Asian Journal of Andrology (2012) 14, 667–668

www.nature.com/aja

RESEARCH HIGHLIGHT

Testosterone therapy and mortality in US veterans

Bu B Yeap[1,2]

Asian Journal of Andrology (2012) **14,** 667–668; doi:10.1038/aja.2012.74; Published online: 23 July 2012

Whether lower testosterone levels are a causal factor or biomarker for disease in older men remains fiercely debated, as randomized controlled trials with endpoints of cardiovascular events or mortality are lacking. Here, a recent retrospective study in US veterans is discussed, which compares mortality rates in men who were and were not prescribed testosterone.

As men grow older, endogenous testosterone levels decline, although it remains unclear whether this is due to ageing per se, or concomitant lifestyle, behavioural, psychosocial or health-related factors.[1–3] Lower testosterone levels in older men have been associated with poorer health outcomes, including frailty,[4] reduced sexual activity,[5] increased risk of diabetes[6] and manifestations of cardiovascular disease.[7–9] A meta-analysis of observational studies in middle-aged and older men concluded that low endogenous testosterone levels were associated with increased risk of all-cause and cardiovascular disease-related mortality.[10] However, there was considerable between-study heterogeneity, suggesting that differences within cohorts might be influencing the associations. The association of lower endogenous testosterone levels with mortality from cardiovascular disease was reinforced by results of a further epidemiological study appearing after the publication of the meta-analysis.[11] Despite the increasing weight of observational data implicating lower endogenous testosterone levels with poorer health outcomes, randomized controlled clinical trials of testosterone therapy have not been powered for endpoints such as incident diabetes or cardiovascular disease.[12] This is understandable as such trials would need to recruit large numbers of men and follow them for an extended duration to accumulate sufficient outcome events. Furthermore, higher doses of testosterone in older men with limited mobility have been associated with cardiovascular adverse events, and there are side effects of testosterone therapy.[13,14] Therefore, more evidence is needed to refine consensus clinical guidelines on the management of men suspected of being androgen deficient.[15]

In this setting, the publication by Shores *et al.*[16] is an important advance, albeit with several limitations. This was a study of 1031 male veterans of average age 62.1 years with low testosterone levels (<8.7 nmol l^{-1}) and no history of prostate cancer who were identified using a Veterans Affairs clinical database. Three hundred and ninety-eight of these men who received testosterone treatment experienced lower mortality compared to 633 untreated men over 40.5 months follow-up (10.3% *vs.* 20.7%, $P<0.001$). Multivariate analysis confirmed a 39% decrease in mortality risk after adjusting for potential confounders (adjusted hazard ratio (HR): 0.61, 95% confidence interval (CI): 0.42–0.88, $P=0.008$). The difference in HR for death between treated and untreated men was particularly noticeable in men with diabetes (prevalent diabetes HR: 0.44, 95% CI: 0.23–0.84, no diabetes HR: 0.72, 95% CI: 0.46–1.13). Incident prostate cancer was diagnosed in 1.6% of treated men compared with 2.0% of untreated men ($P=0.68$).

The main limitation of the study is its retrospective, observational nature which the authors readily acknowledged. This was not a randomized trial, treated men were younger (60.9 years *vs.* 62.8 years) and fewer had coronary heart disease (20.1% *vs.* 23.1%). The statistical analysis sought to adjust for potential confounders, but possibility of confounding remains. In the absence of randomisation, physicians may have selected healthier men for testosterone treatment, or not considered treatment in men who were less well. Selection into the study was based on a single low total testosterone level, while clinical guidelines recommend two morning blood samples.[15] The database did not facilitate ascertainment of symptoms relevant to the diagnosis of hypogonadism. These and other shortcomings of the study, including limited clinical data and information on the underlying diagnoses, the relatively short duration of treatment and follow-up, lack of data for on-treatment testosterone levels and lack of cause-specific mortality data, have been summarized insightfully by Wu.[17] Nevertheless, the statistical analyses demonstrate that the observed differences in mortality outcomes were unlikely to have arisen by chance, although this does not exclude the finding arising due to residual confounding and/or bias in how treatment groups were formed. The authors concluded that testosterone therapy was associated with decreased mortality in an observational cohort of middle-aged and older veterans, with the qualification that the results should be viewed cautiously and could not be interpreted as showing beneficial effects of testosterone or as establishing a causal relationship.

