

## The Testosterone Controversy - with references

Adapted from an article posted by William Faloon of [Life Extensions](#)

Testosterone levels are **high** in young men, but **plummet** during aging. Despite compelling findings of efficacy, conventional doctors still question the value of **testosterone replacement** in maturing men. This oversight is causing **needless** heart attacks and strokes. Low testosterone is associated with excess **abdominal fat**,<sup>1-4</sup> loss of **insulin sensitivity**,<sup>5,6</sup> and **atherosclerosis**.<sup>7,8</sup>

A critically important role of **testosterone** is to enable **HDL** to remove excess **cholesterol** from the arterial wall and transport it to the liver for disposal. This effect of enhancing HDL is termed "**reverse cholesterol transport**" and is vital to preventing arterial occlusion.<sup>9,10</sup>

Cardiologists routinely prescribe **statin drugs** to lower **LDL**, a lipoprotein that transports **cholesterol** from the liver to the arteries. These same doctors, however, fail to maintain sufficient **testosterone** levels in their patients to enable **HDL** to remove cholesterol buildup in the arteries. This is one reason why statin drugs have not always been shown to work in older men, who require functional **HDL** to keep arterial linings free of excess cholesterol. <sup>11,12</sup> Numerous studies document the vital role that testosterone plays in maintaining youthful metabolic processes throughout the body.<sup>6,7,13-21</sup> A large new study confirms the deadly impact of low testosterone in older men.<sup>22</sup>

What's scary are clinical trials designed by doctors who have no idea how to achieve *youthful* hormone levels. Men who enroll in these studies are subjected to **lethal dangers** because **testosterone** and **estrogen** blood levels are not properly balanced. Cells throughout a man's body are laden with **receptor sites** that are activated by the hormone **testosterone**. When testosterone is available to bind to these receptor sites, good things happen such as **elevated mood** and **improved cognition** in response to plentiful testosterone being available to the brain.<sup>23-25</sup> Be it muscle, bone, vascular, or nerve tissue, testosterone provides critical command signals for your cells to behave in a youthful manner.<sup>8,26-33</sup> As testosterone levels diminish, degenerative processes set in.

### New Published Study Confirms Testosterone's Benefits

Of considerable interest is the relationship between testosterone blood levels and cardiovascular events such as heart attack and stroke. In a revealing new study, researchers identified **2,416** men (aged 69-81 years) who were not on any kind of testosterone-affecting treatment. These men were subjected to a battery of blood tests that included **total testosterone** and **estradiol** (estrogen). The first observation was that men with **increasing** levels of **testosterone** had a **decreased** prevalence of **diabetes**, **hypertension**, and **body fat mass**. Compared to men with the highest testosterone levels, those with low testosterone were twice as likely to have a history of **cardiovascular disease**. It was also observed that men with the **highest testosterone** levels were the most **physically active**.<sup>17</sup> This large group of men was followed for an average of **5.1 years**. Men in the **highest quartile** of **total testosterone** (above **550 ng/dL**) had a **30% lower risk** of cardiovascular events. Any level of total testosterone below **550 ng/dL** resulted in significant increased risk, thus helping to establish a minimal baseline as to where **total testosterone** should be to guard against heart attack or stroke. **Estradiol** levels measured in this group appeared to be mostly in safe ranges and did not impact incidence of cardiovascular events. Data was tabulated based on hospital reports and/or death certificates for heart attack, stroke, unstable angina, bypass surgery, or stenting.

The four quartiles of **total testosterone** in this large group of older men were:

Quartile 1: Total testosterone below **340 ng/dL**.

Quartile 2: Total testosterone between **341-438 ng/dL**.

Quartile 3: Total testosterone between **439-549 ng/dL**.

Quartile 4: Total testosterone above **550 ng/dL**.

Of interest was the finding that **Quartiles 1, 2, and 3** had about the same risk of cardiac adverse events. It was only in **Quartile 4** (when total testosterone exceeded **550 ng/dL**) that the **30%** reduction in cardiovascular events occurred. This finding showed that it did not matter if these men's total testosterone was very low (below **340 ng/dL**) or moderately low (up to **549 ng/dL**)...they all had a similar increased risk for suffering a cardiovascular event. Only when total testosterone exceeded **550 ng/dL** did cardiovascular risk plummet.

