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Testosterone deficiency syndrome (TDS) and the heart

This editorial refers to 'Low testosterone levels are associated with increased risk of mortality in a population-based cohort of men aged 20–79†', by R. Haring *et al.*, on page 1494

A low testosterone [hypogonadism or testosterone deficiency syndrome (TDS)] may be present in 30% of men and present in a number of different ways.¹ One of the problems in detecting TDS is the lack of awareness of its existence amongst the general medical community including cardiologists. In addition, the signs and symptoms may unhelpfully not be specific to TDS (*Table 1*). With the accumulating evidence of an association between TDS and cardiovascular co-morbidities and an increased risk of mortality when compared with men with normal testosterone levels, there is a compelling need to screen men at risk of low testosterone levels.²

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Table 1
 Signs and symptoms
 indicative of TDS

There is increasing evidence that TDS is associated with all-cause mortality and in particular cardiovascular death. Haring and colleagues add to the growing evidence of the importance of a link in a prospective population-based study (mean follow-up 7.2 years) showing in a sample of men aged 20–79 years that a testosterone level <8.7 nmol/L (250 ng/dL) doubled the risk of all-cause mortality independently of age, waist circumference, cigarette smoking, excess alcohol, and decreased physical activity.³

A recent observational prospective study from Florence investigated the relationship between low total testosterone levels in 1687 men with erectile dysfunction (ED) and fatal or non-fatal major adverse cardiovascular events (MACEs).⁴ Men with a testosterone <8 nmol/L (230 ng/dL), after adjusting for age and chronic diseases, at a mean follow-up of 4.3 ± 2.6 years had a significantly increased incidence of fatal MACEs [hazard ratio (HR) = 7.1 95% confidence interval (CI) (1.8–28.6), *P* <0.001]. In the 6 year CHIANTI study, the same unit suggested that declining testosterone levels were a strong independent predictor of mortality in men.⁵

The EPIC-Norfolk (European Prospective Investigation into Cancer in Norfolk) study performed in the UK was a nested case-control study designed to evaluate any association between testosterone levels and all-cause cardiovascular disease (CVD) and death from cancer.⁶ During follow-up, 1489 men lived from entry between 1993 and 1997 to 2003

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and controls were matched for age and date of baseline visit. Total testosterone concentrations at baseline were found to be inversely related to all-cause mortality ($n = 825$), CVD deaths ($n = 369$), and deaths from cancer ($n = 304$). After adjusting for confounding variables, an increase of 6 nmol/L (173 ng/dL) in serum testosterone was associated with a 14% decrease in death rate regardless of age (above or below 65 years of age). Men in the highest testosterone quartile had a 30% lower risk of death compared with those in the lowest. As occult illness at entry may have distorted the findings, in an additional analysis all those who died in the first 2 years of the study were excluded and the findings were unchanged. The study can be criticized for only including a single testosterone sample and not free or bioavailable testosterone which binds to the androgen receptor, but single measures are believed to be accurate for population studies.⁷

The Rancho-Bernardo area study prospectively followed up 794 men aged 50–91 years, evaluating the link between testosterone levels and all-cause mortality over a 20 year period.⁸ Men in the lowest quartile of testosterone levels were 40% more likely to die than those in the highest quartile—mainly from CVD and respiratory disease. These findings were independent of age, obesity, hyperlipidaemia, and lifestyle, and were in line with the Norfolk study. The authors concluded that low testosterone levels (<12.5 nmol/L) could be a predictive marker for men at high risk of CVD.

In a retrospective study of 858 male veterans over 40 years of age without a diagnosis of prostate cancer, ~20% had total testosterone levels <10.4 nmol/L (300 ng/dL) and the survival rate decreased, as did the testosterone level (HR 1.88; 95% CI 1.34–2.63; $P < 0.001$) after adjustments for clinical co-variables over an 8 year period.⁹

Whilst some cross-sectional and prospective studies have found no significant relationship between testosterone levels and CVD, the evidence overall, particularly from the large recent studies, does point to testosterone having a pathogenic role in CVD.^{2,10} As TDS is associated with type 2 diabetes, metabolic syndrome, visceral fat accumulation, abnormalities of coagulation, inflammatory cytokines, and dyslipidaemia, its importance is clearly integral to other CVD risk factors.^{2,10,11}

Whilst there is no evidence that testosterone replacement reduces CVD risk or all-cause mortality (randomized trials are needed), we have good evidence that replacement may be symptomatically beneficial in hypogonadic men with angina or heart failure.^{12,13} Importantly, there is no evidence that replacement increases CVD risk.

In practice consider measuring testosterone (before 11 a.m. to avoid diurnal variation) in those who appear symptomatic or have a chronic illness or erectile dysfunction.¹⁴ Total testosterone levels <8 nmol/L (2.31 ng/mL) or free testosterone (not bound to sex hormone-binding globulin and non-bioavailable, therefore a more accurate but more expensive measurement) <180 pmol/L (52 pg/mL) require replacement therapy.¹⁵ Total levels >12 nmol/L (3.46 ng/mL) or free testosterone levels >250 pmol/L (72 pg/mL) do not, and a trial of therapy can be considered in between 8 and 12 nmol/L total testosterone. Though the link between testosterone replacement and prostate cancer is not proven, monitoring prostate-specific antigen is currently advised and urological advice sought where appropriate. Regular checks on liver function (toxicity is very rare) and polycythaemia are also advised and caution advocated in men with sleep apnoea which may worsen.¹⁴ Oligospermia or azoospermia which may not be reversible can occur, so it is important to check men who wish to preserve their fertility. Monitoring response to replacement therapy should be at 3–6 month intervals.

TDS can symptomatically benefit from replacement therapy which is safe

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