# Cardiovascular Issues in Hypogonadism and Testosterone Therapy

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**A systematic literature search was conducted to investigate the cardiovascular issues related to hypogonadism and testosterone therapy. Vascular cells contain sex steroid hormone receptors. Testosterone can exert effects on the vascular wall, either by itself or through aromatization as estrogen. Hypogonadism is associated with central obesity; insulin resistance; low levels of high-density lipoprotein (HDL); high cholesterol levels; and high levels of low-density lipoprotein (LDL), triglycerides, fibrinogen, and plasminogen activator–1. Some observational studies show a correlation between low testosterone and cardiovascular disease (CVD), and others show no correlation. Interventional studies do not reveal a direct long-term relation between testosterone therapy and CVD. Short-term data suggest cardiovascular benefits of testosterone. Testosterone therapy has beneficial and deleterious effects on cardiovascular risk factors. It improves insulin sensitivity, central obesity, and lowers total cholesterol and LDL. In some studies, testosterone therapy has an HDL-lowering effect, and in other studies this effect is insignificant. This should not be assumed to be atherogenic because it might be related to reverse cholesterol transport and effects on the $HDL_3$ subfraction. The cardiovascular effects of testosterone therapy may be neutral to beneficial. There is no contraindication for testosterone therapy in men with CVD and diagnosed hypogonadism with or without erectile dysfunction. Caution should be exercised regarding occasional increases in hematocrit levels, especially in patients with congestive heart failure. Conversely, evidence does not support testosterone therapy in aging men for the purpose of cardiovascular benefit, despite claims to this effect. Further research on the cardiovascular benefits and risks of testosterone is strongly recommended.** **© 2005 Elsevier Inc. All rights reserved.** **(Am J Cardiol 20052005;96[suppl]:67M–72M)**

Hypogonadism is an important issue in sexual dysfunction and cardiovascular risk. Although classic hypogonadism has been described in regard to genetically based disorders, it is also known to exist as a comorbid condition with other common medical conditions, such as type 2 diabetes mellitus and the metabolic syndrome. Prescription tracking data show that in the past few years, there has been a significant increase in the use of testosterone therapy in the United States.[1] Basic science studies have shown that vascular cells contain steroid hormone receptors and their relevant converting enzymes.[2] Therefore, testosterone can exert effects on the vascular walls either directly by itself or indirectly as estrogen through aromatization.[3] Based on these findings, there is a strong need for accurate information on the cardiovascular benefits and risks of testosterone therapy.

## Methods

A search of the English-language literature was performed on Medline using relevant keywords, including hypogonadism, testosterone deficiency, andropause, testosterone, androgen, dehydroepiandrosterone, cardiovascular disease (CVD), and coronary artery disease (CAD). The search results were sorted by type of study and relevance. The articles were then grouped according to the outline of the sections of this review. Analysis of the literature presented unique challenges. Specifically, problems were encountered in interpreting data on the relation among hypogonadism, testosterone therapy and CVD.[4] First, there is substantial variability in the end points. Second, there are big differences in the type of study designs, including cross-sectional and prospective or randomized cohort studies. Study populations vary. Third, survival bias can influence findings in cross-sectional studies. Fourth, in the area of hypogonadism and testosterone, there are significant measurement and methodologic problems in defining hypogonadism and in measuring testosterone.

## Sex Difference in Cardiovascular Disease

The simple observation that there is a significant sex difference in the morbidity and mortality of CVD has made it tempting to conclude that androgens are responsible for the elevated cardiovascular risk in men. A related hypothesis is that the lack of estrogens in men might be the cause of the difference in cardiovascular sex risk. However, in recent

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years there have been significant counterarguments. A major counterargument is based on the geographic and ethnic differences in the prevalence of CVD.[4] Morbidity and mortality from CVD in Northern and Eastern Europe compared with Southern Europe and Japan varies from 5- to 10-fold.[5] This suggests that other risk factors may be more important than sex. The narrowing sex gap after middle age adds another counterargument minimizing a possible causative role of sex hormones in CVD. The multifactorial nature of the pathogenesis of atherosclerosis minimizes the importance of testosterone as a single explanatory factor of the sex difference.

