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Editorial

Testosterone Making an Entry Into the Cardiometabolic World

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Testosterone, the predominant sex hormone in men, is produced by the testes under stimulation by the gonadotrophs in the pituitary, which in turn are controlled by gonadotropin-releasing hormone neurons in the hypothalamus. A young adult man generally produces 3 to 10 mg of testosterone daily, which translates into serum values of 300 to 1000 ng/dL. The consequences of classical male hypogonadism (primary or secondary) have been long known to physicians and patients alike and include decreased libido, erectile dysfunction, osteoporosis, reduced sexual hair, and changes in body habitus. Recently, we have come to appreciate that reductions in serum testosterone resulting from aging or chronic disease have signs and symptoms similar to those seen in classical male hypogonadism, along with increased fat mass, decreased lean body mass, decreased muscle strength, and diminished quality of

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life.¹ During the past decade, reports have been trickling in, mainly from laboratory and epidemiological studies (and a few clinical studies), linking differences in serum testosterone levels to various cardiovascular risk factors and also directly to cardiovascular disease and death. The article by Khaw et al² in this issue of *Circulation* is another link to this growing chain.

Article p 2694

Thirteen years ago, Phillips et al³ reported that low total and free testosterone levels were inversely linked to coronary artery disease, even after adjusting for age and adiposity. This observation still holds true, as was recently supported by a study showing that men with angiographically proven coronary artery disease had lower levels of testosterone than those of controls.⁴ Furthermore, testosterone levels were negatively correlated to the degree of coronary involvement. A few population-based studies have been published that relate low serum testosterone level with risk of death. A study of male veterans showed that low testosterone was associated with increased risk of death⁵; however, it was a retrospective study, and the subjects were a clinic-based Veterans Administration population, who tend to have greater medical morbidity, rather than healthy men living in the community. Recently, a prospective population-based study of 794 men, 50 to 91 years of age, in the Rancho Bernardo community, looked at the relationship of testosterone with all-cause death over the subsequent 2 decades.⁶ The authors found that men whose total testosterone levels were in the lowest quartile, defined as <241 ng/dL, were 40% more likely to die than were men with higher androgen levels. These findings were independent of age, adiposity, lipids, adipokines, and lifestyle. In cause-specific analyses, low testosterone predicted increased risk of death due to cardiovascular and respiratory disease. The findings of this study are not surprising given the fact that low testosterone is independently associated with many of the individual risk factors for heart disease. For example, testosterone levels are inversely related to fat mass in men.⁷ Indeed, men undergoing androgen deprivation for the treatment of prostate cancer have higher body mass index and fat mass than age and disease-matched controls.⁸ This role of fat mass regulation by androgens is further supported by the fact that testosterone administration decreases adiposity in men.⁹ Because fat mass is an independent predictor of cardiovascular death, it seems that testosterone is an important player in regulating this cardiovascular risk.

In addition to body mass index and fat mass, testosterone has been linked to other cardiovascular risk factors. The vascular system seems to be an important target of androgen action, and current evidence suggests that androgens are beneficial to the vascular system. Older clinical trials, though not as rigorously conducted, showed that testosterone replacement relieved symptoms of angina and peripheral vascular disease.¹⁰ Almost half a century later, experimental studies showed that acute treatment with testosterone results in dilatation of the coronary arteries in animals.¹¹ Subsequently, a clinical trial showed that transdermal testosterone therapy improved exercise-induced myocardial ischemia (measured as time to ST depression) during an exercise stress test in men with stable angina.¹² These vasodilatory effects of testosterone on coronary and other vasculature are confirmed by the findings that men with prostate cancer undergoing androgen-deprivation therapy experience an increase in central arterial pressure (reflecting stiffening of large arteries).¹³ Similarly, in population studies, systolic and diastolic blood pressures have been shown to be inversely correlated with testosterone level.¹⁴

In addition to vasomotor regulation, testosterone levels are also inversely related with arterial calcification. In the Rotterdam Study, the association between total and bioavailable testosterone with aortic atherosclerosis was evaluated in 504 nonsmoking men ≥ 55 years of age.¹⁵ Compared with men with levels of total and bioavailable

testosterone in the lowest tertile, men in the highest tertile had a risk reduction of 60% to 80% of severe aortic atherosclerosis. Adjustments for age and cardiovascular risk factors did not influence these results. Given that aortic atherosclerosis was assessed by radiographic detection of calcification in the abdominal aorta, it is likely that subclinical atherosclerosis was not detected in this study. Another prospective study of elderly men (mean age 77 years) showed free testosterone concentration to be inversely related to the progression of intima-media thickness of the common carotid artery after adjustment for age and other risk factors.¹⁶ Hence, it appears that arterial stiffening and increased atherosclerosis are 2 mechanisms by which male hypogonadism may contribute to high risk of death.

