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AS WE SEE IT

A New, Independent Risk Factor for Heart Disease

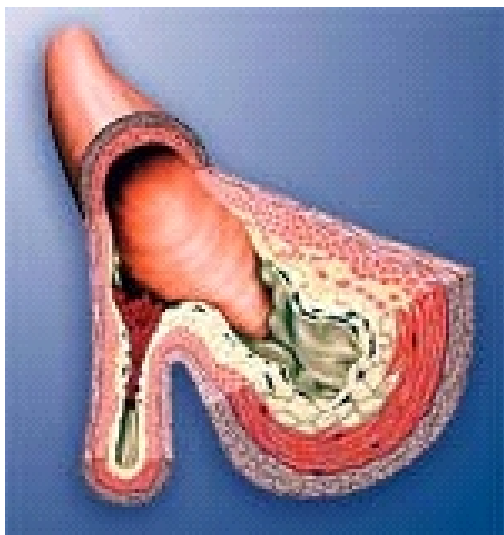
Conventional doctors have long recognized obesity, cigarette smoking, high blood pressure, elevated cholesterol, and diabetes as major risk factors for a heart attack. A startling report reveals a new, independent risk factor that markedly affects the severity of coronary artery disease.

As most Life Extension members know, angina and heart attacks often manifest when the major coronary arteries become occluded with unstable atherosclerotic plaque. In a newly published study, doctors measured the degree of coronary artery disease using angiographies and then carefully evaluated all of the known risk factors that could explain the blocked coronary arteries.

The surprising finding from this new study is that blood pressure, cholesterol, diabetes, smoking, and body mass index may not be the major predictors of degree of coronary artery blockage. Instead, the three independent risk factors that predicted the severity of coronary artery occlusion were age, high-density lipoprotein (HDL), and free testosterone. In this instance, "independent risk factor" means that if you did everything else recommended to protect your heart, you would still be at greater risk for serious coronary artery blockage if you had low testosterone and low HDL.



William Faloon



In this study, aged men with low free testosterone and low HDL showed more severe coronary blockage, leading the doctors to conclude:

"These findings, together with the findings of previous studies from other laboratories, raise the possibility that in men selected for coronary arteriography, age, HDL, and free testosterone may be stronger predictors of degree of coronary artery disease than are blood pressure, cholesterol, diabetes, smoking, and body mass index (BMI)."¹

What These Findings Mean to You

The aging arterial system, along with low levels of beneficial HDL, has long been associated with coronary artery disease. The unexpected finding in this study was that low free testosterone is also an independent predictor of the degree of coronary artery disease in men.

Life Extension members take many steps to protect their arterial systems against the deleterious effects of aging. They keep homocysteine, low-density lipoprotein (LDL), glucose, C-reactive protein, and other atherosclerosis-inducing factors at the lowest possible levels.

Artery-protecting HDL can be increased by taking high doses of niacin and chromium, and/or one glass of red wine per day.²⁻⁶ Increasing free testosterone is relatively simple to do in any man who does not have prostate cancer.

Over the past year, a remarkable number of studies have confirmed that low testosterone adversely affects cardiovascular health. We will discuss these reports and also update members on the latest studies about testosterone and prostate cancer risk.

Testosterone and Stroke Risk

One way to evaluate one's risk for a stroke is to undergo a sonogram to measure carotid artery thickness. When excess occlusion is detected, a risky surgical procedure (carotid endarterectomy) is performed to restore blood flow to the brain.

In a study published by the American Heart Association in April 2004, sonograms were used to measure the carotid intima-media thickness in 195 independently living elderly men in 1996 and again in 2000. The researchers also measured blood levels of free testosterone in these men.

The results showed that men with low testosterone had a 3.57 times greater progression of carotid intima-media thickening than those with higher testosterone levels. These associations were independent of body mass index, waist-to-hip ratio, hypertension, diabetes, smoking, and serum cholesterol levels. The doctors concluded:

*"Low free testosterone levels were related to intima-media thickening of the common carotid artery in elderly men independently of cardiovascular risk factors."*⁷



Testosterone for Chronic Heart Failure

Chronic heart failure is a disabling condition characterized by exercise intolerance and shortness of breath. The disease arises from prolonged inflammatory cytokine activation that also causes severe muscle wasting. Testosterone increases anabolic function, improves arterial dilation, augments cardiac output, and is known to have anti-inflammatory activities. Low testosterone is a common characteristic in men suffering from heart failure.



