Title:

Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy.

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Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy

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The Endocrine Society of Australia formulated guidelines for testosterone prescribing in 2000, aiming to restrict inappropriate usage.[1] Since then, prescriptions of testosterone have risen dramatically in Australia and elsewhere without any new proven indications, consistent with its use extending beyond the treatment of men with pathological hypogonadism due to pituitary or testicular disease.[2-4] Controversy has arisen over the role of testosterone treatment in older men with medical comorbidities who have low levels of circulating testosterone, in the absence of hypothalamic, pituitary or testicular disease.[5] There are gaps in the evidence base in relation to the potential benefits of testosterone treatment in men with obesity or type 2 diabetes and those receiving long term glucocorticoid or opioid therapy, who may exhibit low levels of circulating testosterone. There is also ongoing debate about the risk of cardiovascular adverse events related to testosterone treatment.[6] In view of the rising rates of testosterone prescription, in 2015 the Australian Government tightened the criteria for which testosterone therapy would be subsidised in the absence of pathological hypogonadism.[7] In this context, the Endocrine Society of Australia commissioned a position statement to update its 2000 guidelines and to inform the recommended management of men with androgen deficiency.

Methods

The Council of the Endocrine Society of Australia invited the authors of the 2000 guidelines and new authors with recognised expertise in this field to participate in a working group in 2014. A distinguished endocrinologist (H G B) was appointed to chair the working group. Extensive communication within the working group took place by email before and after a face-to-face meeting in Adelaide on 26 August 2015. All competing interests of participating authors were declared. Members of the group were asked to identify, consider and cite relevant evidence, sourced from their personal knowledge and searches of the literature, and to consider previous published guidelines. Controversies were resolved by discussion within the group. The draft statement was submitted to the Council of the Endocrine Society of Australia, who provided feedback. The working group responded to the feedback, and the final version of the position statement was approved and submitted for publication in April 2016. This article forms Part 1 of the position statement, focusing on assessment of male hypogonadism, including the indications for testosterone therapy. Part 2 will deal with treatment and therapeutic considerations.[8]

Abstract

Introduction: This article, Part 1 of the Endocrine Society of Australia's position statement on male hypogonadism, focuses on assessment of male hypogonadism, including the indications for testosterone therapy. (Part 2 will deal with treatment and therapeutic considerations.)

Main recommendations: Key points and recommendations are:

- Pathological hypogonadism arises due to diseases of the hypothalamus or pituitary gland (hypogonadotropic hypogonadism) or testes (hypergonadotropic hypogonadism). It is a clinical diagnosis with a pathological basis, confirmed by hormone assays.
- Hormonal assessment is based on measurement of circulating testosterone, luteinising hormone (LH) and follicle-stimulating hormone (FSH) concentrations. Measurement of sex hormone-binding globulin levels can be informative, but use of calculated free testosterone is not recommended for clinical decision making.
- Testosterone replacement therapy is warranted in men with pathological hypogonadism, regardless of age.
- Currently, there are limited data from high-quality randomised controlled trials with clinically meaningful outcomes to justify testosterone treatment in older men, usually with chronic disease, who have low circulating testosterone levels but without hypothalamic, pituitary or testicular disease.
- Obesity, metabolic syndrome and type 2 diabetes are associated with lowering of circulating testosterone level, but without elevation of LH and FSH levels. Whether these are non-specific consequences of non-reproductive disorders or a correctable deficiency state is unknown, but clear evidence for efficacy and safety of testosterone therapy in this setting is lacking.
- Glucocorticoid and opioid use is associated with possibly reversible reductions in circulating testosterone level, without elevation of LH and FSH levels. Where continuation of glucocorticoid or opioid therapy is necessary, review by an endocrinologist may be warranted.

Changes in management as result of the position statement: Men with pathological hypogonadism should be identified and considered for testosterone therapy, while further research is needed to clarify whether there is a role for testosterone in these other settings.

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Recommendations

Pathological hypogonadism: clinical diagnosis

Hypogonadism refers to a pathological disorder of the hypothalamic—pituitary—testicular (HPT) axis that results in the testes being unable to produce both physiological levels of testosterone (androgen deficiency) and adequate numbers of functional sperm for paternity (male infertility).[9,10] Thus, in its complete form, hypogonadism affects both virility and fertility. In many infertile men, virility may be relatively preserved, as the germinal epithelium is more vulnerable to both congenital and acquired defects.

