Why the evidence for testosterone therapy adds up

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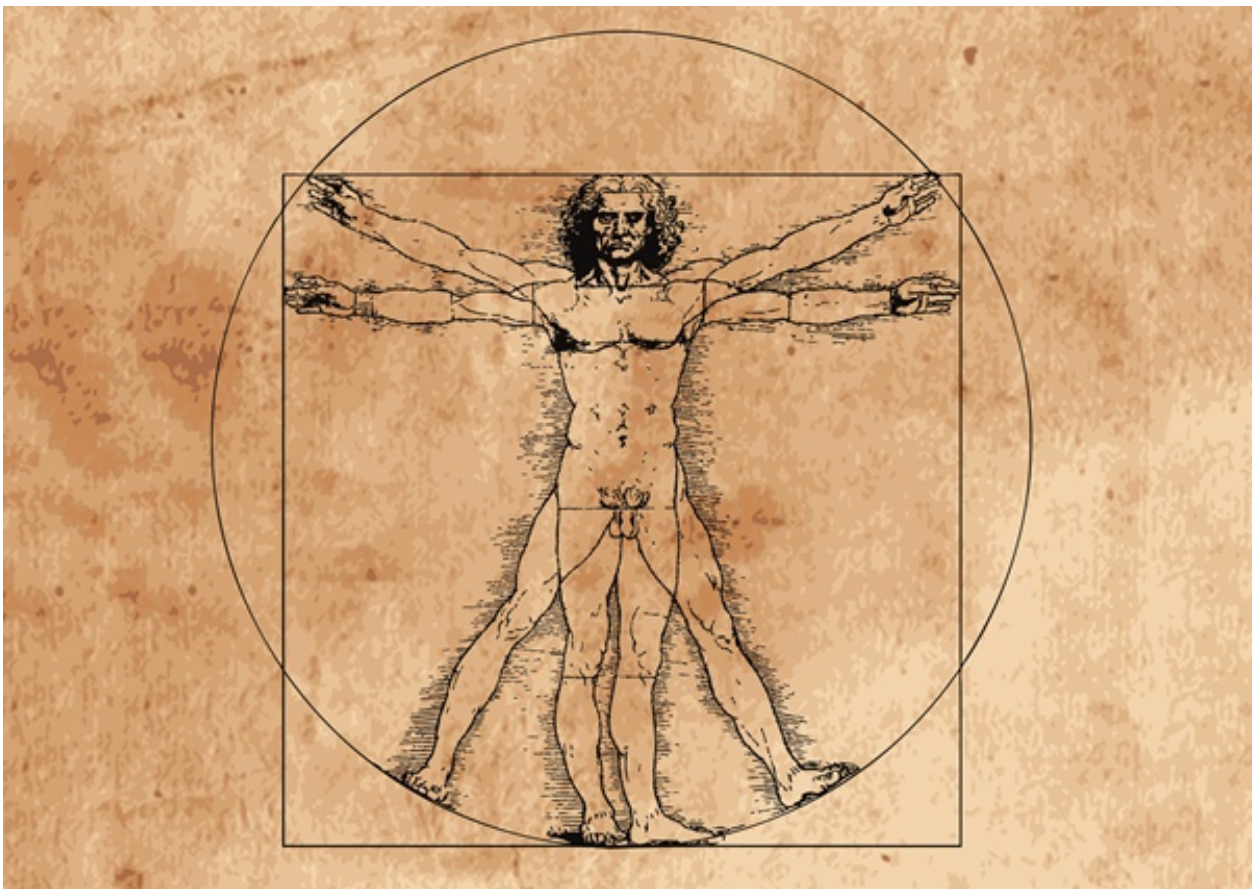

A closer examination of the evidence on testosterone therapy for men shows why the animosity surrounding the treatment is based on flawed assumptions.

