Testosterone levels and cardiovascular disease

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The marked gender differences in prevalence of coronary heart disease between men and premenopausal women have previously been attributed to potentially beneficial effects of oestrogen, but interventional studies did not support a protective role of oestrogen against development of coronary heart disease. Emerging data suggest that reduced testosterone levels in men may be associated with increased cardiovascular risk. Previous mainly cross-sectional studies have suggested an association between low testosterone concentrations and a more adverse metabolic profile,[1] and thus increased risk of cardiovascular disease. Nevertheless, several earlier small prospective studies did not detect any association between testosterone concentrations and cardiovascular disease.[1] In the more recent European Prospective Investigation into Cancer in Norfolk Study, endogenous testosterone concentrations at baseline were found to be inversely associated with all-cause mortality and cardiovascular mortality among men aged 40–79 without cardiovascular disease or cancer at baseline.[2] Furthermore, this risk association persisted, despite correction for traditional cardiovascular risk factors, suggesting that the benefit may involve additional pathways. Several other studies have linked low testosterone with cardiovascular disease and increased mortality[3] and, along with the increasing research on the clinical impact of age-related physiological decline in androgens, have led to rekindled interest in the potentially cardioprotective role of testosterone.

Although abuse of testosterone is linked with increased risk of cardiovascular disease and sudden death, higher testosterone levels within the physiological range have been found to be associated with a more favourable cardiometabolic profile; and conversely, low testosterone has been linked to elevated triglyceride and low high-density-lipoprotein-cholesterol levels, central obesity, glucose intolerance and diabetes.[1 4 5] This is partly due to the increased lipoprotein lipase and triglyceride uptake by adipocytes, leading to central obesity and insulin resistance (figure 1). The central obesity further leads to increased peripheral conversion of testosterone to oestradiol through increased aromatase activity, thereby further exacerbating this vicious cycle. Reduced testosterone concentration is associated with a proinflammatory state with increased levels of several inflammatory mediators such as TNF-α and IL-1β, which can be ameliorated with testosterone replacement.[6]

In addition to proatherogenic effects mediated by insulin resistance and altered lipid profile, testosterone has also been found to have direct effects on the vasculature. Testosterone induces coronary vasodilation and was found to benefit men with chronic stable angina.[7] Androgen receptors have been demonstrated to be present in the myocardium and may mediate some of the effects of testosterone on the cardiac renin–angiotensin system and cardiac remodelling. Deficiency of testosterone and other anabolic hormones are associated with the severity of heart failure, as well as increased mortality.[8] Testosterone induces expression of heat shock protein 70 in cardiac myocytes, and therefore may play an important role in preconditioning and protection against cardiac ischaemia.[9] In a cross-sectional study, patients with coronary heart disease were found to have lower levels of androgens.[10]

The study by Malkin *et al* (***see page 1821***) adds to this emerging picture. While several studies have demonstrated a link between reduced testosterone concentrations and increased cardiovascular mortality, these have in general excluded patients with pre-existing cardiovascular disease or those at high risk of cardiovascular disease. Whether the relationship applies to subjects with established cardiovascular disease was not clear. In their study, which included 930 men with angiographically proven CHD followed up for a mean duration of 7 years, there was a high prevalence of low testosterone at baseline ranging from 17 to 24% depending on the definition used. Importantly, low testosterone as defined by baseline serum bioavailable testosteorne <2.6 nmol/l was found to be an independent predictor of all-cause and vascular mortality.[11]

What is the implication of this study to clinical practice? Should we consider including testosterone measurements in the evaluation of cardiovascular risk in male patients? Biochemical assessment of testosterone levels needs to be performed with several caveats. Testosterone concentration is well known to be highly variable, and can be affected by acute or chronic concomitant illness. In their study cohort, subjects with inflammatory conditions, recent myocardial infarction, decompensated heart failure or elevated C-reactive protein were carefully excluded in order to minimise this effect.