Most often, hypogonadism is due to congenital or acquired defects of the testes (primary testicular failure), in which case levels of gonadotropins (luteinising hormone [LH] and follicle-stimulating hormone [FSH]) are elevated (hypergonadotropic hypogonadism). A failure of hypothalamic—pituitary stimulation with onset before or after puberty (hypogonadotropic hypogonadism) is less common.[11] Rarely, there can be combined defects at both levels, presenting special diagnostic and therapeutic challenges (Box 1).

Although inaccurate, the term "hypogonadism" is often used interchangeably with "androgen deficiency", as most often the problems concern whether testosterone treatment is required or justified for androgen deficiency. Accordingly, this position statement focuses primarily on the management of androgen deficiency, while fertility is mentioned only when relevant.

The diagnosis of androgen deficiency requires an initial careful clinical assessment to determine whether a compatible presenting symptom complex exists (Box 2). A comprehensive medical history, including information on smoking and the use of medication, alcohol and other recreational drugs, in particular androgens, is required. In addition, a focused review of the reproductive system should include any developmental history of undescended testes or other genital abnormalities, pubertal development, prior fertility, erectile function, sexual desire and any history of pelvic surgery, genital trauma or infection. The physical examination must include height and weight (and, if obese, waist circumference), a check for gynaecomastia, the adequacy of age-appropriate virilisation and especially scrotal palpation, using an orchidometer

to assess testicular volume (usually 15—35 mL in men aged 21—35 years with normal reproductive function[12]).

Initial hormonal assessment

Having identified the possibility of pathologically based androgen deficiency on clinical grounds, laboratory testing is undertaken. Measurement of serum testosterone levels is not otherwise warranted (eg, for population screening). A serum total testosterone level, together with serum LH and FSH levels, should be measured early in the morning, between 08:00 and 10:00, as testosterone levels may be lower during the remainder of the day.[13] Fasting results in higher serum testosterone levels.[14] This time frame should be adjusted for shiftworkers or men who are sleep-deprived for any reason, in whom measurement shortly after waking may be preferred.[15]

Accurate testosterone assays are required. As most laboratories offer immunoassays that exhibit non-specificity and method-dependent bias, mass spectrometry is preferred where available.[16] Serum testosterone level peaks at about the age of 20 years[17] and gradually declines thereafter as age-related comorbidities accumulate.[18] In men aged 21—35 years with normal reproductive function (ie, proven normal testes and semen analysis), the reference interval for total testosterone measured using mass spectrometry is 10.4—30.1 nmol/L.[12] The reference interval using mass spectrometry in unselected young men is 7.4—28.0 nmol/L.[19] In very healthy men aged 70—89 years, the reference interval using mass spectrometry is 6.4—25.7 nmol/L.[20] The differences between the reference intervals for younger and older men may represent unresolved confounding by underlying reproductive and other health disorders that accumulate with age. At high and low ends of the reference interval, serum testosterone level must be interpreted in relation to serum sex hormone-binding globulin (SHBG) level. Furthermore, reference intervals of testosterone immunoassays vary between methods, as these direct immunoassays do not correspond accurately to mass spectrometry-based measurements. Even lower thresholds defined by mass spectrometry are not 100% sensitive or specific for the detection of androgen deficiency due to pathological hypogonadism. Clearly normal serum testosterone and LH levels

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1 Classification and clinical characteristics of pathological hypogonadism

Abnormalities of the testes causing primary testicular failure

- Low testosterone levels, impairment of spermatogenesis and elevated gonadotropin levels
- When severe, fertility may require assisted reproduction or donor sperm (or adoption)

Abnormalities of the hypothalamus or pituitary gland causing secondary testicular failure

- Low testosterone levels, impaired spermatogenesis, low or low—normal gonadotropin levels
- Natural fertility can be restored with gonadotropin therapy
- Evaluation may find pituitary tumour or systemic illness and other hormonal deficiencies

Abnormalities of both hypothalamus—pituitary gland and testes (uncommon)

- Low testosterone levels, impairment of spermatogenesis and variable gonadotropin levels, depending on whether primary testicular failure or secondary testicular failure (eg, due to glucocorticoid excess or alcoholism) predominates ◆

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2 Presenting clinical features of androgen deficiency (post-pubertal onset)