In a report published this year, 20 men with an average age of 62 took part in a randomized study in which testosterone or placebo was injected every two weeks for 12 weeks. Compared to the placebo group, men receiving testosterone could walk 3.5 times farther. Mean symptom scores and a critical blood measurement of heart function (brain natriuretic peptide) improved in men receiving testosterone, but not in the placebo group. A trend toward improved mood scores was noted in the testosterone group, which is important because men with chronic heart failure have high rates of depression. The doctors concluded that 12 weeks of testosterone treatment led to significant improvements in physical capacity and symptoms.⁸

Testosterone and Glycation

The best way to measure long-term blood sugar levels is the hemoglobin A1c test. A higher percentage of hemoglobin A1c is correlated with increased cardiovascular mortality. Elevated hemoglobin A1c percentage may also be an indicator of how much age-accelerating glycation is occurring throughout the body.

A study published in February 2004 measured blood levels of testosterone in 1,419 men and compared them to the percent-ages of hemoglobin A1c.⁹ The findings showed that men with elevated hemoglobin A1c (and diabetes) had lower levels of testosterone and that these associations were independent of obesity and body fat distribution.

Life Extension has published extensively about the lethal dangers of glycation, whereby sugar molecules bind with amino acids to form nonfunctioning structures in the body called advanced glycation end products. As large amounts of proteins become glycated, tissues throughout the body become nonfunctional. The proteins of diabetics are highly prone to glycation because of poor glucose control.¹⁰⁻¹²

The arterial system is a major casualty of the glycation process. This new study reveals how low testosterone may increase the glycation process, and helps explain why testosterone deficiency has been associated with increased risk of cardiovascular disease and atherosclerosis in men.

Most Life Extension members take carnosine to help slow the glycation process, which is a normal (albeit pathological) aspect of aging.⁹ This latest study indicates that overweight and diabetic men should seek to maintain high-normal testosterone levels.

Testosterone and Ejection Fraction

One way to measure the heart's pumping capacity is to measure how much blood it pumps after each beat compared to the amount of blood remaining in the heart. This measurement is called the ejection fraction. Healthy people have an ejection fraction of 56-78%, while those with congestive heart failure are often well below 30%.

In a study published in August 2003, 96 men underwent ejection-fraction testing and coronary artery angiograms to measure the degree of coronary occlusion. The ejection fraction was substantially lower in men with low testosterone levels. Men with the lower ejection fractions averaged only 28% of the free testosterone level of men with the higher ejection fractions. The findings also showed that men with proven coronary artery disease had about 50% less total and free testosterone than healthy controls.

This is the first study in a clinical setting to show that low levels of free testosterone are characteristic of patients with low ejection fraction.¹³

In a related study, 12 men with stable chronic heart failure were enrolled in a crossover trial in which they received either testosterone or placebo and were monitored over six hours. The subjects were then switched the next day, receiving the second treatment and repeated cardiac output monitoring. Compared with placebo, testosterone treatment resulted in a relative increase in cardiac output. This was accompanied by a reduction in systemic vascular resistance compared to baseline. These maximal changes coincided with peak elevation in serum bioavailable testosterone. The doctors concluded that administration of testosterone increases cardiac output acutely, apparently via reduction of left ventricular after-load.⁹

These two studies corroborate the previously discussed findings indicating that testosterone replacement could be of enormous benefit to men with heart disease.

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Recent Animal Studies

Two recent animal studies further document testosterone's positive effects on the heart and arterial system.

One study published in December 2003 examined the coronary arteries of rabbits. Testosterone administration was found to relax the rabbits' coronary arteries, which suggests that humans suffering angina could benefit from testosterone.¹⁵

Another study published in October 2003 investigated the impact of testosterone on myocardial ischemia-reperfusion injury and corresponding intracellular calcium metabolism.¹⁶ This is a way of simulating what happens when a person suffers an acute coronary artery occlusion (heart attack) and is able to be revived in a hospital.

