Lower testosterone predicts ill-health in older men

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Testosterone levels in men decline with age and in older men, lower levels are associated with poorer cognitive function, osteoporosis, cardiovascular risk and mortality. However, whether low testosterone is a marker of ill-health or a significant causative factor remains under debate. Additional observational studies would help in design of large-scale randomised controlled trials to test whether interventions that raise testosterone levels could prevent ill-health in ageing men. Until such data are available, men should engage in healthy lifestyle behaviours that may preserve circulating testosterone. Testosterone therapy should only be considered for those with a proven diagnosis of androgen deficiency

Testosterone circulates bound to either sex hormone-binding globulin (SHBG) or albumin, with a small fraction unbound or free. Testicular secretion of testosterone is regulated by pulsatile release of luteinising hormone (LH) from the pituitary. In men, total and free testosterone levels decline with increasing age while the prevalence of ill-health increases. Associations between lower testosterone levels and health outcomes in men will be reviewed here, and the potential for preventing the age-related decline in male testosterone levels discussed.

Testosterone, cognitive function and depression

Several observational studies have reported an association between higher testosterone levels and better performance on various tests of cognitive function or memory in middle-aged and older men. However, other studies have reported inconsistent results.

One of the largest studies of the endocrinology of male ageing is the *West Australian Health In Men Study* (HIMS) which examined testosterone, SHBG and LH in over 4,000 men aged 70 years and above. In separate cross-sectional analyses from HIMS, lower free testosterone level was associated with worse scores on the Standardised Mini Mental State Examination and with more depressive symptoms.

Some trials of testosterone supplementation, while of limited size and duration, have reported positive changes in cognitive function or memory. Thus additional prospective studies are needed to clarify the roles of endogenous and exogenous testosterone in the prevention of age-related cognitive decline.

Testosterone, body composition and osteoporosis

Men who are androgen deficient have reduced lean or muscle mass, increased fat mass and are at risk of osteoporosis and fracture. Testosterone replacement in hypogonadal men increases lean and reduces fat mass, and improves bone mineral density. However, data are lacking to support such interventions in men with normal testosterone levels.

There is ongoing debate over thresholds of testosterone at which men should be considered androgen deficient. In a recent consensus statement, total testosterone levels <8 nmol/L in at least two separate early morning samples are consistent with androgen deficiency in symptomatic men, while men with total testosterone levels >12 nmol/L generally would not require testosterone therapy.

Testosterone, cardiovascular disease and mortality

Lower total or free testosterone levels are associated with metabolic syndrome and Type 2 diabetes in middle-aged or older men, and these conditions carry increased risk of cardiovascular disease.

Lower testosterone levels are associated with preclinical atherosclerosis measured by carotid intima-medial thickness, calcific aortic atherosclerosis and peripheral vascular disease in ageing men. Lower total testosterone levels predict increased mortality in middle-aged and older men, although there are negative studies and in one study higher free testosterone was associated with ischaemic heart disease mortality. Associations between lower testosterone and incident cardiovascular events are less clear.

HIMS reported cross-sectional associations between lower total testosterone and SHBG with metabolic syndrome in non-diabetic older men, and in a longitudinal analysis found that lower total or free testosterone levels predicted incident stroke and transient ischaemic attack in older men.

Overall, observational data support the hypothesis that lower total or free testosterone levels contribute to cardiovascular risk in ageing men, but randomised controlled trials with cardiovascular endpoints are needed.

Can age-related decline in testosterone levels be reduced?

Additional observational studies, particularly longitudinal analyses of sex hormones as predictors of incident cardiovascular events, would inform the planning and conduct of randomised controlled trials of testosterone supplementation in ageing men. These should evaluate safety as well as efficacy, incorporating outcomes of cognitive function, body composition and cardiovascular events.

Until such studies are completed, lifestyle measures that might prevent or ameliorate the age-related decline in circulating testosterone can be considered.

Avoiding obesity (high body mass index or waist circumference) is important as these factors are strongly associated with reduced testosterone levels. In HIMS, greater engagement in a range of healthy lifestyle behaviours including smoking cessation, physical activity, healthy eating and avoiding excess alcohol and overweight predicted higher subsequent total testosterone and SHBG in older men.

Therefore these healthy lifestyle behaviours should be widely encouraged. ■