Non-specific symptoms

- Lethargy, fatigue
- Decreased energy and/or endurance
- Low mood, irritability, poor concentration, impaired short term memory, sleepiness
- Deteriorating work performance
- Hot flushes

Organ-specific symptoms

- Bone: osteopenia, osteoporosis, fracture/loss of height
- Muscle: reduced muscle mass and strength (sarcopenia)
- Adipose tissue: increased fat mass
- Breast tissue: gynaecomastia

Sexual and reproductive symptoms

- Decreased libido
- Erectile dysfunction (uncommon as a presenting feature of androgen deficiency, and then only at very low serum testosterone levels) ◆

(using clinical judgement to assess assay results for individual men) exclude androgen deficiency.

Confirmatory blood testing

An initial low serum testosterone level, especially when accompanied by a serum LH level that is within the reference interval, should be confirmed, as up to 30% of men (of any age) who have an isolated initial low serum testosterone level will have a normal serum testosterone level on repeat measurement.[21,22] Unless one measurement of serum testosterone, LH and FSH levels is clearly diagnostic of pathological hypogonadism, at least two measurements of serum testosterone, LH and FSH are recommended to diagnose androgen deficiency in the appropriate clinical and pathological context. SHBG measurement can be helpful, as certain conditions are associated with marked changes in SHBG level that in turn affect total testosterone levels and their interpretation. Mildly elevated SHBG levels are seen with ageing, but SHBG can be markedly increased by hyperthyroidism, liver disease and anti-epileptic therapies; and accompanied by elevated total testosterone levels without evidence of androgen excess. Conversely, SHBG levels are suppressed with obesity, insulin resistance and exposure to exogenous androgens; in which case, serum testosterone concentrations below the reference interval, especially with normal serum LH and FSH levels, do not confirm a diagnosis of androgen deficiency. There is no evidence that free or bioavailable testosterone levels, which are usually not directly measured but calculated with various formulae (lacking validation in some cases),[23] are a better measure of androgen status than total testosterone level. Moreover, reference intervals for these are even less well defined than those for measured testosterone concentrations. Therefore, they are not recommended for clinical decision making.

Additional investigation of hypogonadal men

A further round of investigations is recommended for men with suspected hypogonadotropic hypogonadism, to identify uncommon but treatable underlying disorders. These include:

- serum prolactin test (for prolactinoma and macroadenoma with pituitary stalk compression)
- iron studies and full blood count (for haemochromatosis and thalassaemia)
- hypothalamic–pituitary magnetic resonance imaging, if there is a clinical or biochemical suspicion of pituitary or hypothalamic disease
- anterior pituitary function test (for hypopituitarism and/or hyperfunctioning adenoma).

For men with suspected hypergonadotropic hypogonadism (primary testicular failure), additional evaluation is warranted in situations where knowing the aetiology will inform clinical management for fertility through in vitro fertilisation procedures:

- karyotyping (for suspected Klinefelter syndrome)
- Y chromosome microdeletion analysis.

Management decisions should only be made after a systematic approach to the diagnosis of hypogonadism, seeking to distinguish between pathological and functional causes of a low serum testosterone level. The features of pathological androgen deficiency depend on the age of onset and its severity and duration. Pre-pubertal androgen deficiency may manifest as micropenis and testicular maldescent (although not all cases of micropenis or testicular maldescent are due to hypogonadism) and, later, with delayed puberty and excessive long bone growth (eunuchoidal

proportions). Post-pubertal onset produces typical yet often non-specific features that vary depending on the rate and extent of the fall in testosterone levels (Box 2). Conversely, the positive predictive value of non-specific symptoms for androgen deficiency can be low even in conjunction with a reduced serum testosterone level; hence the necessity for a careful clinical evaluation to look for an underlying pathological cause. In some cases, the diagnosis is easily appreciated, but, in others, limited or subtle features or an insidious onset leave even profound androgen deficiency overlooked. A striking example is the failure to diagnose Klinefelter syndrome in more than half of all men with the condition, which is the commonest chromosomal disorder in males (about one in 580) and a cause of adult androgen deficiency. Yet, invariably, a clinical examination reveals the characteristically small testes, and most affected men benefit from lifelong testosterone replacement therapy (TRT).[24] The cause of this diagnostic failure is that many men go through life without a medical genital examination, where the clinical findings would promptly suggest the diagnosis.

