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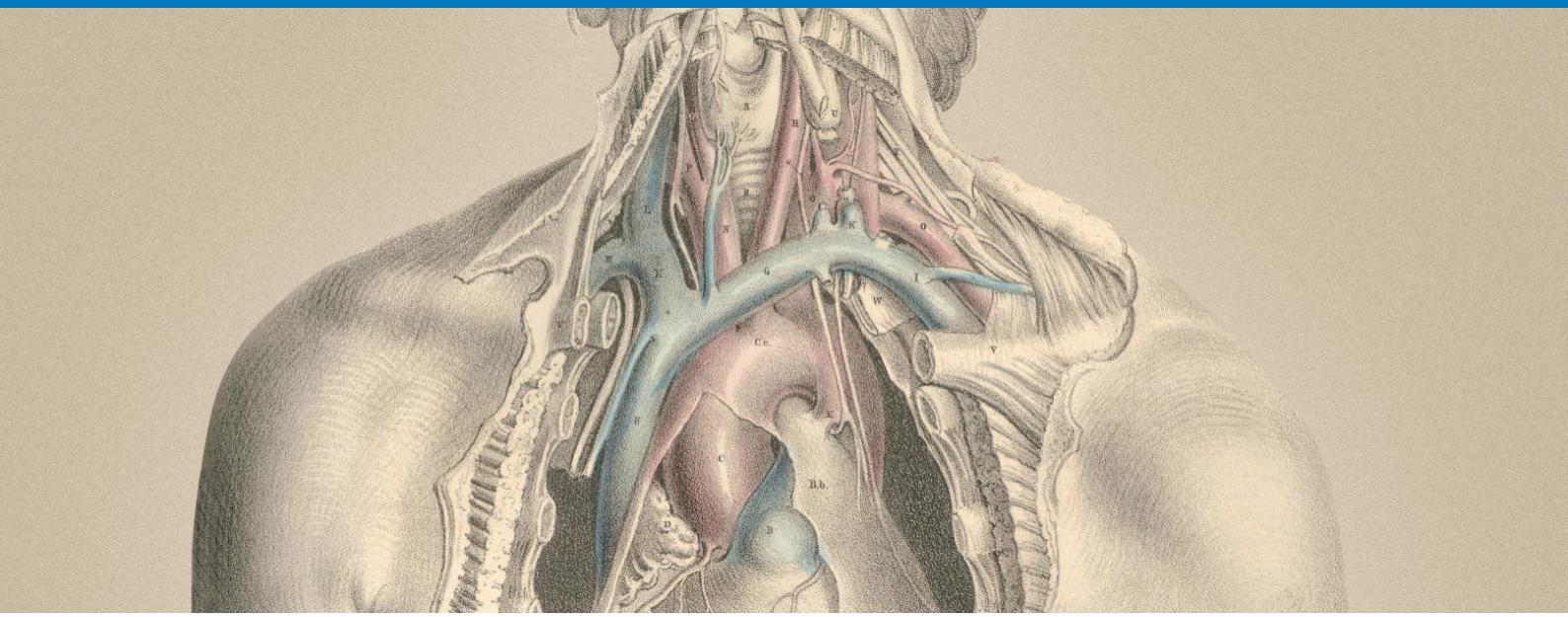
Cardiovascular Risk and Testosterone Supplementation



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This article examines the evidence for the cardiovascular safety of testosterone replacement therapy in older men with non-specific symptoms and unexplained low testosterone levels.

Introduction

Concerns have been raised about testosterone replacement therapy, particularly in middle-aged and older men. Testosterone replacement therapy may be a risk to cardiovascular health, but a clear picture has not yet emerged.[1,2] This possibility follows the increasing use of testosterone replacement therapy in men who do NOT have established disorders of the hypothalamo-pituitary-testicular axis. Such men often present with nonspecific symptoms (tiredness, lethargy, loss of vitality, reduced libido) associated with low or normal testosterone levels. There has been a marked rise in the United States of America in testosterone prescriptions for the ill-defined disorder of 'andropause' or 'late-onset hypogonadism'.[3]