Few topics arouse more passion than the subject of testosterone therapy in men and recent debates in *The Pharmaceutical Journal* (*The Pharmaceutical Journal* 2017;298;100) confirm this. We all have an emotive view on the subject, usually with little knowledge of the evidence base. Some parties in recent discussions have clearly been selective in their source of evidence, often historical or anecdotal. Those of us who deal with men presenting with clear physical problems, most commonly erectile dysfunction, low sexual desire, reduced physical strength and low energy, in the presence

of confirmed low testosterone levels, regularly see the benefits of therapy. This is not a case of the 'male menopause' because this condition does not exist; 80% of men maintain testosterone levels throughout life. Testosterone therapy is not an elixir of youth, a magic bullet or an aphrodisiac. In this article, I will explain how testosterone therapy is indicated for a defined symptomatic hormone deficiency that is predominantly a consequence of metabolic syndrome and type 2 diabetes. Men deserve to be diagnosed and treated in the same way that we screen and treat hypothyroidism, which is also an age-related hormone deficiency, often without a clear cause, and seen predominantly in women.

Understanding testosterone deficiency

In order to understand why testosterone therapy is needed and why it is effective, it is important to understand what we are trying to treat with the drug.

The current guidelines from the International Society for Study of the Ageing Male, European Association of Urology, International Society for Sexual Medicine, and British Society for Sexual Medicine define hypogonadism (HG) or testosterone deficiency (TD) as ''a biochemical syndrome associated with advancing age and characterised by a deficiency in serum androgen levels with or without a decreased genomic sensitivity to androgens. It may result in significant alterations in the quality of life and adversely affect the function of multiple organ systems."[1],[2],[3],[4]

Men with low levels usually have defined medical reasons — testicular disease or cardio-metabolic disease such as type 2 diabetes

Around three-quarters of men maintain testosterone levels throughout life[5]. Those with low levels usually have defined medical reasons, such as testicular disease or cardio-metabolic disease such as type 2 diabetes, where the prevalence of low testosterone levels is 40%[6]. There is no such thing as 'male menopause' (a media concoction), nor is testosterone therapy an elixir of youth or about helping old men to find their 'mojo'.

The above guidelines recommend the measurement of testosterone as mandatory in all men with erectile dysfunction and that men with total testosterone (TT) levels below 8nmol/l should normally be offered treatment and that those with levels 8–12nmol/l should be considered for a minimum six-month trial of therapy according to severity of symptoms. In 2017, the American College of Endocrinology recommended testosterone measurement in all men with type 2 diabetes, a body mass index greater than 30kg/m^2 or

a waist circumference more than 102cm. This suggests that testosterone deficiency is an important health issue[7].

The Princeton III guidelines for the management of erectile dysfunction and cardiovascular disease[8] highlighted that measurement of testosterone was mandatory in all men with erectile dysfunction (ED) and suggested that TT was an independent marker for future cardiovascular (CV) events. Multiple long-term longitudinal studies have shown that low TT and free testosterone (FT) are associated with increased cardiovascular and all-cause mortality[9],[10],[11],[12], after adjusting for other CV risk factors[11],[12], especially in men with pre-existing metabolic disease and type 2 diabetes[13]. A five-year follow-up from the European Male Aging Study in 2013 concluded that ED and low TT independently predicted mortality and that men with both conditions were at particularly high risk[14].

It is strange that low testosterone, a strong predictor for type 2 diabetes, is completely ignored in the UK

Several longitudinal studies have shown that low levels of TT and FT independently predict the later development of type 2 diabetes, with a three- to four-fold risk[15],[16]. It is strange that such a strong predictor for type 2 diabetes is completely ignored in the UK. Holmboe *et al.* reported on 5,250 men from the Danish population followed up for 29 years and showed that low TT and low sex hormone-binding globulin (SHBG, a glycoprotein that binds to the two sex hormones: androgen and oestrogen) were strongly associated with the development of type 2 diabetes. Because there was no effect of luteinising hormone, the authors concluded that primary HG was not a risk factor for type 2 diabetes but that low TT should be considered a risk marker[17].

Evidence for testosterone therapy

Perhaps a reason why scepticism exists around testosterone therapy is that testosterone deficiency syndrome cuts across several specialities. Endocrinologists are not trained in sexual medicine and do not read urology or sexual medicine journals; and urologists do not read endocrine journals; and cardiologists read only cardiology journals. Patients present with bothersome symptoms that they want treated. They do not want a philosophical dissertation on ageing or theology, they want their health and their relationship back. We do not tell patients that blindness, deafness, dementia and loss of teeth are “just part of ageing” and we would treat hypothyroidism at age 100 years without a moment’s thought that this is an endocrine condition associated with ageing.