Testosterone replacement in men with pathological hypogonadism

Indications and non-indications for testosterone therapy are shown in Box 3. The justification for testosterone treatment is to restore physiological androgen status to that comparable with eugonadal men. This will relieve the symptoms and signs of androgen deficiency. In this context, TRT refers to replacing the deficient hormone to restore physiological levels. The case for TRT is well established for androgen-deficient men with proven hypothalamic, pituitary or testicular disease, comparable with hormone replacement in other established deficiency states, such as adrenal failure (Addison disease) or hypothyroidism. TRT aims to establish or maintain secondary sexual characteristics, sexual function, body composition (including bone density) and well-being. In certain cases, such as late-diagnosed Klinefelter syndrome, symptoms may be subclinical, as men may be accustomed to their hypogonadism, yet will nevertheless note marked improvement in their health with TRT.

TRT should never be commenced before diagnostic work-up is complete and a clear pathological diagnosis has been made, for several reasons. First, failure to do so may overlook underlying abnormalities, such as a pituitary tumour. Second, exogenous testosterone suppresses the HPT axis so that once testosterone treatment has commenced, accurate evaluation for an underlying aetiology is problematic. An extended period of monitoring after testosterone is withdrawn may be needed to determine whether adequate endogenous testosterone production is present. Third, TRT for pathological hypogonadism is expected to be lifelong. Fourth, testosterone treatment in men without pathological hypogonadism compromises fertility, whereas in men with secondary hypogonadism, spermatogenesis can be restored with gonadotropin treatment.[25] Contraindications to TRT are shown in Box 4. Age per se is neither an indication for testosterone treatment nor a contraindication to treating men who are androgen deficient due to pathological hypogonadism. In very old men with other comorbidities, individual consideration of the benefits versus risks of treatment is warranted. Ongoing testosterone replacement in older men with pathological hypogonadism is generally no more risky than in younger men, except for the occasional need to initiate treatment slowly and cautiously.

Hypogonadotropic hypogonadism in the presence of a proven aetiology (eg, pituitary tumour or its treatment by surgery or radiotherapy) usually requires TRT and treatment of coexisting anterior pituitary hormone deficiencies. Specific dopamine agonist

3 Use, misuse and abuse of androgens

Use (physiological treatment with testosterone replacement for androgen deficiency in men with pathological hypogonadism)

Primary testicular failure:

- Klinefelter syndrome
- Testicular trauma, torsion, removal
- Testicular infection
- Testis atrophy of any cause

Hypogonadotropic hypogonadism (secondary testicular failure):

- Congenital: Kallmann syndrome, variants without anosmia
- Acquired: prolactinoma, pituitary tumour, surgery, radiotherapy
- Delayed puberty

Subject of ongoing research

- Middle-aged and older men*
- Androgen deficiency secondary to chronic disease and ill health*
- Hormonal male contraception*

Pharmacological (non-androgen-deficiency states)

Typically treated with androgens other than testosterone and necessitating evaluation for efficacy, safety and affordability, as for other non-hormonal drugs:

- Osteoporosis
- Steroid-induced bone loss
- Anaemia due to bone marrow or renal failure
- Advanced breast cancer
- Cachexia/wasting
- Alpha-1 antitrypsin deficiency

Misuse (use without a valid medical indication)

- Male infertility
- Sexual dysfunction/impotence (in the absence of proven androgen deficiency)
- "Male menopause", "andropause", "low T", "late-onset hypogonadism"
- Non-specific symptoms (lethargy, tiredness, low energy)

Abuse (absence of a medical indication)

- Sporting: elite competitive power sports (boxing, wrestling, sprinting, weightlifting, football)
- Recreational: bodybuilding
- Cosmetic: "body beautiful" subculture
- Occupational: security, police, armed forces

* Use in these conditions remains to be fully evaluated for safety and efficacy in randomised placebo-controlled clinical trials. ◆

4 Contraindications and precautions in testosterone treatment

Contraindications

- Advanced, metastatic or incurable prostate cancer
- Breast cancer

Precautions

- Undiagnosed palpable prostate abnormalities, with or without elevated serum prostate-specific antigen level*
- Severe lower urinary tract symptoms (International Prostate Symptom Score >19)
- Untreated polycythaemia
- Untreated severe obstructive sleep apnoea†
- Unstable or inadequately treated cardiac disease (eg, poorly controlled cardiac failure or ischaemia, recent cardiovascular events)
- When fertility is desired
- When subject to occupational drug testing

