Benefits of testosterone replacement

GEOFF HACKETT

It is unhelpful to compare the decline in testosterone levels with age in men with the menopause in women, as most men maintain adequate levels of androgens throughout their life.1 Testosterone deficiency syndrome (TDS) is strongly associated with type 2 diabetes, metabolic syndrome and obesity. TDS is both a precursor to these conditions and a consequence, as low testosterone (below 10.4nmol/l) in younger men has been shown in multiple studies to lead to a four-fold risk of type 2 diabetes and increased all-cause and cardiovascular mortality.2–7

NORMAL TESTOSTERONE LEVELS: THE EFFECTS OF HEALTH AND AGEING

Attempting to produce age-related normal levels of testosterone is unhelpful, as the diagnosis of TDS or hypogonadism is dependent on a combination of symptoms and low testosterone levels. The European Male Ageing Study1 showed that the best predictive symptoms of hypogonadism are erectile dysfunction (ED), loss of morning erections and reduced libido; these symptoms are therefore likely to have greater impact on younger men as relationships and families are affected and younger men demand treatment for bothersome symptoms.

There are many parallels with hypothyroidism, with a prevalence increasing with age, no age-related normal values, more impact in younger patients and management targeted at a combination of relieving symptoms and returning levels to normal ranges. Younger patients may require greater thyroid-stimulating hormone suppression to relieve symptoms. Overtreatment of hypothyroidism is also associated with considerable health risks, yet missing a diagnosis of hypothyroidism (but not hypogonadism) would cause doctors to fear a complaint of negligence.

MEASURING SERUM TESTOSTERONE: POTENTIAL PITFALLS

We manage many conditions on a pragmatic basis and it becomes easy to use the complexity of testosterone metabolism and measurement as an excuse to avoid treatment. Target levels for lipid management imposed by NICE are based on total cholesterol8 (sometimes fasted, sometimes not), yet we know that high- and low-density lipoprotein cholesterol and triglycerides are important. Hypertension is managed routinely on casual measurement. Sex hormone-binding globulin influences thyroid metabolism, but the impact of oral contraceptives and hormone replacement therapy is frequently ignored. Once again,
the combination of clinical symptoms and abnormal biochemistry should influence the decision to treat men with TDS.

**SERUM TESTOSTERONE: THE EFFECTS OF COEXISTING DISEASE**

Testosterone deficiency syndrome has been clearly shown to be both a cause and a consequence of visceral adiposity\(^8\)\(^{–}\)\(^{12}\) and in most cases it is impossible to determine which came first. In managing cardiovascular disease, we treat all risk factors concurrently, even though we know that weight reduction and lifestyle change will lower cholesterol and blood pressure, because we know that early intervention with statins and antihypertensives saves lives.

Intensive long-term lifestyle change has been shown to produce modest improvement in testosterone and sexual function at about two years, but the majority of men presenting with ED and low desire do so at a stage of catastrophic impact on their marriage or relationship. Although philosophical discussion on lifestyle has a place for these men, it usually needs to be combined with medical therapy. Recent publications suggest that the long-term treatment of TDS may be associated with marked sustained weight loss.\(^8\)\(^{,}\)\(^{13}\)

**HEALTH EFFECTS OF DECLINING TESTOSTERONE LEVELS**

In their article, Sally Thrower and Bushra Ahmad quote only Society for Endocrinology guidelines. The paradox of male hypogonadism is that the three common symptoms most specifically related to low testosterone are ED, loss of morning erections and diminished libido; management pathways mean that these men are referred primarily to urologists and sexual medicine physicians, who follow guidelines from the European Association of Urology (EAU), European Society for Sexual Medicine (ESSM), International Society for Sexual Medicine (ISSM), British Society for Sexual Medicine (BSSM) and International Society of Men’s Health (ISMH).\(^{14,}\)\(^{15}\)

These guidelines clearly define the levels at which the various symptoms and signs of hypogonadism become evident. NICE guidance and the Quality and Outcomes Framework for GPs require that all men with type 2 diabetes be asked annually about ED and assessed according to published guidelines.\(^8\)\(^{,}\)\(^{10,}\)\(^{12}\) As 75 per cent of men with type 2 diabetes have ED,\(^{10,}\)\(^{12}\) and all the above guidelines list testosterone measurement as mandatory in all men with ED, quoting hypogonadism as a curable cause of ED,\(^{14,}\)\(^{15}\) there is considerable support for treating men with ED and low testosterone prior to using other drugs.