The clinical context is critical when discussing cardiovascular risk. Australian guidelines for the evaluation and management of androgen deficiency in adult males were recently revised.[4,5] Testosterone replacement therapy is warranted in men with the clinical and biochemical features of androgen deficiency, in whom disorders of testicular function or the hypothalamo-pituitary system

Take Home Messages

- Testosterone replacement therapy is recommended for men with established androgen deficiency due to disorders of the hypothalamo-pituitary system and/or testicular dysfunction.
- Low serum testosterone levels are known to be associated with ageing, obesity and a range of chronic diseases, including diabetes and chronic renal disease.
- Evidence for whether testosterone replacement therapy increases cardiovascular risk is conflicting.
- Clinicians are advised to consider co-morbidities associated with low testosterone. They should prioritise attention to cardiovascular risk factors in older men with symptoms, once established disorders causing androgen deficiency have been excluded.

are demonstrable, irrespective of age. This is in common with international guidelines.[6]

- The aim of testosterone replacement therapy is to correct a deficiency with physiological levels of testosterone and its metabolites (dihydrotestosterone and oestradiol), to meet the needs of the reproductive system, metabolism, fat, muscle, bones and sexuality. As cardiovascular disease is a major cause of morbidity and mortality, good clinical practice requires an 'age-appropriate' review of general health, comorbidities and lifestyle risk factors. Testosterone replacement therapy is not regarded as an additional cardiovascular risk factor when used in men with established testicular or hypothalamo-pituitary failure.

Serum Testosterone as a Biomarker of Health

The issue of cardiovascular risk arises when one considers testosterone replacement therapy in men without defined disorders of the hypothalamic–pituitary-testicular axis. A low serum testosterone is increasingly regarded as a 'biomarker' of health, reflecting the effects of ageing and particularly obesity, insulin resistance, diabetes and chronic renal, liver or vascular disease. Importantly, higher testosterone levels were consistently found in men aged forty to eighty years who self-reported 'excellent or good health'.[7]

If there is an intrinsically age-related failure of the hypothalamic–pituitary–testicular axis in men, it occurs very late in life (after eighty years) in contrast to female menopause.[8] Catchy terms, such as 'andropause', lack physiological meaning. Nonetheless, the popular press and the Internet provide a powerful stimulus for men to seek treatment.

The impact of body mass index on serum testosterone levels is striking and many obese men and/or men with diabetes have low testosterone levels. This 'reset' of the hypothalamic–pituitary-testicular axis often features reduced sex hormone binding globulin levels and reduced total serum testosterone (and to a lesser extent free testosterone) estimates, below the reference interval for healthy young men. Typically, luteinising hormone (LH) and prolactin levels are normal.

In the European Male Ageing Study, mean testosterone levels in obese men were approximately 6nmol lower than lean age-matched controls.[9] These changes are reversible. A 15% reduction in weight has been shown to be associated with a 5nmol increase in testosterone, and a 2.2IU/L increase in LH levels.[9] Weight loss by diet, exercise or bariatric surgery all increase serum testosterone levels.[10]

This suggests that rather than a true androgen deficiency state, the primary driver of lower testosterone levels is the underlying illness(es). It is possible that testosterone replacement therapy might be beneficial in some chronic disease states by acting as a 'drug' therapy; for example to improve metabolic health or physical function in frailty states. But such usage must await guidance from placebo-controlled randomised control trial (RCT) studies to understand its benefits and risks, especially cardiovascular risks.

Cardiovascular Risk Evidence

Epidemiological studies relate low testosterone to higher rates of metabolic syndrome,[11] cardiovascular disease and overall mortality.[12] However, associations do not prove causation, nor help understand potential mechanisms. Observational studies on cardiovascular risk with testosterone replacement therapy are conflicting. A United Kingdom study suggested that there might be an increased risk of venous thromboembolism after commencement of testosterone replacement therapy, particularly in the first six months of treatment.[13]