The rabbits were first castrated in order to deplete testosterone, and were then given testosterone or placebo. After two weeks of treatment, the hearts were removed and placed on an artificial apparatus where they were deprived of blood flow (no blood flow ischemia) for 30 minutes and then re-perfused for 30 minutes. Compared to placebo, the recovery of contractile heart muscle function was greater in the testosterone-treated rabbits. Calcium overload influx into the cells was lower in the testosterone group compared to placebo. This is important because one of the irreversible effects of cardiac ischemia (caused by no blood flow to a portion of the heart) is excess calcium infiltration into cells that permanently damages the delicate intracellular machinery, thus making resuscitation impossible.

The scientists concluded: "Administration of testosterone significantly improves recovery from global ischemia." For humans, this means that having adequate testosterone levels may significantly enhance the chances of being revived following a heart attack.

Testosterone and Prostate Cancer Risk

Many doctors are still under the impression that testosterone causes prostate cancer. The preponderance of evidence indicates otherwise.



Back in 1999, we wrote an extensive protocol describing how aging men could safely boost their free testosterone levels.¹⁷ Because there was such a strong perception that testosterone augmentation could increase the risk of prostate cancer, we did a MEDLINE search for all published studies relating to serum testosterone and prostate cancer. Of the 27 studies we found on MEDLINE, only five indicated that men with higher testosterone levels had a greater incidence of prostate cancer, whereas 21 studies found that testosterone was not a risk factor and one study was considered neutral. Thus, in 1999, the score was 21 to 5 in favor of testosterone not increasing prostate cancer risk.

Some recent studies have clarified this debate more definitively. A study published in December 2003 analyzed blood samples of 300 cases of prostate cancer diagnosed between 1987 and 1998 and compared them to 300 matched controls. Higher concentrations of testosterone were not associated with increased prostate cancer risk. In fact, men with the highest levels of free testosterone were 26% less likely to have prostate cancer than men with the lowest levels of free testosterone.¹⁸

A study published in January 2004 compared 708 men who were diagnosed with prostate cancer to 2,242 men who were not diagnosed with it. The results showed that higher levels of testosterone correlated with a decreased risk of prostate cancer. Men with the highest free testosterone levels were 18% less likely to have prostate cancer than men with the lowest levels.¹⁹

A study published in December 2003 was particularly revealing. A group of 75 men with low testosterone and a precancerous prostate lesion (called high-grade prostatic intraepithelial neoplasia) were administered testosterone replacement therapy for one year. The men all underwent prostate biopsy to rule out frank prostate cancer, and their blood was tested for prostate-specific antigen (PSA). After one year of testosterone drug therapy, these men did not have a significantly greater increase in PSA or risk of cancer than the men without precancerous lesions. The doctors concluded that testosterone replacement therapy is not

contraindicated in men with precancerous lesions.²⁰

In a study published in May 2003, a test that measures testosterone bioactivity in the blood was used to compare men with benign prostate enlargement to those with newly diagnosed prostate cancer. Men with prostate tumors had lower testosterone bioactivity. Levels of free testosterone did not differ between the two groups.²¹

Unfortunately, one new unpublished report contradicts the other four recently published positive studies. In this study, stored blood samples of several different hormones were measured in 111 prostate cancer victims out of a group of 759 aged men. The findings showed that higher levels of free testosterone resulted in a significant increase in prostate cancer risk. Higher levels of DHEA and other sex hormones did not result in increased prostate cancer risk. The doctors who conducted this study cautioned that men on testosterone replacement therapy should be advised that they might be increasing their risk of prostate cancer. Of course, the news media reported on this one negative study while ignoring the four recent positive studies.²²

Flaws in Prostate Cancer Studies

Conventional medicine continues to focus on relatively narrow parameters when seeking to define disease risk factors. In other words, when evaluating the effects of higher testosterone levels on prostate cancer incidence, researchers fail to measure numerous other factors that may either increase or decrease one's risk.

