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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, CANADA

Scientific Update™

Anti-anginal and Lipid-lowering effects of Chronic Oral Androgen Supplementation In Elderly Male Patients with Coronary Heart Disease.

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The effects of hormone replacement therapy on cardiovascular disease in women are still controversial despite years of observational studies and recent, randomized, clinical trials. Estrogen replacement therapy in women can affect several disease states including coronary artery disease (CAD), venous thromboembolism and stroke. Unfortunately, much less is known about the effects of androgen replacement on any of these disease states in men. Androgens have been regarded as an adverse factor in CAD because younger men are more likely to develop this disease than are women of the same age.[1] The concept that physiological levels of androgens cause atherosclerosis evolved over many years and gained acceptance even though the evidence to support it was scant. Indeed, it is quite possible that women are protected due to higher levels of estrogens, rather than men being at greater risk because of higher levels of androgens. Interestingly, a study of the biographies of great opera singers demonstrated that the life expectancy of the *castrati* was not significantly different from age-matched, intact, male singers, suggesting that androgens did not have a significant effect in decreasing survival.[2]

The arguments that have been used to link testosterone and atherosclerosis include the fact that body fat distribution in men (central obesity) is more likely to be associated with CAD. As well, the adverse effects of potent, synthetic androgens on plasma lipids have been extrapolated to the effects of physiological levels of testosterone. For instance, this has been the case of the lipid effects of athletes who have abused anabolic steroids, but it may not be appropriate to extrapolate these observations to the effects of physiological androgen replacement under the supervision of a physician.[3-5] Additional studies in female-to-male transsexuals (genetic females) and healthy females demonstrated that long-term treatment with high-dose androgens was associated with impaired vascular reactivity as measured by studies of brachial artery flow-mediated dilatation. Extreme caution should be exercised when interpreting these results and they should not be extrapolated to the possible effects of physiological androgen replacement in normal men.

Some studies have documented potentially detrimental effects of testosterone in animal models of atherosclerosis. For example, one study demonstrated that testosterone worsens the endothelial dysfunction associated with smoking in a hypercholesterolemic rabbit model of atherosclerosis.[6] Studies in a classic, non-human, primate model of atherosclerosis, the cynomolgus monkey fed a lipid-rich diet, showed that coronary atherosclerosis was approximately twice as extensive in testosterone-treated animals relative to untreated controls but, paradoxically, testosterone reversed atherosclerosis-related impairment of endothelium-dependent vasodilator responses.[7] Another study in the same model utilized the anabolic steroid, nandrolone decanoate, and demonstrated significantly greater coronary atherosclerosis, but also larger coronary artery lumen, in monkeys treated with this steroid.[8] Both studies were conducted only in female cynomolgus monkeys and no similar long-term experiments have been reported in male animals. A small, short-term study evaluated the effect of testosterone on plasma lipids and eicosanoids in male cynomolgus monkeys. The animals that received testosterone had a significant increase in thromboxane A2 and a decrease in high-density lipoprotein (HDL) cholesterol compared with control monkeys.[9] Again, it may not be appropriate to extrapolate these results to the potential effects of physiological testosterone replacement in male animals, let alone in men. In addition, basic

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studies have been used to support the hypothesis of pro-atherogenic effects of androgens. In cultured human umbilical vein endothelial cells, pre-treatment with dihydrotestosterone resulted in a dose-dependent increase in the adhesion of monocytes and in the expression of vascular cell-adhesion molecule-1 (VCAM-1).[10] The clinical implications of these findings for androgen replacement in healthy men are unknown.

Potentially beneficial effects of androgens in cardiovascular disease

The prevalent view that androgen replacement therapy has exclusively or predominantly negative effects on the cardiovascular system is being increasingly challenged by many recent studies. Among the reported potential benefits are a lowering of plasma levels of triglycerides and lipoprotein(a), an increase in fibrinolytic activity, and small shifts away from central obesity.

