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How to manage low testosterone level in men:

a guide for primary care

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Submitted: 7 October 2019; **Editor's response:** 31 October 2019; **final acceptance:** 14 November 2019.

70: 364–365.
DOI: https://doi.org/10.3399/bjgp20X710729

INTRODUCTION

Male hypogonadism is a clinical syndrome characterised by testosterone deficiency and impaired spermatogenesis; due either to diseases of the hypothalamus or pituitary gland, or of the testes themselves.[1] The diagnosis requires the presence of clinical features consistent with lack of testosterone plus the finding of persistent and unequivocally low serum testosterone levels. Failure to recognise and treat men with hypogonadism may predispose them to long-term health problems, such as anaemia, osteoporosis, depression, or sexual dysfunction.

Over recent years, there has been a surge in testosterone prescriptions for men with sexual dysfunction or putative age-related decline in testosterone,[2] possibly reflecting pharmaceutical promotion, or sharing of misleading information on the internet. With growing demands and expectations of men worried about their wellbeing, there is a real risk of overdiagnosis and unnecessary treatment with testosterone. Suboptimal sampling conditions can lead to misinterpretation of serum biochemistry, and the long-term risks of testosterone therapy for men not having verified hypogonadism may be underestimated by 'enthusiasts'.

DIAGNOSTIC CHALLENGES

Diagnosis of hypogonadism

Routine screening for hypogonadism in asymptomatic men is not recommended, except in certain conditions (Supplementary Figure S1). Clinical features of hypogonadism are not limited to sexual symptoms — reduced libido, erectile dysfunction (ED), and loss of waking erections. Anaemia, osteoporosis, and vasomotor sweating or flushing are frequently present; indeed, older men may not volunteer sexual symptoms, having ascribed them to ageing.

Sampling conditions

Testosterone secretion has diurnal variation and is suppressed post-prandially, so serum testosterone and sex-hormone binding globulin (SHBG) should be measured between 7.00 am–11.00 am following an overnight fast. Most testosterone is protein-bound in the circulation and the unbound free testosterone (FT) represents only 2–4% of the total. In men with high or low SHBG levels, total testosterone may give a misleading measure of androgenicity, and estimating FT via mass-action equation (for example, www.issam.ch/freetesto.htm) becomes worthwhile, but otherwise total testosterone is the parameter to follow. Men with obesity and insulin resistance may have very low SHBG levels; hence normal FT despite having a low total testosterone. Conversely, men with high SHBG levels may have low FT despite normal total testosterone.

Testosterone readings below the reference range on at least two different occasions, at least 4 weeks apart, are consistent with hypogonadism, but the underlying cause should then also be ascertained.

PRIMARY, SECONDARY, AND FUNCTIONAL HYPOGONADISM

The first step in establishing aetiology is measuring serum luteinising hormone (LH) and follicle stimulating hormone (FSH) levels (Supplementary Figure S1 and Supplementary Box S1). Primary hypogonadism (PH) results from intrinsic testicular dysfunction, being characterised by low testosterone, raised LH and FSH, and can thus be reliably diagnosed under almost all blood-sampling conditions.[3] PH affects 1–2% of older men and it is associated with increased risk of type 2 diabetes mellitus (T2DM).

Secondary (or central) hypogonadism (SH) is characterised by low testosterone with low-to-normal LH and FSH levels. SH is caused by impaired hypothalamo-pituitary function (see Supplementary Box S1) and, hence, serum ferritin and pituitary hormone profile (serum prolactin, cortisol, and thyroid hormones) plus imaging is warranted.

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Provenance

Freely submitted; externally peer reviewed.

Competing interests

Channa N Jayasena received an honorarium for debating the safety of testosterone therapy at a meeting organised by the Society of Endocrinology sponsored by Besins Healthcare. Richard Quinton has received honoraria and hospitality from Bayer UK.

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Crucially, the biochemical signature of SH (pathologically low LH and FSH levels) may be indistinguishable from that of non-gonadal illness (NGI) — where there is physiological suppression of LH and FSH (for example, due to obesity and T2DM) that resolves upon recovery.

Although testosterone, along with other androgens, is a banned substance under doping regulations for sport, its use by non-professional athletes — or even men who wish to achieve a more sculpted musculature — seems to be increasingly pervasive. Some of these men will then seek NHS prescriptions for testosterone, or referral to a specialist by their GP.

MANAGEMENT GUIDELINES

Unlike men with infertility and erectile dysfunction, for whom there are established UK guidelines,[4,5] there is no single UK consensus on how to approach male hypogonadism. Our suggested algorithm in Supplementary Figure S1 provides a pragmatic approach to low testosterone, taking into account the best evidence and practice within the NHS.

SAFETY OF TESTOSTERONE AND OTHER CONSIDERATIONS

In men with verified hypogonadism, testosterone therapy maintains secondary sexual characteristics, improves psychological and sexual function, bone and muscle health, and reduces anaemia and frailty. The only contraindications are baseline erythrocytosis, a desire to father children, active prostate or breast cancer, decompensated cardiac or liver disease, and imminent end-of-life.

Testosterone may cause erythrocytosis,[6] which can increase the risk of cardiovascular events, so haematocrit should be checked before initiation and annually during therapy. Although it is not now considered to promote development of de-novo prostate cancer, it may however increase the risk of detecting subclinical prostate cancers through prostate-specific antigen (PSA) screening, thereby predisposing men to invasive prostate biopsies.[6,7] International guidelines[1,3,8] recommend measuring PSA at baseline and 3–6 months after starting testosterone initiation in men aged ≥40 years, with annual surveillance thereafter. The role of digital rectal examination continues to be debated,[6] but a urology referral should be considered for those men with a rising PSA.

Exogenous testosterone may suppress spermatogenesis and men desiring fertility should thus be referred to local reproductive services before starting.

With injectable testosterone, measurement of testosterone levels is best done at 'trough', immediately before an injection is due. For men using gels, serum testosterone should be measured at least 4 hours after the last application. Other things being equal (haematocrit, bone density, and symptoms), treatment aims to achieve testosterone levels in the reference range (mid-range for gel; low end at trough for injectables). Decision to continue testosterone therapy requires ongoing holistic review of the original indications for initiating it — along with intended benefits of continuing — versus the potential risks of therapy.

In men with functional hypogonadism arising in relation to NGI (such as men with obesity, T2DM, or any other long-term illness), studies have yielded contradictory data in respect of cardiovascular safety and clinical efficacy of testosterone. Therefore, first-line management of men with NGI should include an optimisation of their other medical comorbidities, and trial of phosphodiesterase inhibitors for those with ED.

WHAT IT MEANS FOR GENERAL PRACTICE

Primary care physicians can confidently diagnose PH, but SH can be tricky for generalists to disentangle from NGI; nevertheless, primary care physicians have important roles in this area. First, they can order further investigations pending specialist review and, second, when NGI with potentially reversible/functional cause of low testosterone has been identified — rather than true SH — they are key to delivering long-term chronic disease management, which — based on current evidence — should not usually involve testosterone.

SUMMARY

Men are increasingly seeking testosterone measurement for a variety of reasons and GPs are thus faced with a burgeoning number of 'low testosterone' results needing to be actioned. As the diagnosis of hypogonadism is not always straightforward, careful clinical and biochemical assessment is essential prior to prescribing.

Funding

Ahmed Al-Sharefi is funded by an Imperial College Healthcare Private Services Fellowship. Channa N Jayasena is funded by a National Institute for Health Research Post-Doctoral Fellowship.