

Testosterone and Heart Disease

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Introduction

Two recent trials suggest that testosterone replacement therapy may increase the risk of heart disease and/or stroke. 1, 2

These were poorly designed studies which conflict with numerous previous medical trials that show the beneficial effects of testosterone on the heart and that low testosterone levels in males are associated with an increased risk in the development of heart disease.

The following is a comprehensive review of the medical literature on low testosterone being associated with an increased risk in the development of cardiovascular disease and that testosterone replacement at appropriate levels not only decreases the risk of heart disease but can also be used to treat coronary disease.

Low Testosterone Levels and Increased Risk of Heart Disease

Men with coronary heart disease had a significantly lower total testosterone, free testosterone, and bioavailable testosterone. 3

Low endogenous testosterone concentrations are related to mortality due to cardiovascular disease and other causes. 4, 5

Study showed a possible correlation between lower testosterone levels, erectile dysfunction and conditions associated with higher cardiovascular risk. 6

Study showed that men with coronary heart disease that were under the age of 45 had total and free testosterone levels significantly lower than controls. 7

Serum free testosterone levels were found to be inversely related to carotid intima-media thickness (IMT) and plaque score. 8

Low testosterone levels have been found to be associated with atherosclerosis in men. 9

Low Testosterone Levels and Increase Risk of Diabetes Type II and Metabolic Syndrome

Low testosterone levels are associated with an increased risk for the development of type II diabetes and metabolic syndrome. 10, 11, 12, 13, 14

Since low testosterone has been shown to lower blood sugar levels, the Endocrine Society now recommends measurement of testosterone in all male patients with type II diabetes mellitus.

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Low Testosterone Levels Are Associated with an Increased Risk of Mortality

Study showed that low testosterone predicts mortality from cardiovascular disease. 16

Study showed that low testosterone levels were associated with an increased risk of all-cause mortality independent of numerous risk factors. Serum testosterone levels were inversely related to mortality due to cardiovascular disease and cancer. 17

Low endogenous testosterone levels are associated with an increased risk of death from all causes and cardiovascular death. 18

Low Testosterone Levels and Increased Risk of Hypertension

Study showed that low total testosterone concentrations are predictive of hypertension, suggesting total testosterone as a potential biomarker for increased cardiovascular risk. 19

Low Testosterone and Congestive Heart Failure

In males with heart failure, low serum androgens were associated with an adverse prognosis.

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In men with chronic heart failure, anabolic hormone depletion is common and deficiency of each anabolic hormone is an independent marker of poor prognosis. 21

Testosterone Replacement and Heart Disease

Study showed that for all-cause mortality, for each increase of six nanomoles of testosterone per liter of serum was associated with an almost fourteen percent drop in the risk of death. 22

Study revealed that testosterone replacement was associated with a decrease in HDL-C and lipoprotein a. 23

The mechanism of testosterone replacement decreasing lipids may be due to testosterone's positive effects on abdominal fat and insulin resistance. 24

Short-term administration of testosterone induces a beneficial effect on exercise-induced myocardial ischemia in men with coronary heart disease. This effect may be related to a direct coronary-relaxing effect of testosterone. 25

Short-term intracoronary administration of testosterone, at physiological concentrations, induces coronary artery dilatation and an increase in coronary blood flow in men with established coronary heart disease. 26

Low-dose supplementation with testosterone in men with chronic stable angina reduced exercise-induced myocardial ischemia. 27

Testosterone replacement has been shown to increase coronary blood flow in patients with coronary heart disease. 28, 29

Transdermal testosterone replacement has been shown to improve chronic stable angina by increasing the angina-free exercise tolerance vs. controls that were getting placebos. 30

Another study showed that testosterone replacement reduced exercise induced myocardial ischemia. 31

Testosterone is a coronary vasodilator by functioning as a calcium antagonistic agent. 32

Testosterone replacement therapy in hypogonadism moderates metabolic components associated with cardiovascular risk. 33

Testosterone replacement has been shown to decrease inflammation and lower total cholesterol. 34

Testosterone replacement in patients with congestive heart failure has been shown to improve exercise capacity, improve insulin resistance, and improve muscle performance. 35

Testosterone replacement has been shown to be helpful in patients with severe heart failure. 37

In this review of the medical literature one can see that numerous studies have shown that low testosterone levels are associated with an increased risk of heart disease and that testosterone replacement therapy is associated with a decreased risk of developing heart disease and is even beneficial in patients that already have coronary vascular disease.