## Serum Testosterone, Cardiovascular Disease, and Animal Studies

There are a number of animal models with high-fat diet– and/or injury-induced CAD. In addition, there are animal models for genetic atherosclerosis.[6,7] In 16 different studies, inconsistent and conflicting results were provided on the relation of testosterone and CAD.[6]

**Human observational studies:** In a comprehensive review in 2003, 39 observational studies were reported: 32 were cross-sectional studies, 16 showed no association, and another 16 studies showed that lower testosterone was associated with high prevalence of CAD. There were 7 prospective cohort studies or nested control studies. None of these studies showed any association between testosterone levels and CAD. It should be noted that no single study showed an association between increased testosterone level and symptoms of CAD.[4]

**Induced hypogonadism:** Among the ways to understand the effect of testosterone is to observe the effects of induced hypogonadism. Hypogonadism is induced medically or surgically in patients with metastatic prostate cancer. In such cases, induction of hypogonadism results in increased insulin resistance and increased body fat mass.[8]

**Steroid hormone abuse:** The reverse of this observation is to investigate the effects of sex steroid abuse. This occurs in men involved in competitive athletics and bodybuilding. There are an estimated 1 million current or former abusers of steroid hormones.[4,9] Between 1987 and 1998, there were only 17 case reports of cardiovascular events in such young men.[4,10] On the face of it, there is no apparent increase in the incidence of cardiac cases from this population. Obviously, however, there is a significant underreporting in abuse cases. Large cohort studies are not available.

**Testosterone interventional studies:** Testosterone has been shown both in vitro and in vivo to cause vasodilatation of the coronary arteries. In a study of elderly men with CAD, coronary artery dilation and improved coronary blood flow were reported with direct intracoronary infusion of physiologic amounts of testosterone.[11] In a randomized, double-blind, placebo-controlled study of men with chronic stable angina, positive treatment responses were reported after daily application of a low-dose transdermal testosterone patch for several weeks.[12] Patients with a lower baseline level of testosterone exhibited increased treatment responses.

## Effects of Hypogonadism and Testosterone on Cardiovascular Risk Factors

Multiple cross-sectional studies have shown inverse correlations between testosterone levels and triglycerides, total cholesterol, low-density lipoprotein (LDL), fibrinogen, and plasminogen activator–1.[13–21] Other studies have shown inverse correlations between testosterone levels and body mass index (BMI), waist circumference, waist/hip ratio, amount of visceral fat, serum leptin levels, serum insulin levels, and serum free fatty acid concentrations.[22–24] In a case-control study of 50 age- and race-matched men, low testosterone was associated with higher BMI, systolic blood pressure, fasting serum glucose, serum insulin, and levels of all lipids except high-density lipoprotein (HDL) and apolipoprotein A1.[25] The findings of these observational studies support the hypothesis that low testosterone is a component of a multidimensional metabolic syndrome characterized by obesity, diabetes, hypertension, dyslipidemia, and a procoagulant/antifibrinolytic state. In a case-control study of men with diabetes and matched controls, levels of dehydroepiandrosterone DHEA sulfate, dihydrotestosterone, total testosterone, and bioavailable testosterone were significantly lower in patients with diabetes versus controls.[26] A large European population-based study recently showed that hypogonadism is associated not just with individual components of the metabolic syndrome but also with the entire syndrome itself (as defined by World Health Organization [WHO] criteria).[26] Hypogonadism can predict the subsequent development of diabetes and the metabolic syndrome in middle-aged men.[27,28] Hypogonadism may also be involved in the pathogenesis of these disease processes. However, although obesity, insulin resistance, and hypogonadism may be linked, the exact causal relations among them remain unclear.[29]

Testosterone is known to have beneficial effects on glucose regulation. In human studies of obese men with diabetes and hypogonadism, the administration of testosterone resulted in reduced fasting glucose, increased insulin sensitivity, and decreased glycosylated hemoglobin.[30,31] In studies of patients with prostate cancer undergoing androgen-deprivation therapy, increased serum insulin concentrations have been noted, despite no change in glucose levels.[8,32] This suggests an underlying resistance to insulin and a subsequent need for higher serum levels to achieve euglycemia.