Physicians and journal editors may have preconceived views on testosterone and interpret studies based on these preconceptions

Physicians and journal editors may have preconceived views on testosterone and we often select and interpret studies based on these preconceptions. TD is a highly symptomatic condition and double-blind placebo-controlled trials of sufficient duration are difficult to conduct. Testosterone replacement therapy (TRT) is associated with multiple time-related improvements that, to the specialist with a narrow interest, might not seem impressive but, put all together, result in benefit that is highly meaningful to the patient. For example, studies on sexual function for three months will usually show benefit only in desire, because ED in TD is related to structural and functional changes in the penis that only manifest at six months and improve progressively over several years[18]. Loss of visceral fat and increase in lean muscle can take 12 months[19]; the sceptic will seek short duration studies and state that findings were inconclusive.

The 'negative' evidence

Critics of TT will often cite research papers that prove a negative effect of TT on men's health. Below are some of them, along with explanations about why these conclusions are flawed.

A retrospective US study of 8,709 men with baseline TT of 10.4nmol/L or less undergoing coronary angiography involved follow-up for a mean of 840 days. In the cohort of 7,486 patients not receiving testosterone therapy, 681 died, 420 had a myocardial infarction and 486 had stroke. Among 1,223 patients receiving testosterone therapy, 67 died, 23 had myocardial infarction and 33 had stroke. These absolute event rates suggested a protective effect for TT. Complex statistical analysis (using >50 co-variates, but excluding baseline testosterone level and presence of ED) reversed the trend and concluded that there was a greater risk in the TT group[20].

There were concerns that 1,132 patients experiencing events were excluded because they were prescribed TT after the event. When challenged, the authors revised the number to 132, but conceded that 104 women had wrongly been included in the results. Subsequently, 27 medical societies demanded that this paper be retracted from the medical literature, but unfortunately it remains the most quoted paper on this subject[21].

Finkle *et al.* studied prescribing data in men treated with TT, but with no data on blood results or symptoms, and therefore effectively no diagnosis. Non-fatal coronary events were the major endpoint, assessed in the 12 months before and 3 months after therapy, even though benefits of TT would take much longer. They reported a small increase in

non-fatal cardiac events in men started on TT, more marked in those with increased risk. Overall events in the study were lower than predicted from comparable research. Although widely quoted in public media, several design flaws and statistical analyses have discredited this paper[22].

Consider the impact of papers where measurements were not taken before or during the study. Such papers should be in the editorial waste bin

Consider the impact of papers on hypertension or dyslipidaemia, where no measurements were conducted before or during the study to confirm any diagnosis, and prescriptions were issued with no evidence of compliance and with only three months' follow-up from insurance databases. Consider a study on the impact of a treatment for prostate cancer where 104 women were included. Such papers should only see the lining of the editorial waste paper bin.

A recent sub-study from a trial reported increased atheroma in men taking testosterone compared with placebo, although coronary calcification, the current UK standard, was improved with testosterone. Close examination of the data revealed that, by chance, baseline atheroma levels were 50% higher in the placebo group. These were therefore not comparable groups. Patients and GPs were informed of these high baseline levels for clear ethical levels and men at high risk were referred to cardiologists for stenting, bypass and more aggressive risk reduction. Therefore this ceased to qualify as a randomised controlled trial. The authors reported no coronary events, which is not possible. If taken at face value, how can testosterone be dangerous if no cardiac events occurred in 12 months in a group of elderly men with significant atheroma? Unfortunately, this paper and the associated editorial, published in *JAMA*, were already widely reported in the media before peer review highlighted these severe limitations[23].

In the Testosterone in Older Men (TOM) study, frail elderly men were treated with up to 150mg of testosterone gel, above the summary of product characteristics of the drug. The testosterone group had more patients with cardiovascular disease at baseline. Ankle oedema and dizziness were classified as cardiac events and electrocardiogram changes not confirmed by cardiologists. Two men died, both in the treatment group and the study was stopped prematurely. No other testosterone study has shown this effect[24]. In a trial of 790 men, seven died at 12 months on placebo and three on TT but this was classified as "not significant"[25].