* Urological evaluation may be required. Testosterone treatment may be acceptable in men with screen-detected organ-specific prostate cancer after definitive or clinically adequate prostate treatment. † Testosterone treatment only transiently worsens severity of obstructive sleep apnoea; this is not an absolute contraindication. ◆

therapy is required for hyperprolactinaemia, to not only suppress serum prolactin and restore testosterone but also to reduce tumour size and progression, as well as compressive symptoms. Iron chelation therapy may be required for congenital or acquired haemochromatosis.

Testosterone not justified in older men with chronic disease in the absence of pathological hypogonadism

Declines in serum testosterone level with age, in the order of 0.5–2% per year in reportedly healthy men, have been taken by some to imply a gradual change in the HPT axis with age.[18,26] Modest changes in gonadotropin-releasing hormone pulsatility and Leydig cell responsiveness have provided mechanistic support but no aetiological basis for age-related dysfunction. Terms

such as "late-onset hypogonadism" or "andropause" have been created to foster the idea that this decline in serum testosterone level, in isolation and without regard to pathological hypogonadism, can be considered an androgen-deficient state.[27]

In men (of any age) with intrinsically normal HPT function, systemic illness and accumulation of comorbidities, including renal, cardiac, inflammatory and mental health disorders, are associated with reduced levels of circulating testosterone. Not surprisingly, such men have a higher risk of serious intercurrent illness and earlier mortality. These men may have symptoms and signs resulting from the underlying (non-reproductive) disorder that overlap with those of androgen deficiency. In this setting, a low testosterone level is a biomarker for the underlying poor health.

While healthy older men exhibit lower testosterone concentrations on average than do healthy, reproductively normal younger men,[12,20] there are no convincing data that healthy ageing necessarily results in a lowering of serum testosterone level to an extent that constitutes a clinical deficiency. Observational studies have reported independent associations of lower circulating androgen levels with poorer health outcomes in older men, including cognitive decline,[28] frailty,[29,30] incidence of stroke[31] and mortality.[32] However, other longitudinal studies indicate that a substantial proportion of the age-related fall in testosterone may be accounted for by obesity, burden of disease and medication use.[33,34] In one cross-sectional study, a sample of men recruited for self-reported excellent health showed stable serum testosterone and LH concentrations into their eighth decade.[14] The prevalence of middle-aged and older men who have both low circulating testosterone levels and sexual dysfunction is relatively low — about 2% in the European Male Aging Study.[35] However, while that study interpreted declining serum testosterone levels as causing sexual dysfunction, there is evidence that sexual activity modestly increases serum testosterone levels[36] and sexual inactivity is associated with decreased serum testosterone levels.[37]

In the United States, the Testosterone Trials showed a moderate improvement in sexual function in older men with a baseline testosterone level <9.5 nmol/L who were treated with

testosterone.[38] At present, there is limited evidence showing clear benefit of treating older men with low−normal testosterone concentrations in the absence of pathological hypogonadism. While further research in this area is important, the immediate priority for these men is to identify and optimally manage any underlying medical comorbidity or mood disorder, such as depression. Where the diagnosis of hypogonadism is unclear, review by an endocrinologist may be warranted.

Obesity

Obesity is consistently associated with lower levels of circulating testosterone in cross-sectional studies and predicts declining testosterone levels in longitudinal studies. Serum LH and FSH levels are almost invariably normal in this setting. This association likely reflects predominantly reversible suppression of the HPT axis mediated by central adiposity, although testosterone treatment exhibits moderate effects in reducing fat mass and increasing lean mass.[39-42] Successful weight loss, whether by diet or surgery, can lead to substantial increases in testosterone levels in obese men, whereas an 18-week randomised controlled trial (RCT) of testosterone treatment in obese men with sleep apnoea showed no benefit compared with placebo in terms of bodyweight or metabolic syndrome.[43] The increase in testosterone level is proportional to the amount of weight lost: 10% weight loss increases testosterone by 2−3 nmol/L, whereas in morbidly obese men, profound weight loss after bariatric surgery can raise testosterone levels by > 10 nmol/L.[44]