The age-related decrease in testosterone normally seen in aging men is associated with a progressive loss of

TABLE 1

| Study | Design | Patients (N) | Patient Status at Study Entry | Treatment | Follow-up (mo) | Effects on Obesity Parameters | Effects on Lipid Panel | Effects on Cardiovascular Status | Effects on Diabetic Parameters | Additional Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Wang et al[33] | Randomized | 227 | Hypogonadism | 1% Testosterone gel, permeation-enhanced testosterone patch | 3 | ↑ Lean mass<br>↓ Fat mass<br>↓ % Fat | | | | Dose-response treatment effect in the T gel group. |
| Katznelson et al[35] | Open label | 29 | Hypogonadism | Oral testosterone enanthate | 18 | ↓ SC fat<br>↓ % body fat<br>↑ Lean muscle mass | ↑ LDL, HDL, TG | | | |
| Li et al[31] | | 86 | Hypogonadism | Oral testosterone undecanoate | 2 | ↓ Waist/hip ratio | No change in TC, TGs | ↓ BP | | |
| Boyanov et al[30] | Randomized | 48 | Hypogonadism<br>↑ Type 2 DM<br>↑ Visceral obesity | Oral testosterone undecanoate | 3 | ↓ Body weight<br>↓ Waist/hip ratio<br>↓ % Body fat | No change | ↓ BP | ↓ $HbA_{1c}$ | |
| Wittert et al[34] | Randomized | 76 | Healthy, >70 yr | Oral testosterone undecanoate | 12 | ↑ Lean body mass<br>↓ Fat mass | No change in plasma TGs, TC, and LDL-C<br>↓ HDL | No change | | |
| Marin[36] | Double blind | | Abdominal obesity | Transdermal testosterone, dihydrotestosterone | 9 | ↓ Visceral fat mass (T) | ↓ LPL activity plasma cholesterol, TGs (T) | ↓ Diastolic BP | ↑ Insulin sensitivity<br>↓ Fasting blood glucose (T) | No change in femoral adipose tissue |
| Zgliczynski et al[42] | Open label | 22 | 22 Hypogonadal, elderly(11 hypopituitarism, 11 healthy hypogonadic) | IM testosterone enanthate | 12 | | ↓ TC<br>↓ LDL, TGs, HDL | | | Same results in the 2 groups with different etiology of hypogonadism |
| Dobs et al[43] | Open label | 29 | Hypogonadism Open-label, multicenter study | Permeation-enhanced testosterone transdermal system | 12 | | ↓ HDL<br>↑ Cholesterol/ HDL ratio<br>↑ TGs small decrease in LDL and TC | | | * |
| Smith et al[8] | | 22 | Prostate cancer | Androgen-deprivation therapy | 6 | ↓ Lean body mass<br>↑ Fat mass | No change in lipids | ↑ Large artery stiffening<br>No change in peripheral BP | ↑ Serum insulin<br>No serum glucose change | * |

TABLE
Continued

| Study | Design | Patients (N) | Patient Status at Study Entry | Treatment | Follow-up (mo) | Effects on Obesity Parameters | Effects on Lipid Panel | Effects on Cardiovascular Status | Effects on Diabetic Parameters | Additional Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Dockery et al[32] | | 16 | 16 Men with prostate cancer, 15 men with arterial stiffness | GnRH analogues | 3 | No change in BMI | ↑ TC<br>↑ HDL-C<br>No change in LDL-C, TGs | ↓ Systemic arterial compliance<br>↑ Central pulse-wave velocities | ↑ Serum insulin<br>No change in serum glucose | |
| Webb et al[11] | | 13 | CAD | Intracoronary infusion of testosterone for 3 min | NA | | | Coronary artery dilation and ↑ coronary blood flow | | * |
| English et al[12] | Randomized, double-blind, placebo-controlled | 46 | Chronic stable angina | Transdermal testosterone patch | 3 | | | ↓ Exercise-induced myocardial ischemia | | * |
| Ozata et al[39] | Open label | 22 | Idiopathic hypogonadotrophic hypogonadism | hCG/hMG | 3 | | No change in TGs, LpA-I: A-II, HDL-C, $HDL_3$, apo A-I, apo B ↑ TC, LDL, LpA-I, $HDL_2$ | | | * |
| | | 9 | Klinefelter syndrome | Testosterone enanthate | 3 | | No change in TGs, LpA-I: A-II, HDL-C, $HDL_3$, apo A-I<br>↑ TC, LDL, LpA-I, $HDL_2$, apo B. | | | |
| Tan et al[38] | Open label | 11 | Hypogonadism | IM testosterone enanthate | 3 | | No change in TC, TGs, apo B, apo(a), LpA-I, LpL activity<br>↓ $HDL_{3c}$, LDL-C, TG, apoA-I, LpA-I:A-II<br>↑ $HDL_{2c}$, hepatic lipase | | | |
| Kenny et al[49] | Randomized, controlled | 44 | Hypogonadism | Transdermal testosterone | 12 | | No change in TC, TGs, LDL-C<br>↓ $HDL_2$. | No change in vascular reactivity | | |

