Testosterone and Atherosclerosis Progression in Men

There is a widespread perception that the gender differences in the prevalence of coronary artery disease (CAD) are due to higher testosterone concentrations in men and that testosterone supplementation in men would adversely affect the plasma lipoprotein profile, therefore increasing the risk of atherosclerotic heart disease. The case reports of cardiovascular accidents among athletes who had abused androgenic steroids have strengthened this notion; however, there are no data substantiating a cause-and-effect relationship between androgens and cardiovascular disease. The manuscript by Fukui et al. (1) in this issue of *Diabetes Care* adds to a growing body of epidemiological data demonstrating that low testosterone concentrations in men are associated with a higher risk of CAD.

Since there are currently no intervention studies of the effects of long-term testosterone administration on CAD, inferences about the risks of testosterone administration have been derived from studies assessing the effect of testosterone on lipoprotein metabolism, markers of inflammation, and insulin sensitivity. The effects of androgen supplementation on plasma lipids depend on the dose, the route of administration (oral or parenteral), the type of androgen (aromatizable or not), and the subject population (whether young or old and hypogonadal or not). While supraphysiological doses of testosterone and nonaromatizable androgens undoubtedly decrease plasma HDL cholesterol levels (2–4), physiologic testosterone replacement in older men has been associated with only a modest or no decrease in plasma HDL cholesterol (5,6). Cross-sectional studies of middle-aged men (7) find a direct, rather than inverse, relationship between serum testosterone levels and plasma HDL cholesterol concentrations. It has also been suggested that the decrease in HDL cholesterol with testosterone administration might be the result of increased cholesterol efflux from endothelial macrophages stimulating reverse cholesterol transport; therefore, a beneficial effect arises from this, rather than the detriment of increased HDL catabolism (8). Testosterone administration to men has very little effect on total cholesterol, triglycerides, and overall LDL levels, but does decrease LDL particle size (9,10).

In cross-sectional studies, there is a direct correlation between circulating testosterone concentrations and tissue plasminogen activator activity and an inverse relationship between testosterone and plasminogen activator inhibitor-1 activity, fibrinogen, and other prothrombotic factors, suggesting an antithrombotic effect of testosterone (11,12). In prospective studies, increasing testosterone concentrations by testosterone enanthate or hCG administration had no significant effect on inflammation-sensitive markers (13,14).

As men age, their testosterone levels decline (15) and fat mass increases (16). Serum testosterone levels are correlated inversely with fat mass, particularly visceral fat area (17). Testosterone replacement in young (18) and older hypogonadal men (19) is associated with a reduction in overall fat mass and inhibition of uptake of labeled triglycerides and enhanced lipid mobilization in visceral fat (20). The induction of androgen deficiency in young men is associated with a decrease in lipid oxidation rates and an increase in total fat mass (21). Marin et al. (22,23) have reported that testosterone supplementation of middle-aged men with truncal obesity and low-normal testosterone levels is associated with a reduction in visceral fat volume, serum glucose concentration, blood pressure, and an improvement in insulin sensitivity, suggesting that testosterone is an important regulator of regional fat metabolism. Surgical castration in rats impairs insulin sensitivity; testosterone replacement reverses this derangement (24). However, high doses of testosterone impair insulin sensitivity in castrated rats. These data suggest that testosterone effects on insulin sensitivity are biphasic; both low and supraphysiologic testosterone concentrations are associated with suboptimal insulin sensitivity. Androgens also increase insulin-independent glucose uptake (25) and modulate LPL activity (26). These observations need further confirmation but suggest a decrease in risk factors for CAD.

Whether variation of testosterone within the normal range is associated with risk of CAD remains unclear. Of the 30 studies reviewed by Alexandersen et al. (27), 18 reported lower testosterone levels in men with CAD, 11 found similar testosterone levels in control subjects and men with CAD, and 1 found higher levels of DHEAS. Prospective studies (28) have failed to reveal an association of total testosterone levels and an onset of CAD.

Testosterone has been reported to improve angina pectoris in men with CAD (29) and delay the onset of ischemia induced by exercise (30), but these findings have not been consistent (31). Testosterone infusion also acutely improves coronary blood flow. More studies are needed to determine the effects of testosterone administration on vascular reactivity and the underlying mechanisms. Studies by Yue et al. (32), demonstrating testosterone-induced endothelium-independent relaxation of rabbit coronary arteries via potassium conductance, are interesting in this regard.

Testosterone retards atherosclerosis progression in animal models of atherosclerosis (33,34). In the LDL receptor–deficient mouse model of atherosclerosis, orchiectomy is associated with accelerated formation of early atherosclerotic lesions in the aorta. Testosterone supplementation retards the progression of atherosclerotic lesions, an effect that is blocked by concomitant administration of an aromatase inhibitor (34). Testosterone effects on atherosclerosis progression are independent of plasma lipids. Taken together, these data provide evidence that testosterone, through its conversion to estradiol, can retard the progression of atherosclerosis in these animal models.

Testosterone therapy produces no significant improvement in tests of walking distance or in a variety of other objective tests for peripheral arterial disease, including venous filling time, muscle blood flow, and plethysmography (35). However, this might reflect limited data available from only two trials rather than the lack of a real effect.

One important confounding factor in a number of epidemiological studies has been the influence of sex hormone–binding globulin (SHBG) concentrations on the measured testosterone concentrations. Because 30–50% of circulating testosterone is bound to SHBG, total concentrations are lower in men with low SHBG concentrations. Obese men have lower SHBG concentrations and lower free testosterone concentrations than those who are not obese (36,37). An epidemiological study has also reported an inverse association between serum free testosterone levels and visceral obesity (17). In some, though not all of these studies, including the study in this issue of *Diabetes Care* (1), free testosterone concentrations were measured by a tracer analog method. Measurements of free testosterone by this method are affected by the prevalent SHBG concentrations, leading some experts to question the validity and accuracy of this method. Because of the dependence of the total and free testosterone levels by tracer analog methods on SHBG concentrations, we cannot exclude the possibility that the relationship between measured testosterone concentrations and visceral fat and atherosclerosis might reflect the relationship between SHBG and these outcomes. Because insulin is known to inhibit SHBG, obese and insulin-resistant men with higher insulin levels would be expected to have lower SHBG levels and, consequently, lower testosterone concentrations.

The available data suggest that serum testosterone levels in the range that is mid-normal for healthy young men are consistent with an optimal cardiovascular risk profile at any age, and that testosterone concentrations either above or below the physiologic male range may increase the risk of atherosclerotic heart disease. Studies in LDL receptor–deficient mice provide compelling evidence that testosterone retards early atherogenesis, and that the effects of testosterone on atherogenesis are mediated through its conversion to estradiol in the vessel wall. The effects of testosterone replacement on cardiovascular risk in humans have never been directly examined.

Prescription sales of testosterone products have been increasing at an alarming rate. Sales have grown 1,700% in the last 10 years and approximated 400 million dollars in 2002 (38). These trends in testosterone sales are of great concern because the long-term risks and benefits of testosterone replacement in older men are largely unknown. Even small changes in the incidence rates of atherosclerotic heart disease would have an enormous public health impact because of the high prevalence rates of this disorder in the general population. Therefore, prospective, long-term, placebo-controlled, randomized clinical trials of the effects of testosterone replacement on atherosclerosis progression and cardiovascular event rates are long overdue.

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