So why did the two recent studies show that there was an increased risk of developing heart disease in male patients that were prescribed testosterone replacement therapy?

There are **five** serious flaws associated with the two recent trials.

Firstly, estrone and estradiol levels were not measure in the subjects in the studies. High estrogen levels in males have been found to be associated with an increase risk in the development of heart disease and stroke. Estrogen levels may elevate due to an increase in

aromatase activity, alteration in liver function, zinc deficiency, obesity, abuse of alcohol, drug-induced estrogen imbalance, and ingestion of estrogen-containing foods or environmental estrogens.

High Estrogens are Associated with an Increased Risk of Heart Disease and Stroke

Study showed that high estradiol in males was associated with an increased risk of stroke. 38

Study showed that elevated circulating estradiol is a predictor of progression of carotid artery intima media thickness in middle age men. 39

High estradiol levels in men were associated with acute myocardial infarctions. 40

High estrone and low testosterone levels were associated with promoting the development of atherogenic lipid milieu in men with coronary heart disease. 41

Low testosterone and elevated estradiol was associated in this study with lower extremity peripheral artery disease in older men. 42

Men with myocardial infarction had high estradiol and low testosterone levels. 43

Elevated levels of estradiol in men were associated with an increase incidence of strokes, peripheral vascular disease, and carotid artery stenosis compared to subjects with lower estradiol levels. 44

Elevated levels of estrogen in men are associated with an increased risk of heart disease. 45

Secondly, having erythrocytosis is associated with an increased risk in the development of heart disease and thrombosis. 46 A major study on the risk and benefits of testosterone replacement suggests that a baseline hematocrit should be checked at three and six months and then every six to twelve months. If the hematocrit is more than fifty-four percent then testosterone therapy should be stopped until the hematocrit is at a safe level. 47 Hematocrit levels were not measure in these two trials.

Thirdly, in both studies not all patients had follow-up testing of testosterone levels. Therefore, dosages of testosterone may have been higher than needed. Supraphysiological levels of testosterone can induce nitric oxide production and cause oxidative stress which induces endothelial dysfunction. 48

Fourthly, some of the men in these trials were using testosterone injections, which are nonphysiologic since they have peak and trough levels over the weekly or biweekly dosing. This issue was wonderfully discussed by Cappola in her review of Vigen's study. 49

Lastly, testosterone can convert to dihydrotestosterone (DHT) which has been shown to enhance early atherosclerosis. 50 The conclusion of the author of this trial was that the findings highlighted a new androgen receptor/nuclear factor-kappaB mediated mechanism for vascular cell adhesion molecule-1 expression and monocyte adhesion operating in male endothelial cells that may represent an important unrecognized mechanism for the male predisposition to atherosclerosis. The higher the dose of testosterone that is prescribed the more it is converted by 5 alpha-reductase into DHT. In these two recent trials that suggest that testosterone replacement increases the risk of heart disease in men, DHT levels were not measured.

Conclusion

Given the plethora of medical studies indicating the beneficial effects of properly prescribed testosterone, one would have to conclude that these two recent medical trials are poorly designed and their conclusion is flawed. Some of the patients did not have repeat testosterone levels measured. Consequently, the patients may have had supraphysiological levels of testosterone. In addition DHT, estrone, estradiol, and HCT levels were not addressed. Furthermore, the medical literature has shown that hormones in the body are a symphony and this web of interconnection was not considered.

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