EDITORIAL COMMENT

Andropause and Intima Media Thickness*

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The universal gender difference in coronary heart disease suggests biology rather than environment, and the female advantage has long been attributed to a cardioprotective effect of estrogen (1). This thesis is now being challenged by observational studies of postmenopausal women that failed to show an association between endogenous estrogen concentrations and future cardiovascular risk and by clinical trials that failed to show that estrogen therapy reduced the risk of coronary artery disease (2).

An alternate hypothesis for the gender differences is that testosterone is the bad actor, explaining men’s higher risk of heart disease. No clinical trials of physiologic testosterone therapy with clinical heart disease outcomes in men have been reported, but epidemiologic studies do not support this thesis either. Cross-sectional studies tend to show higher levels of estradiol and lower levels of testosterone in men with coronary heart disease, and prospective studies show no independent association of circulating sex steroid concentrations with subsequent heart disease (3).

In this issue of the Journal, Mäkinen et al. (4) report that the common carotid intima media thickness (IMT) correlated inversely with serum testosterone and directly with luteinizing hormone (LH) in middle-aged Finnish men, independent of age, cholesterol, body mass index, blood pressure, and smoking.

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The exposure and outcome variables appear to be well measured. Blood for hormone assays was obtained after an overnight fast. Hormone assays were above the level of sensitivity and showed good interassay coefficients of variation. However, testosterone was measured only once, although there is considerable day-to-day variation. Carotid ultrasounds were measured by experienced sonographers using a standard protocol. Sonogram readers were unaware of participants’ clinical details, and there was good between-visit and between-observer variation. That said, the reader might ask: what can we learn about low testosterone and cardiovascular disease from this paper?

A first question is: Who are the participants in this study? Men were selected from a population-based cohort—they were not patients who complained of andropause symptoms or were suspected of having cardiovascular disease. Good, because this suggests less bias of ascertainment. Only population-based data can provide an estimate of how common the levels of low testosterone, and its putative symptom complex, are in the population. In this Finnish study, unlike previous studies, men were relatively young (mean age, 57 to 58 years) to be expected to have low testosterone levels. They were selected for having at least two of three symptoms thought to be associated with low testosterone plus either a serum testosterone of <9.8 nmol/l or a LH of >6.0 U/l in the presence of normal testosterone, as a marker for compensated hypogonadal status. Among the 1,764 men who met the symptom criteria (decreased strength, decreased libido, and depression in the past five years), only 99 had low testosterone or high LH levels and were free of known heart disease, hypertension, and diabetes. Thus, the first important message is that very few middle-aged men with common symptoms that might be attributed to testosterone deficiency actually have low testosterone levels.

A second question is: how internally consistent are these results? Carotid ultrasound was performed in 96 of the 99 men with andropause symptoms and low testosterone or high LH levels. The comparison group was 140 men selected because they met neither the symptom nor hormone criteria. Table 1 of the paper shows that these two groups differed by male aging symptom score and by testosterone, as per protocol, but the only other significant risk factor differences were lower estradiol levels and more obesity in andropausal men. These andropausal men had a much greater maximum IMT of the carotid bulb and common carotid than men in the comparison group without low testosterone. The common carotid IMT correlated inversely with serum testosterone (p = 0.003) and positively with LH (p = 0.006).

A third question is: how externally consistent are these results? Previous studies have shown that low testosterone is associated with carotid IMT (5–8) and that IMT is a good marker for current atherosclerosis and future cardiovascular events (9,10). However, risk factors that predict atherosclerosis may not necessarily be the determinants of clinical events. In the case of estrogen therapy for women, it remains possible that estrogen delays atherosclerosis (11) but increases cardiovascular events by inflammation or thrombosis or some other means (2). Thus, it will be important to assess the cardiovascular safety of testosterone supplementation in any testosterone treatment trials by preplanned collection of cardiovascular events. Heart disease is a more common cause of morbidity and mortality than prostate cancer, despite the greater attention and anxiety attributed to the latter.
The fourth and final question is: what is the mechanism for this testosterone-IMT association that was independent of age, cholesterol, body mass index, blood pressure, and smoking? Although the beneficial effects of testosterone in animal studies have been shown in one study to be mediated by an increase in estradiol levels due to aromatization of testosterone (12), estradiol levels were associated with andropause but not with IMT in the present study. Furthermore, by what means would LH “with a normal testosterone” be strongly associated with atherosclerosis as estimated from carotid IMT?

Sales of testosterone “replacement” therapies to middle-aged men are increasing rapidly (13). It seems urgent to unravel the association between andropause symptoms and testosterone, which co-existed in only 6% of middle-aged men in this study.

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REFERENCES