The Society for Endocrinology guidelines strongly suggest measuring testosterone in all men with sexual problems and all men with type 2 diabetes, and the overwhelming evidence that ED is a predictor of cardiovascular events means that men over 40 are routinely being asked about ED; if present, testosterone measurement should be conducted in all cases.

Hypogonadism must be the only condition in modern medicine where the specialists do not routinely manage the three most common symptoms of that condition.\(^1\) Health providers have compounded the problem by choosing to view sexual symptoms as lifestyle or even recreational issues. A further complication is that multiple studies have shown that oral medications used to treat ED are much less effective in hypogonadal men and that non-responders can be converted to responders if testosterone levels below 10.4nmol/l are treated. When low testosterone is detected in a man with ED, urology and sexual medicine guidelines strongly suggest that the treatment of comorbidities (especially low testosterone) are at least as important as specific therapy for ED.

**TREATING TESTOSTERONE DEFICIENCY IN THE OLDER MAN**

**Risks and benefits**

Sally Thrower and Bushra Ahmad quite rightly recognise the multiple beneficial effects of TRT, and few other treatments show such a diverse profile for potential health improvement.\(^9\)\(^{–}\)\(^{12}\)\(^{,}\)\(^{16,}\)\(^{17}\) It is difficult in the modern world to decline treatment on the basis of age; for example, we continue to use statins in patients in their 80s and 90s, in spite of trials showing questionable benefits and high side-effect profiles. As men are remaining in better health for longer, they are demanding active sex lives for longer and it is inappropriate for a physician to decide at what age a couple does not justify treatment for an active sex life, which, for them, may be a huge priority.

Anemia is a feature of hypogonadism, and an increase in haematocrit is an important component of clinical improvement. Hypogonadism has been shown to be associated with increased risk of stroke and transient ischemic attack.\(^4\) No meta-analyses of testosterone therapy have shown an increased risk of cardiovascular events; rather, there has been a trend for reduced risk.\(^16,\)\(^{19}\) Modern treatments such as gels and depo-testosterone undecanoate are associated with decreased risk of cardiovascular events.\(^7\)

Total cholesterol is consistently lowered by TRT and the balance on lipid profiles across the studies is favourable. None of the published guidelines has shown any evidence for an increase in prostate cancer. There is a tendency for BPH to improve,\(^{8,}\)\(^{11}\) as testosterone improves pelvic blood flow, reduces insulin resistance, reduces sympathetic overactivity and potentiates the effect of phosphodiesterase-5 inhibitors,\(^{15}\) which are now licensed to treat BPH. The EAU guidelines\(^{15}\) concluded that there was no evidence for a link with sleep apnoea or male-pattern baldness and that acne and gynaecomastia are rare problems in younger men, usually associated with supraphysiological levels. Reduced spermatogenesis can be an issue for younger men but is usually reversible.\(^{15}\)

**Who to treat?**

The EUA, ESSM, ISSM, BSSM and ISMH guidelines all agree that men with a total
testosterone level of less than 8nmol/l (free testosterone <180pmol/l) should be treated and that those with a total testosterone level of 8–12nmol/l should be considered for a trial of treatment according to symptoms. However, recent studies suggest that a trial of three to six months might not be long enough, as therapeutic levels must be consistently attained for clinical benefit. Erections continue to improve for up to 18 months and loss of visceral fat and improved insulin resistance are progressive for up to four years. As long-acting testosterone undecanoate reaches peak steady state after five injections, with 12-week intervals, a three-month trial is clearly inadequate. In practice, choosing a three-month trial, particularly if combined with a negative counselling approach, sets the patient up for failure.

CONCLUSIONS
There is universal agreement that TRT should not be given unless there is clear evidence of symptoms supported by biochemically low testosterone. The key issue is that patients should be assessed for symptoms that are important to them and not according to the agenda of the physician. Clinical trials of therapy need to be of sufficient duration and certainly longer than the six months suggested by some guidelines. The potential benefits of the treatment need to be mentioned, as well as the possible impact of not treating the condition. Counselling in terms of possible side-effects of physiological replacement needs to be evidence based and not exaggerated scaremongering from anecdotal cases related to anabolic steroid abuse.

Declaration of interests
Geoff Hackett is an occasional speaker and researcher for Lilly and Bayer.

REFERENCES