apo = apolipoprotein; BMI = body mass index; BP = blood pressure; BPH = benign prostatic hypertrophy; CAD = coronary artery disease; DM = diabetes mellitus; GnRH = gonadotropin-releasing hormone; hCG/hMG = human chorionic gonadotropin/human menopausal gonadotropin; $HbA_{1c}$ = hemoglobin $A_{1c}$; HDL = high-density lipoprotein; IM = intramuscular; LDL = low-density lipoprotein; Lp = lipoprotein; LPL = lipoprotein lipase; NA = not available; SC = subcutaneous; TC = total cholesterol; TGs = triglycerides; ↑ = increased; ↓ = decreased.

muscle mass and increase in body fat. Findings in a study of 227 men with hypogonadism receiving testosterone therapy—either in the form of a gel (50 mg/day or 100 mg/day) or a permeation-enhanced patch (5 mg/day)[33] showed that after 90 days of treatment, all groups demonstrated an increase in lean body mass. Notably, the groups of men treated with the 100 mg/day testosterone gel showed a >2-fold increase in muscle mass relative to the other groups ($p = 0.0002$), suggesting a possible dose-response relation between testosterone replacement and muscle mass. This dose-response relation was not observed for the changes in fat mass. Other studies of oral testosterone therapy have documented increased lean body mass, weight loss, decrease in percent body fat, and decrease in waist/hip ratio.[30,31,34,35] A double-blind study of men with central obesity treated with transdermal testosterone showed a decrease in the visceral fat, but not in the femoral fat in the men treated with testosterone.[36] It is possible that testosterone may regulate body composition by preferentially inducing pluripotent mesenchymal cell differentiation toward a myogenic lineage and away from an adipogenic lineage.[37]

Whereas observational studies have shown a consistent association between low testosterone and high cholesterol levels, studies of testosterone therapy have shown inconsistent results. It has been suggested that testosterone may actually decrease HDL concentrations and have a potentially atherogenic effect. However, as shown by Tan et al,[38] the testosterone-induced reduction in HDL is specifically in $HDL_3$ cholesterol, which is thought to be the least antiatherogenic subfraction. Concentrations of $HDL_2$ and apolipoprotein A1, which are 2 molecules with high antiatherogenic activity, have actually been found to be increased with testosterone administration.[38,39] In studies in elderly men, it was found that androgen administration is associated with only a slight decrease or no change in serum HDL concentrations.[40–44] Apart from lowering serum HDL concentrations, no other effects of testosterone—atherogenic or antiatherogenic—were noted in the literature.

## Other Hormones: Dehydroepiandrosterone and Estrogens

Among the hormones that attracted substantial attention is DHEA. Epidemiologic and experimental studies have failed to show any relation between DHEA and CVD.[4,41] Estrogens are important in maintaining normal carbohydrate and lipid metabolism. Estrogens increase HDL, but they also have thromboembolic effects. The traditionally presumed atheroprotective effect lacks evidence.[4,41]

## Research Recommendations

Further well-controlled studies are recommended to assess the potential cardiovascular benefits and possible risks of testosterone therapy. More research is also recommended to assess the potential cardiac effects—whether positive or negative—on the combination of phosphodiesterase-5 inhibitors and testosterone.

## Conclusion

Endogenous effects of testosterone do not sufficiently account for sex differences in CVD morbidity and mortality. Hypogonadism is associated with central obesity, insulin resistance, low HDL, low cholesterol, and high LDL, triglyceride, and fibrinogen levels. Short-term outcomes suggest CVD benefits of testosterone in aging men, whereas results of preclinical studies are inconclusive. Overall, there is evidence to support the conclusion that the cardiovascular effects of testosterone therapy may be considered neutral to beneficial. There is no contraindication for testosterone therapy in men with risk factors or overt CVD with a clinically diagnosed hypogonadism (Table 1).[8,11,12,30–36,38,39,42–44]


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