Metabolic syndrome and diabetes

Men with metabolic syndrome have lower circulating testosterone levels compared with men without, and lower testosterone and SHBG levels are associated with increased risk of developing metabolic syndrome.[45] Similarly, men with diabetes have lower testosterone concentrations than men without, and men with low testosterone levels are more likely to develop type 2 diabetes.[46] Serum LH and FSH levels are almost invariably normal in these men. A recent meta-analysis of RCTs of testosterone treatment in men with metabolic syndrome or diabetes showed a marginal improvement in indices of insulin sensitivity with testosterone, but no evidence of better glycaemic control.[47] Priority should be given to implementing lifestyle measures (especially exercise and dietary measures to lose excess weight) and optimising glycaemic control in the setting of diabetes. Such weight loss has many other demonstrable symptomatic and metabolic benefits. Persistently low testosterone levels despite successful weight loss should prompt reassessment to ensure a diagnosis of pathological hypogonadism has not been missed.

Glucocorticoid and opioid use

Use of systemic glucocorticoids has been associated with lower levels of circulating testosterone in men.[48] In an RCT of 51 men receiving long term glucocorticoid therapy (5 mg or more of prednisone daily for at least 6 months or 1000 μg or more of inhaled steroid plus at least one course of oral prednisone within the past 6 months), 12 months of treatment with either testosterone or nandrolone (a minimally aromatisable androgen) increased muscle mass and reduced fat mass.[49] In that study, testosterone increased lumbar bone mineral density and quality of life, while nandrolone did not.[49] Opioid analgesia suppresses gonadotropin release, resulting in low levels of circulating testosterone, and there are data indicating that opioid treatment is associated with lower circulating testosterone levels.[50-53] In a recent RCT, in which 84 men receiving opioid analgesia for chronic non-cancer pain and with baseline testosterone levels < 12.2 nmol/L (average, 8.7 nmol/L) were randomly assigned to receive testosterone or placebo, there was no significant effect of testosterone treatment on the primary outcome of self-reported pain or on opioid dosage.[54] Testosterone improved one out of eight measures of experimental pain perception and reduced body fat, compared with placebo.[54] Further studies are needed to determine whether testosterone therapy would effectively and safely improve health and functional outcomes in men receiving glucocorticoid or opioid therapy.

Where possible, removal of relevant glucocorticoid or opioid medications should be attempted, as this should reverse functional gonadal axis suppression and safely raise testosterone levels, with effective improvement in health and functional outcomes. The underlying strategy directs the focus back to primary health disorders, as these may be treatable and reverse the decline in serum testosterone levels. Where continuation of glucocorticoid or opioid therapy is necessary, review by an endocrinologist may be warranted for assessment and discussion of the risks versus benefits of different interventions. It is possible that therapeutic roles for androgens exist; however, additional evidence is needed from properly designed placebo-controlled RCTs with outcomes related to patient health and functional improvement.

Conclusions

Pathological hypogonadism can present in many ways, such as psychosexual symptoms or unexplained osteoporosis, anaemia or reduced muscle mass, and the diagnosis can be missed. It is a clinical diagnosis with a pathological basis, confirmed by low testosterone levels. TRT is warranted in men with pathological hypogonadism to alleviate symptoms and signs of androgen deficiency, and it may have marked benefits in these men. By contrast, in men with preserved spermatogenesis and without pathological hypogonadism, testosterone treatment is expected to impair fertility. In the absence of hypothalamic, pituitary or testicular disorders, testosterone therapy is not justified in older men with medical comorbidities. Obese men who may have reduced testosterone levels should be encouraged to lose weight using a combination of diet and exercise. Currently, there is limited evidence for the efficacy and safety of testosterone treatment in men with diabetes and those receiving glucocorticoid or opioid therapy. Further evidence from well-conducted RCTs is required before such treatments can be fully evaluated.

Importantly, men who have classic causes of pathological hypogonadism that have been missed earlier in life, or men who have developed disorders of the HPT axis, may present at any age; there is universal agreement that such men should be identified and considered for treatment. It is important not to miss a diagnosis of pathological hypogonadism in a man who may coincidentally have diabetes or another comorbidity (including among older men with chronic disease), or to confuse it with non-specific effects of systemic disease on the reproductive system.

The recommendations given in this position statement are based on data from a limited number of RCTs, as well as non-randomised clinical studies and observational studies. As such, further research is warranted, which may have an impact on the recommendations.

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