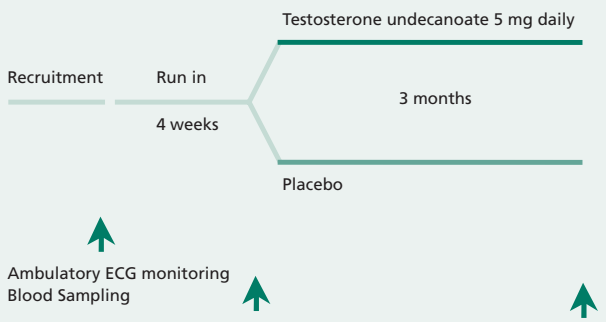
Interestingly, in most studies, men with coronary heart disease have lower androgen levels than matched control groups. Serum concentrations of the adrenal androgen dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) decline with age more markedly than other sex hormone levels. The levels of these androgens were assessed in the Massachusetts Male Aging Study. The correlation of androgen levels with heart disease was studied after controlling for a comprehensive set of potential confounding elements including serum lipid and hormone levels, as well as smoking, alcohol intake, obesity, hypertension, diabetes, diet, medication, physical activity, and psychological measures. The subjects were men (n=1709), aged 40-79 years, who had been randomly sampled from the Massachusetts state census listing. Multiple logistic regression analysis indicated a strong independent role for DHEAS as a predictor of heart disease (serum DHEAS levels exhibited an inverse correlation to CAD), after controlling for age and all the potential confounding variables. The DHEAS effect was not decreased by controlling for the use of cardiac, vasodilator, antihypertensive, or lipid-lowering medication.[11] Subsequently, results of a prospective follow-up of the same population confirmed that both low DHEA and DHEAS predicted the development of CAD between the baseline and the follow-up analysis over a 9-year interval.[12] Similarly, plasma levels of DHEA and dihydrotestosterone were found to be significantly decreased in young men, aged 26-40 years, with a prior history of myocardial infarction, compared with healthy aged-matched controls.[13] In angiographic studies, an inverse correlation was also observed between testosterone or DHEAS levels and angiographically defined CAD. In other words, the lower the androgen levels, the greater the extent of the disease. Additionally, men with CAD were found to have lower levels of androgens than men with normal coronary angiograms.[14-16]

Changes in total testosterone over 13 years were examined in a group of men who participated in the Multiple Risk Factor Intervention Trial (MRFIT). In a multivariate analysis controlling for obesity and other lifestyle covariates, a decrease in endogenous testosterone level with age in men was associated with an increase in triglycerides and a decrease in HDL-cholesterol. There was no significant correlation between change in testosterone and change in total and low-density lipoprotein (LDL) cholesterol or blood pressure.[17] Obviously, none of these studies prove a cause and effect relationship between low androgen levels and CAD, as it is possible that the decline in androgen levels was actually caused by the disease state. Nevertheless, these intriguing results must be used to generate hypotheses and to probe possible links between androgens and atherosclerosis.

Interesting studies are emerging that begin to provide some answers about the potentially beneficial mechanisms of action of androgens on the cardiovascular system. A recent study examined the effects of replacement with natural androgens on aortic atherosclerosis in castrated, cholesterol-fed, male rabbits. Natural androgens inhibited the development of atherosclerosis in a way that could be only partially explained through lipid-mediated effects.[18] As well, beneficial effects of testosterone replacement on lipids and lipoproteins have been reported in hypogonadal and healthy elderly men. These effects consisted of small decreases in total and LDL cholesterol without significant changes in HDL cholesterol.[19,20] Studies of vascular function have demonstrated that testosterone directly relaxes precontracted rabbit coronary arteries, and that acute intracoronary infusions of testosterone increase coronary blood flow *in vivo* by a mechanism that is, at least partially, endothelium-dependent.[21,22]

More importantly, a number of recent studies have examined the effects of androgens on vascular function in men. The acute administration of testosterone to men with CAD was found to improve endothelial function as measured by flow-mediated brachial artery reactivity.[23] In studies that used a direct assessment of coronary endothelial function, the short-term intracoronary administration of physiological concentrations of testosterone induced coronary artery dilatation and increased coronary blood flow in men with established CAD.[24] As well, the effect of acute testosterone administration on exercise-induced myocardial ischemia was evaluated in 14 men with CAD and low plasma testosterone concentrations in a randomized, double-blind, crossover study. Testosterone increased time to 1-mm ST-segment depression compared with placebo by 66 seconds ($P = 0.016$), suggesting a beneficial effect of testosterone on myocardial ischemia in these patients.[25] In a separate study performed after the withdrawal of anti-anginal therapy, 14 men with CAD underwent 3 exercise tests on 3 different days (baseline and either testosterone or placebo, administered in a random order). The exercise tests were performed 30 minutes after the administration of 2.5 mg of testosterone IV or placebo. Compared to placebo, testosterone significantly increased time to 1-mm ST-segment depression, total exercise time, heart rate at the onset of 1-mm ST-segment depression and at peak exercise, and the rate-pressure product at the onset of 1-mm ST depression and at peak exercise.[26] Recently, a randomized, double-blind, placebo-controlled study of low-dose, transdermal, testosterone therapy in men with chronic stable angina was reported. Active treatment with the testosterone patch resulted not only in a significant reduction in exercise-induced myocardial ischemia, but also in significant improvements in parameters of quality-of-life such as pain perception and role-limitation resulting from physical problems. The magnitude of beneficial responses was greater in patients with lower baseline levels of bioavailable testosterone.[27]

Figure 1: Study protocol[28]



Anti-anginal and lipid-lowering effects of androgens in elderly patients with CAD