Another mechanism by which low testosterone may contribute to a higher death rate is its association with diabetes. Epidemiological studies show that low testosterone levels are independently associated with type 2 diabetes mellitus after adjusting for potential confounders.¹⁷ In fact, lower concentrations of free and bioavailable testosterone even in the normal range are associated with diabetes, independent of adiposity.¹⁸ Furthermore, low total testosterone levels independently predict development of the metabolic syndrome in middle-aged men.¹⁹ A clinical model that further establishes the role of testosterone in the mediation of glucose metabolism is that of androgen deprivation in men with prostate cancer. It is seen that insulin resistance develops within a few months of initiation of androgen-deprivation therapy¹³; however, when men undergoing long-term androgen deprivation are studied, in addition to hyperinsulinemia, they have a higher prevalence of hyperglycemia and metabolic syndrome.^{20,21} This relationship between hypogonadism and hyperglycemia persists even after adjustment for age and body mass index, and the degree of hyperglycemia is directly related to the duration of sex hormone suppression.²² Thus, hypoandrogenism seems to be an early marker for disturbances in insulin and glucose metabolism and may contribute to the pathogenesis of diabetes and metabolic syndrome, thus again contributing to the cardiovascular risk.

Another risk factor linking hypogonadism to cardiovascular disease is the association of androgens with lipids and inflammatory cytokines. Epidemiological data suggest that testosterone levels are associated with a beneficial lipid profile, with negative correlations with total cholesterol, low-density lipoprotein cholesterol, and triglycerides and a positive association with high-density lipoprotein cholesterol.²³ Similarly, there are reports of inverse associations between inflammatory cytokines and testosterone.²⁴ These associations are further validated by clinical trials showing improvement in lipid profile and reduction in inflammatory cytokines with testosterone replacement.²⁵ Additionally, inverse associations between testosterone and plasminogen activator inhibitor I, fibrinogen, and factor VII have been reported in men.¹⁵ Animal experiments also suggest beneficial effects of testosterone on plaque development.²⁶ In summary, these findings suggest that testosterone may influence cardiovascular disease via multiple mechanisms, including changes in body composition, fat metabolism, glucose regulation, vascular mechanisms, and clotting (see the Figure).

In this issue of *Circulation*, Khaw et al² provide more evidence that makes the chain linking low testosterone to risk of death even stronger.² The authors conducted a nested case-control study to determine the association of endogenous serum testosterone with all-cause, cardiovascular, and cancer-related death. The authors compared 825 men, who did not have any cardiovascular disease or cancer at baseline but died during the course of follow-up, with 1489 men who were still alive. The cases and controls were matched for age and date of baseline visit. The authors found that baseline testosterone levels were inversely related to deaths due to all causes, cardiovascular disease, and malignancy, after controlling for the usual confounders (plus dehydroepiandrosterone sulfate and sex hormone-binding globulin). This protective effect of testosterone increased with increasing quartiles, such that men in the highest quartile had a 30% lower risk of death than that of those in the lowest quartile. Even after excluding deaths during the first 2 years of follow-up, this inverse relationship was maintained. In fact, every 6-nmol/L (173-ng/dL) increase in serum testosterone decreased the death rate by 14%, and this benefit was irrespective of patient's age (above or below 65 years of age).

Though the study was well conducted, the findings should be interpreted with caution. First, the testosterone values were based on only a single measurement. Hence, one cannot control for any errors in measurement or transient variation in testosterone secretion. Second, the authors did not measure or calculate either free or bioavailable testosterone, the moiety that binds to the androgen receptor. These measures are more accurate than total testosterone, especially in subjects with obesity or diabetes and in older men because changes in sex hormone-binding globulin levels are expected in such patients. Finally, the authors did not measure estradiol levels. It would have been interesting to see whether these beneficial effects of testosterone are mediated by the testosterone itself or via aromatization to estradiol.

So is low serum testosterone just a marker for sickness (or wellness), or does it have a true pathogenic role? Even though Khaw et al² excluded men with serious disease and also those who died within the first 2 years of baseline visit (assuming that they may have had subclinical illness), the authors were cautious enough (rightly so) in mentioning that they still might have included men with subclinical disease. Nevertheless, on the basis of all the evidence cited in the present editorial, we believe that testosterone has a pathogenic role in the development of cardiovascular disease and is not simply a "marker" for illness and wellness. In terms of death related to cancer and respiratory disease (an association suggested by other reports),²⁷ the exact mechanism by which testosterone may cause an increased risk of death is currently unknown.

Hence, increasing evidence indicates that low androgen levels are associated with all-cause death and especially cardiovascular death. What do we do now on the basis of the reasonably substantial information discussed with regard to testosterone and cardiovascular disease? We believe the answer lies in long-term, double-blind, randomized, placebo-controlled trials of androgen replacement in men with low testosterone levels to evaluate its effects on cardiovascular disease, cardiovascular death, and all-cause death. We cannot assume that testosterone replacement will ameliorate the increased risk seen in these epidemiological studies. We still have not answered questions about the critical level for starting treatment, optimal dose, target testosterone level to be reached, or long-term safety. What we need is a Men's Health Initiative study. With all these data, androgens should no longer be considered as mediators of only sexual function or skeletal health, nor should they be discarded by defaming them as a "fountain of youth," as has been done by some critics of androgen replacement. The aim is to critically evaluate the effects of testosterone treatment by performing large trials, similar to those recently