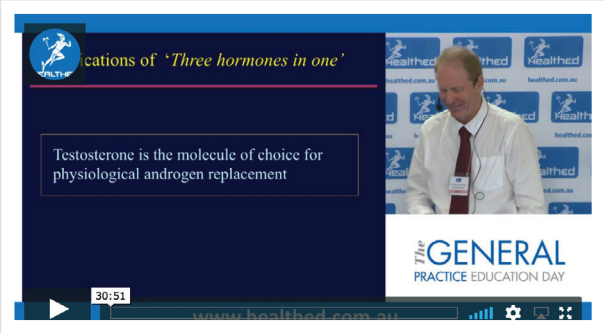
Clearly, one needs RCT data to establish causality. The largest of its type are the United States 'T-trials' which give valuable insight into testosterone replacement therapy risks and benefits.[14] Approximately 800 men received testosterone gel or placebo for twelve months, across seven sub-trials that examined physical and sexual function, vitality, cognition, anaemia, cardiovascular risk markers and bone metabolism. Among the cohort (aged seventy-two plus or minus six years), co-morbidities were common (63% obese, 37% diabetic, 71% hypertensive, 16% past history of myocardial infarction) and reflect the typical population seeking testosterone replacement therapy for symptoms such as tiredness, low libido and erectile dysfunction.

> A UK study suggested there might be an increased risk of venous thromboembolism after commencement of testosterone replacement therapy, particularly in the first six months of treatment.

In these trials, benefits from testosterone gel were seen in aspects of sexual and physical function and bone density, but were modest in extent. It was also unclear whether these benefits persisted beyond twelve months. High rates of cardiovascular disease would be expected in such men. While an excess of cardiovascular adverse events was not seen, the study was not designed to assess cardiovascular safety in the main T-Trial itself. Small RCTs, each subject to methodological criticism, suggested there could be increased cardiovascular adverse events with short-term, high-dose testosterone replacement therapy in frail older men. A T Trial sub-study found an increase in coronary artery plaque value, a surrogate marker of cardiovascular risk.

Video Resources

Causes of Male Infertility
with Prof Robert McLachlan



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Clinical Practice

Testosterone replacement therapy can be used with confidence in men who have established androgen deficiency due to diseases of the hypothalamus, pituitary or testes. However, when we consider the common presentation of older men with vague symptoms (typically attributed by them to low testosterone despite the absence of causal diseases), our attention is best directed to their co-morbidities (such as obesity, sleep apnoea and other medical conditions). We do not have evidence for great benefit, nor a clear understanding of the potential adverse cardiovascular risks of testosterone treatment in this setting.

Emerging RCT data (such as the Australian 'T4DM Trial' that examines testosterone versus placebo in the prevention or reversibility of type 2 diabetes),[15] are needed to establish efficacy and safety of testosterone in men without established androgen deficiency.

Summary

In summary, to date, the benefits of testosterone replacement therapy are not evident[16] or modest at best for men who do not have a true androgen deficiency state.[14] Whilst meta-analyses do not generally suggest increased cardiovascular adverse events,[1,2] no adequately powered RCTs examining 'hard endpoints' (such as myocardial infarction or stroke) have been conducted.

Other factors impact the use of testosterone replacement therapy in ageing men who have multiple medical conditions. The United States Food and Drug Administration published a bulletin in January 2014, raising concerns about the inappropriate use of testosterone replacement therapy and potential cardiovascular side-effects. It required testosterone product labelling to include the possible increased risk of myocardial infarction and stroke. It indicated strongly that testosterone replacement therapy should only be used for defined disorders of the hypothalamic–pituitary-testicular axis.

In July 2017, a United States Federal Court found in favour of a man who had a stroke after testosterone replacement therapy, and found against a testosterone gel drug manufacturer for fraudulent misrepresentation of its safety. Several thousand other lawsuits are currently being processed. Without analysing the merits of any of these cases, one can see the future impact of lawyers on the use of testosterone replacement therapy in older men.

Further Reading

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Yeap BB, Grossmann M, McLachlan RI, Handelsman DJ, Wittert GA, Conway AJ, et al. *Endocrine Society of Australia position statement on male hypogonadism (part 2): treatment and therapeutic considerations.* Med J Aust. 2016 Sep 5; 205(5): 228-31. DOI: 10.5694/mja16.00448

Declaration

Prof McLachlan was commissioned by Healthed for this article. The ideas, opinions and information presented are solely those of the author. The author declares no significant competing financial, professional or personal interests that might influence this article.

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