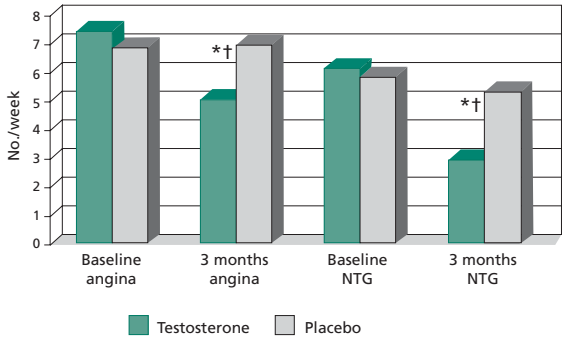
A recent study contributes to understanding the potentially beneficial effects of chronic androgen replacement in elderly men with CAD.[28] This clinical trial evaluated the effects of oral testosterone replacement on the lipid profile and on myocardial ischemia. A total of 94 men, aged >70 years, with one or more documented coronary stenoses of at least 70%, were enrolled in this double-blind, parallel study. The patients were randomized to either testosterone undecanoate 5 mg daily or placebo. Diary cards quantified angina and nitroglycerin consumption. Myocardial ischemia was evaluated by the use of 24-hour 12-lead ambulatory ECG monitoring. Blood samples for androgen and lipid levels were collected at baseline and after 3 months of therapy. The experimental protocol is summarized in Figure 1.

The mean age of the patients was 72.3 years, 32% had suffered a previous myocardial infarction and 43% had undergone previous revascularization with coronary artery bypass grafting or percutaneous coronary intervention. The baseline characteristics are summarized in Table 1. Testosterone replacement resulted in a significant decrease in the number of episodes of angina and in nitroglycerin (NTG) intake both in relation to the baseline and in comparison to placebo at 3 months (Figure 2).

Table 1: Baseline clinical characteristics[28]

	Testosterone	Placebo
Total testosterone (nmol/L)	4 ± 1.2	4.1 ± 1.3
Free testosterone (pmol/L)	33 ± 5.8	32.8 ± 6.4
Previous MI	18	14
Previous CABG/PTCA	21	22
Coronary artery disease		
1 vessel disease	12	14
2 vessel disease	24	25
3 vessel disease	8	6

Figure 2: Effect of testosterone on episodes of angina and nitroglycerin (NTG) consumption[28]

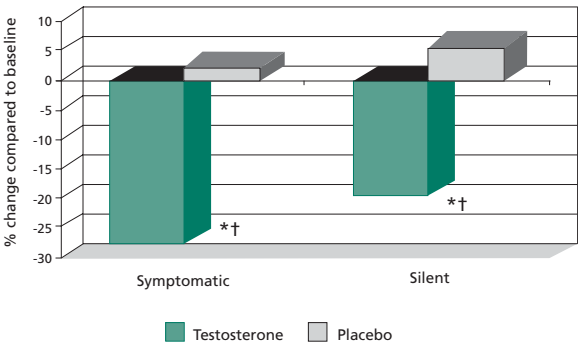


*= $P<0.01$ compared to baseline
†= $P<0.01$ compared to placebo

There was a 23% reduction in the episodes of angina compared to baseline in patients taking testosterone while a trend towards an increase in the frequency of anginal episodes was observed in patients randomized to placebo. Testosterone administration also resulted in a significant decrease in myocardial ischemia measured by ambulatory electrocardiographic monitoring (AEM). Importantly, testosterone treatment was associated with reductions in both symptomatic and silent ischemia (Figure 3). In contrast, in patients receiving placebo there was a trend towards an increase in both of these parameters at 3 months relative to the baseline.

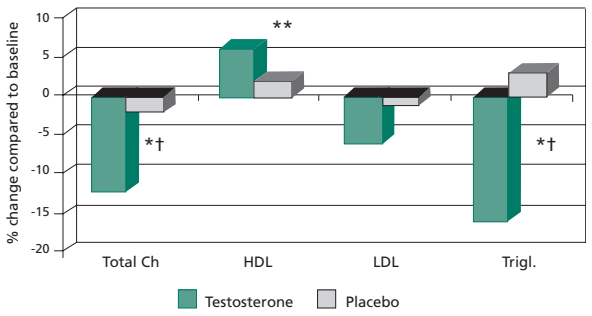
The treatment with testosterone led to significant changes in lipids and lipoproteins. Relative to the baseline levels there was a 12.5% reduction in total cholesterol and a 15% decrease in triglycerides, as well, HDL cholesterol was increased by 5% after 3 months of treatment with testosterone. LDL cholesterol

Figure 3: Effect of testosterone on episodes of myocardial ischemia by AEM[28]



*= $P<0.01$ compared to baseline
†= $P<0.01$ compared to placebo

Figure 4: Effect of testosterone on lipid profile in patients with CAD[28]



*= $P<0.01$
**= $P<0.05$ compared to baseline
†= $P<0.01$ compared to placebo

decreased by 7.5% but this change did not reach statistical significance (Figure 4). No significant changes were seen in the lipids and lipoproteins of those patients randomised to placebo.

In conclusion, this study of elderly men with documented CAD demonstrates that oral testosterone improves myocardial ischemia and results in favorable changes in the lipid profile. On the basis of this new study, and the evidence from previous studies discussed above, further randomized clinical trials are warranted to assess the potential cardiovascular benefits of testosterone replacement in men, and to challenge the prevalent, and possibly mistaken, view that testosterone is associated with an increase in cardiovascular events.

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