Positive studies

Recently, a meta-analysis has reported the positive impact of TT on insulin resistance and glycaemic control plus reduced visceral adiposity, lean muscle mass, sexual desire and erectile function[18].

Seven longitudinal studies have evaluated long-term safety in patients properly diagnosed and treated to target levels for sufficient duration[26],[27],[28],[29],[30],[32],[33] in contrast to the negative studies.

A prospective study of 587 men with type 2 diabetes involved 5.8 years of follow-up [26]. Low testosterone was defined as TT <10.4 nmol/L. The mortality rate was 19.2% in the untreated low testosterone group, 9% in the normal testosterone group and 8.4% in the treated low testosterone group. A similar retrospective US study involved 1,031 hypogonadal men, with 372 on TT. The cumulative mortality was 21% in the untreated group versus 10% in the treated group, with the greatest effect in younger men and those with type 2 diabetes[27].

Hackett *et al.* followed up 857 men with TD and type 2 diabetes for four years. Patients were randomised to long-acting testosterone undecanoate or placebo assessment in a randomised controlled trial. The investigators confirmed that low baseline TT and FT were associated with increased all-cause mortality over the study period. TT and phosphodiesterase 5 inhibitors (PDE5Is) were independently associated with reduced all-cause mortality, with greatest benefit seen in older men[28].

Testosterone therapy was associated with reduced major adverse cardiovascular events and death

Anderson *et al.* studied 5,695 men with low initial TT level and more than three years of follow-up. TT was associated with reduced major adverse cardiovascular events and death over three years compared with no or ineffective supplementation. This study suggested that the favourable effect of TT was predominantly on mortality, rather than number of events, and benefits were associated with achieving therapeutic levels of testosterone. Substantial reduction in major adverse cardiovascular events was seen with angiographically diagnosed coronary artery disease[29].

Sharma *et al.* assessed 83,010 men with low TT levels. The subjects were categorised into three groups: TT with resulting normalisation of TT levels (group 1); TT without normalisation of TT levels (group 2); and did not receive TT (group 3). The all-cause mortality (hazard ratio [HR] 0.53, 95% confidence interval [CI] 0.50–0.55), risk of myocardial infarction (HR 0.82, 95% CI 0.71–0.95) and stroke (HR 0.70, 95% CI 0.51–

0.96) were significantly lower in group 1 versus group 2 (n=25,701, median age 66 years, mean follow-up 4.6 years)[30].

Wallis *et al.* reported a five-year follow-up of 10,311 men on long-term TRT compared with a 28,029 control group and found a decreased risk in all-cause mortality (HR 0.67, 95% CI 0.62–0,73), cardiovascular events (HR 0.84, 95% CI 0.72–0.98) and new cases of prostate cancer (HR 0.60, 95% CI 0.45–0.80)[31].

This year, Cheetham *et al.* retrospectively reported 8,808 testosterone treated and 35,527 untreated men with low testosterone and found a 33% reduction in cardiac events associated with TT[32].

These studies present the most convincing evidence to date for TT being associated with a reduction in all-cause and cardiovascular mortality in men with clearly defined HG treated for sufficient duration to the mid-upper normal range.

Practical issues

The European Male Aging Study (EMAS) showed that loss of sexual desire, ED, and loss of morning erections are the most common symptoms of low testosterone[33]. These men frequently fail with PDE5I treatment, particularly if they also have additional cardiovascular risk. With TT <10.4 nmol/l, testosterone combined with PDE5Is restores sexual function in more than 50%[34] of patients, considerably cheaper than second-line therapies, such as alprostadil injections, intra-urethral pellets or gels. Patients also feel better and there is evidence that the combination of TT and PDE5Is reduces all-cause mortality[35]. Patients expect problems to be addressed by well informed compassionate doctors, not biased evangelical healthcare professionals dispensing their own standards of social justice.

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Without the discovery of sildenafil, we would still be referring all men with ED to psychiatrists, labelling all as psychogenic[4]**.** Pharma advertising would not have been able to increase a market for testosterone over a period of more than 20 years if medication were not effective.

I have personally treated more than 1,000 men with symptomatic testosterone deficiency, following them for longer than ten years and I have published my results. I can

categorically say that (in conjunction with PDE5Is) I have never prescribed any other medicine that has such an impact on the life of my patients, their partners and even their families.

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