This means that findings from both positive and negative studies can be skewed because scientists do not take into account dietary and supplemental intake of nutrients shown to reduce prostate cancer risk, such as lycopene, vitamin D, boron, soy, vitamin E, fish oil, gamma tocopherol, selenium, and indole-3-carbinol. Other dietary factors—such as heavy consumption of saturated fats and high-glycemic foods that increase risk, and regular ingestion of fish, fruits, and vegetables that decrease risk—are also ignored when seeking to determine whether higher testosterone levels increase prostate cancer incidence.²³⁻²⁵

We do not want to criticize these researchers unfairly, as the costs of evaluating blood levels or consumption of nutrients and foods that affect prostate cancer risk are often beyond the financial limits of the grants that fund these studies. In fact, our organization has been a vocal critic of the paucity of government funding aimed at eradicating age-related diseases such as cancer. If more money were available to conduct prostate cancer research, many additional factors could be measured when seeking to identify what aging men should be doing to reduce their risk.

In contrast to researchers who make general recommendations based on limited data, we at Life Extension advocate a much more comprehensive approach. We first examine all of the scientific studies on a particular subject, such as blood testosterone levels and prostate cancer incidence.

In this case, the preponderance of scientific studies (greater than 4 to 1) indicates that higher free testosterone levels do not result in greater prostate cancer incidence.²⁶

We then look at results of the many blood tests we conduct to measure levels of free testosterone, estradiol, and PSA. When looking at these blood reports, it is hard to subscribe to the theory that higher levels of testosterone are a concern when so many men with prostate cancer are already testosterone deficient (by Life Extension standards).

To clarify this point, conventional doctors define low testosterone as being below standard laboratory reference ranges. We, on the other hand, view aging men who are in the lower one-third to one-half of normal reference ranges as being testosterone deficient. Laboratory reference ranges are based on "normal" population averages, and it is quite normal for aged men have low testosterone levels. Humans suffer devastating health consequences in their later years. To circumvent these "normal" pathological changes, we advocate aggressive approaches to counteract the effects of normalcy, including the negative effects associated with low testosterone.

Since prostate cancer is such a widespread problem, most Life Extension members are already taking nutrients and following diets that have been shown to significantly reduce the risk. As evidence accumulates indicating that higher testosterone protects men against a host of age-related disorders, fear of prostate cancer may not be an appropriate reason to allow one's testosterone to remain at less-than-optimal levels. We must emphasize, however, that men with prostate cancer cannot take testosterone-boosting therapies because this hormone stimulates the proliferation of existing prostate cancer cells.

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Millions of Needless Heart Attacks

It is remarkable how ignorant physicians remain about the lifesaving benefits of testosterone replacement therapy. An overwhelming volume of data shows that higher levels of testosterone protect against disorders as diverse as Alzheimer's dementia, type II diabetes, abdominal obesity, osteoporosis, muscle wasting, depression, cognitive decline, loss of libido, inability to achieve erection, inflammatory-related syndromes, and a range of cardiovascular diseases.

The new data presented in this editorial, along with numerous previous studies, indicate that cardiologists have overlooked the remarkable benefits of testosterone replacement in the treatment of their patients. Of particular interest is the ability of testosterone and other hormone replacement therapies to lower cholesterol levels.²⁷⁻²⁹ Doctors are prescribing side-effect-prone statin drugs, when for many patients, testosterone enhancement would reduce cholesterol and possibly C-reactive protein.

The failure of doctors to recognize the critical importance of aging men maintaining youthful testosterone levels has resulted in millions of needless heart attacks.

For many years, the Life Extension Foundation has urged members to have their blood tested for free testosterone and other critical hormones. For those who test deficient for these hormones, we have recommended a variety of approaches that would enable hormone levels to be safely restored to a youthful profile. Our current Male (and Female) Hormone Modulation protocols can be found in our *Disease Prevention and Treatment* reference book, or can be accessed online at our website (www.lef.org).²⁹



For \$75 a year, Life Extension members learn what their doctors are not doing to keep them alive. In the case of testosterone replacement for aging men, this need has been obvious for years.

Do not wait for your doctor to discover the incredible value of testosterone replacement therapy. You may not live that long! Please check your blood for free testosterone, PSA, and other hormones such as estradiol, and then follow our protocols to re-establish your levels to those of a healthy 21-year-old. Most people are pleasantly surprised to find how much better they feel when these critical hormones are restored.

For longer life,

William Faloon

P.S. If your doctor will not prescribe these hormone blood tests, call 1-800-208-3444 to order them directly.

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