Another difficulty of advocating routine testing of testosterone relates to the uncertainty as to how best to separate subjects with a physiological decline in testosterone from those with mild hypogonadism.[12] This is further complicated by the variability and inaccuracies of testosterone measurements by immunoassays, making comparisons across studies difficult to interpret. In clinical practice, the finding of a low testosterone level should be confirmed by repeat testing.[12] Which androgen to measure, and whether to measure sex-hormone binding globulin, total or free testosterone, are other issues still under debate. For subjects with borderline low total testosterone, it is currently recommended that free or bioavailable testosterone should be measured as well.[12]

There has been a marked increase in prescription of testosterone over recent years. While the long-term cardiovascular impact of testosterone supplement in those with low levels remains to be demonstrated, accumulating evidence suggests there is a sound basis for examining this. Clinical studies of testosterone supplementation in men with low testosterone are associated with reduced visceral adiposity, improved insulin sensitivity and an improved metabolic profile. Studies in subjects with cardiovascular diseases also suggested beneficial effects, with improved functional capacity in heart failure[13] and improved symptoms in subjects with coronary artery disease.[7] Testosterone supplement is however not without risks. It may, among other effects, increase the risk of prostatic diseases and erythrocytosis, and exacerbate obstructive sleep apnoea.[12] Nevertheless, the encouraging results from clinical studies so far support

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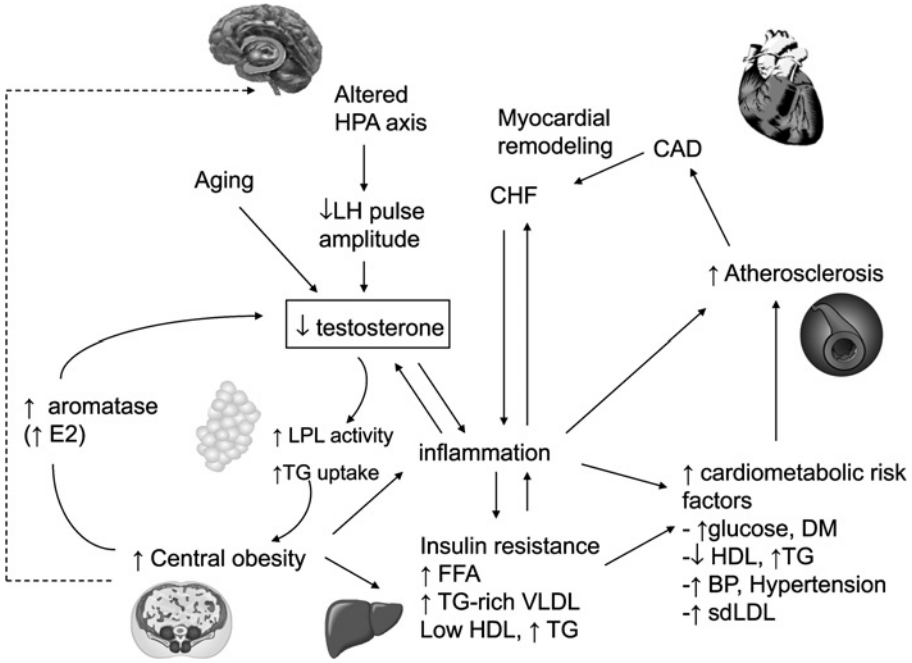

Figure 1 Postulated mechanisms linking low testosterone concentrations with cardiovascular disease in men. CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; E_2, oestradiol; FFA, free fatty acids; HDL, high-density lipoproteins; HPA axis, hypothalamic–pituitary–adrenal axis; LH, lutenizing hormone; LPL, lipoprotein lipase; sdLDL, small, dense low-density lipoproteins; TG, triglycerides; VLDL, very-low-density lipopropteins.

investigating the effects of testosterone supplementation and cardiovascular disease in larger clinical trials.

While the current discussion has focused on the role of testosterone and cardiovascular disease in men, it is important to point out that the relationship between testosterone and cardiovascular diseases is gender-specific. In female subjects, elevated androgens is associated with an increased risk of diabetes and other cardiometabolic complications, contrary to the situation observed in men.[14] This is highlighted by the increased risk of metabolic abnormalities in polycystic ovary syndrome, a condition characterised by hyperandrogenism and anovulatory infertility.[15] Compared with research on oestrogens and cardiovascular disease, the role of androgens in the pathogenesis of metabolic and cardiovascular diseases has taken a backseat for many years. Recent data suggest that this important pathway warrants a lot more attention.

Competing interests None.

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