Recognizing these limitations, these results are very interesting and timely given the considerable attention to testosterone and its effects in ageing men. There is a paucity of data concerning the effect of testosterone therapy on mortality. Randomized clinical trials of testosterone with mortality as an endpoint are lacking and face substantial logistic difficulties. Until such randomized trials are undertaken and the results known, the findings by Shores *et al.*[16] offer some reassurance that testosterone therapy when applied to this group of men was not associated with increased mortality.

[1]School of Medicine and Pharmacology, University of Western Australia, Perth, WA 6160, Australia and [2]Department of Endocrinology and Diabetes, Fremantle Hospital, Fremantle, WA 6160, Australia
Correspondence: Dr BB Yeap (byeap@cyllene.uwa.edu.au)

COMPETING FINANCIAL INTERESTS

Professor Bu B Yeap has received conference support and speaker honoraria from Bayer and Lilly, and a research grant from Lilly.

1 Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB *et al*. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab* 2002; **87**: 589–98.
2 Yeap BB, Almeida OP, Hyde Z, Norman PE, Chubb SA *et al*. Healthier lifestyle predicts higher circulating testosterone in older men. The Health in Men Study. *Clin Endocrinol* 2009; **70**: 455–63.
3 Travison TG, Araujo AB, Hall SA, McKinlay JB. Temporal trends in testosterone levels and treatment in older men. *Curr Opin Endocrinol Diabetes Obes* 2009; **16**: 211–7.
4 Hyde Z, Flicker L, Almeida OP, Hankey GJ, McCaul KA *et al*. Low free testosterone predicts frailty in older men. The Health in Men Study. *J Clin Endocrinol Metab* 2010; **95**: 3165–72.
5 Hyde Z, Flicker L, Hankey GJ, Almeida OP, McCaul KA *et al*. Prevalence of sexual activity and associated factors in men aged 75–95 years: a cohort study. *Ann Intern Med* 2010; **153**: 693–702.
6 Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of Type 2 diabetes. *JAMA* 2006; **295**: 1288–99.
7 Tivesten A, Mellstrom D, Jutberger H, Fagerberg B, Lernfeldt B *et al*. Low serum testosterone and high serum estradiol associate with lower extremity peripheral arterial disease in elderly men. The MrOS Study in Sweden. *J Am Coll Cardiol* 2007; **50**: 1070–6.
8 Yeap BB, Hyde Z, Almeida OP, Norman PE, Chubb SA *et al*. Lower testosterone levels predict incident stroke and transient ischemic attack in older men. *J Clin Endocrinol Metab* 2009; **94**: 2353–9.
9 Yeap BB, Hyde Z, Norman PE, Chubb SA, Golledge J. Associations of total testosterone, sex hormone-binding globulin, calculated free testosterone, and luteinising hormone with prevalence of abdominal aortic aneurysm in older men. *J Clin Endocrinol Metab* 2010; **95**: 1123–30.
10 Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT *et al*. Endogenous testosterone and mortality in men: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011; **96**: 3007–19.
11 Hyde Z, Norman PE, Flicker L, Hankey GJ, Almeida OP *et al*. Low free testosterone predicts mortality from cardiovascular disease, but not other causes. The Health in Men Study. *J Clin Endocrinol Metab* 2012; **97**: 179–89.
12 Cunningham GR, Toma SM. Why is androgen replacement in males controversial? *J Clin Endocrinol Metab* 2011; **96**: 38–52.
13 Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR *et al*. Adverse events associated with testosterone administration. *N Engl J Med* 2010; **363**: 109–22.
14 Fernandez-Balsells MM, Murad MH, Lane M, Lampropulos JF, Albuquerque F *et al*. Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2010; **95**: 2560–75.
15 Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ *et al*. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010; **95**: 2536–59.
16 Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab* 2012; **97**: 2050–8.
17 Wu FC. Caveat emptor: does testosterone treatment reduce mortality in men? *J Clin Endocrinol Metab* 2012; **97**: 1884–6.