal reference range. Monitor trough total T and FBC every 6-12 months.	Dose flexibility and convenient administration, relatively inexpensive. Improves symptoms of androgen deficiency; mostly noticeable in the first days after the injection. SC injection has comparable pharmacokinetics, safety and tolerability to IM injection and can be self-injected.	Potentially unpleasant "peak & trough" symptoms due to supraphysiological T levels post-injection which decline to hypogonadal range by the next injection. Risk of polycythaemia due to supraphysiological T levels. Pain, discomfort at injection site. Lifestyle restrictions for patients not self-injecting.

Bio-adhesive Buccal T tablet *30 mg controlled-release tablets applied to the upper gum twice daily (not available in the UK)*	T is absorbed gradually from the buccal mucosa over 12 h. Applied on healthy, clean gum; the solid tablet softens and moulds to the shape of the gum. Monitor T 2-6 hours post-tablet application, 2-3 weeks post-treatment initiation, aiming for mid-normal reference range total T.	Easy and fast to apply; Effective; serum T levels remain within physiological range with twice daily application without significant peaks and troughs; "easy to remember" administration with teeth brushing daily routine.	Risk of gum-related adverse events reported by 16% of treated men. May detach when eating shortly after application. Takes time to get used to; patient education is vital for medication adherence.
Subcutaneous T implants *Testosterone pellets 100 or 200 mg to a total of 600–1200 mg T per dose (rarely administered)*	3–6 pellets every 4–6 months. Pellets implanted in the subcutaneous adipose tissue with surgical incision under local anaesthetic.	Serum T peaks at 1 month and is sustained in normal range for up to 6 months. Convenience—twice or thrice a year application.	Painful procedure with high risk of infection at the insertion point and scar tissue. Risk of spontaneous extrusion after implantation.
Oral T undecanoate capsules 40 mg *1–3 capsules (40–120 mg) twice or thrice daily with meals*	Taken orally; absorption is improved when taken with fatty meal. Swallow without chewing.	Easy and convenient administration. Suitable for patients who cannot tolerate other forms of treatment and those who require low levels of T, not a preferred treatment option.	Low bioavailability and very high inter- and intra-individual variability in absorption resulting in insufficient serum T levels. Normal serum T level attained for only up to 3–5 h.

983 **Table 3:**

984 **Dosing using prefilled Ovitrelle® (human chorionic gonadotrophin, hCG) 6,500 IU pen**

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Ovitrelle® dose (IU)	No of clicks (calculated dose, IU)
1500	6 (1560)
2000	8 (2080)
2500	10 (2600)
3000	12 (3120)
4000	15 (3900)
5000	19 (4950)

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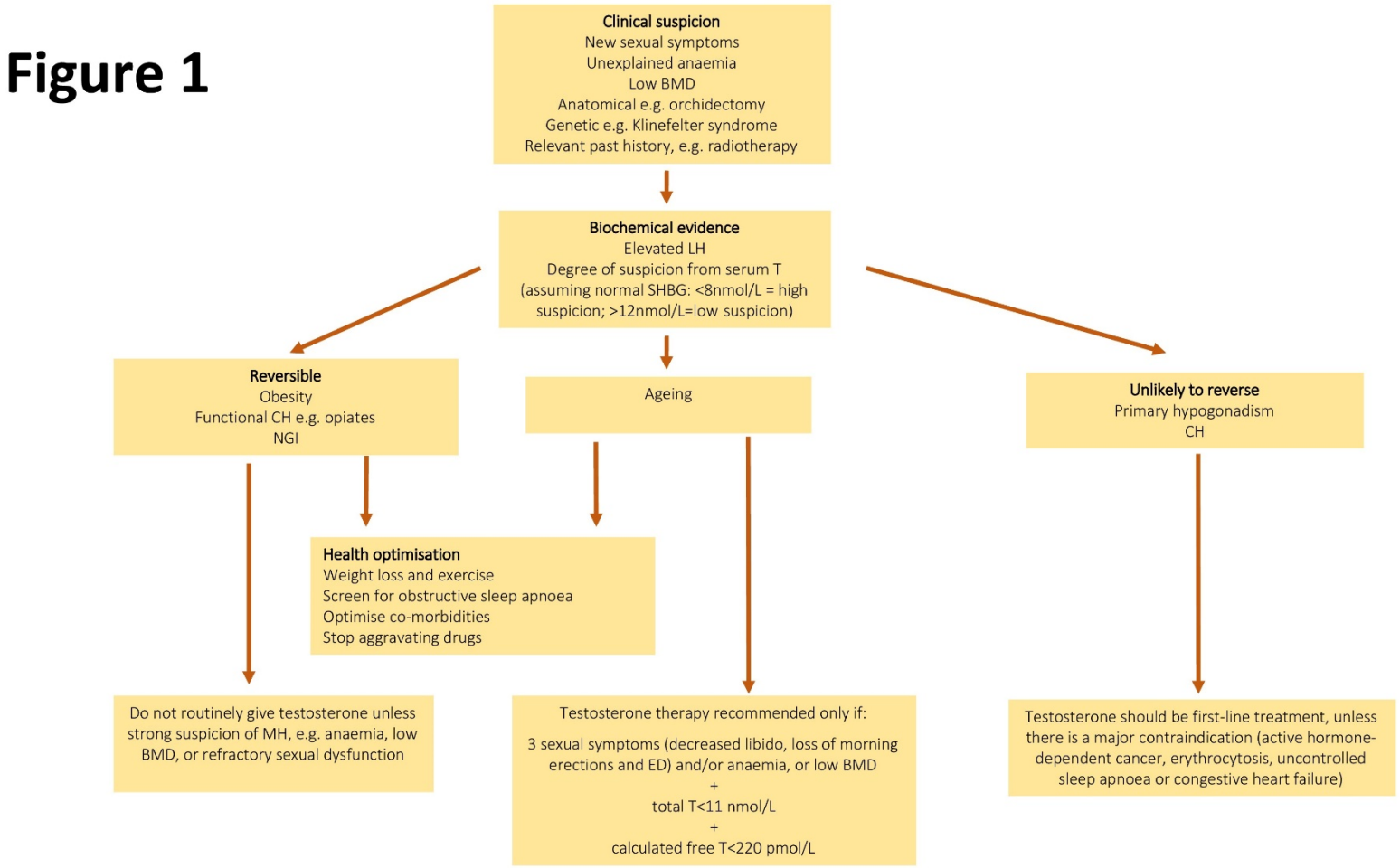
Figure 1: Flowchart for male hypogonadism management

MH, male hypogonadism; TT, total testosterone; LH, luteinising hormone; SHBG, sex hormone binding globulin; CH, central hypogonadism; NGI, non-gonadal illness; BMD, bone mineral density; ED, erectile dysfunction



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