This finding remained consistent for cerebrovascular disease incidence, where men with the highest **total testosterone** (Quartile 4) had a **24%** reduced risk of **transient ischemic attack** or full-blown **stroke**. The researchers noted this association with reduced cerebrovascular risk remained after adjustment for traditional risk factors.

The conclusions by the researchers who conducted this study were:

**"Higher serum testosterone levels are associated with a reduced risk of fatal and non-fatal cardiovascular events in community dwelling elderly men."** <sup>17</sup>

## Many Doctors Know Nothing About Hormone Balance

If you ever wonder why so many deaths are directly caused by medical errors, look no further than the obvious mistakes made by doctors who design human clinical trials.<sup>34-36</sup> It has long been known that aging men are at risk for having excess activity of an enzyme called **aromatase**. The effect of surplus *aromatase* is that too much **testosterone** is converted to **estrogen**.<sup>37,38</sup> Aging men have a propensity to develop dangerously *high levels* of **estrogen** combined with woefully *inadequate testosterone*, though many aging men suffer both low testosterone and estrogen.<sup>39,40</sup> Elevated estrogen can *sharply* increase **heart attack** risk by promoting **platelet aggregation** and **coagulation** in coronary arteries.<sup>41,42</sup> Higher estrogen in men also increases **inflammation** which can cause unstable plaque to rupture and occlude a coronary artery, thus creating a sudden heart attack.<sup>43-45</sup>

Now just imagine designing a study where a huge dose of **testosterone cream** is applied to dilapidated men with a high prevalence of obesity, hypertension, diabetes, and elevated LDL. These men (average age 74) all suffered limited mobility and many had known cardiovascular disease. All these physically impaired men had very low **total testosterone** levels (mean **243 ng/dL**) at baseline, but the doctors never bothered to check their **estrogen** levels. The study was stopped after six to twelve months because the decrepit men receiving testosterone (at a dose more than twice what is typically prescribed) showed a **4.6-fold increase** in adverse cardiovascular events.<sup>46</sup> The purpose of the study was to see if high-dose testosterone cream could improve strength and mobility in these degenerated men. Early results showed it to be effective in improving muscle strength, but the study had to be stopped because too many cardiovascular events occurred. The study authors admitted that the testosterone cream may have converted to **estrogen** and caused these cardiac problems. My question is why they failed to test estrogen levels in the beginning and monitor estrogen after administering high-dose testosterone cream?

**Obesity** alone causes estrogen levels in men to spike.<sup>38</sup> The reason overweight men grow breasts is that abdominal fat tissue synthesizes huge amounts of *aromatase*, which converts their testosterone to estrogen. Obese men with elevated estradiol are strongly advised to take aromatase-inhibiting agents. By applying **high doses** of **testosterone** cream, **estrogen** levels would be expected to spiral upward in many of these unhealthy men, thus predisposing them to cardiovascular events inflicted by **abnormal arterial blood clotting** (thrombosis) and **inflammation**.

Despite these obvious flaws, this negative study was widely circulated in the medical mainstream and used as a basis to advise doctors to prescribe testosterone cream with caution. This is unfortunate as the preponderance of data shows significant protective effects when **testosterone** and **estrogen** are in a *youthful* state of **balance**. Most published studies fail to look at **estrogen** levels in men, despite a massive body of evidence showing significant increases in mortality when estrogen levels are **too high** or **too low**.<sup>47-52</sup>

One might wonder how two studies could come to completely **opposite** conclusions. A 2011 published study of **2,416** men showed a **30%** reduction in cardiovascular events when total testosterone levels exceeded **550 ng/dL**.<sup>17</sup> Yet an unpublished report released in 2010 of less than **700** men stated that cardiovascular events more than **doubled** when total testosterone exceeded **495 ng/dL**.<sup>53</sup> One problem relates to differing laboratory methodologies whose results vary more than professionals like to admit. This means that some of these studies may not have accurately measured testosterone blood levels. In the most recent positive study showing a **30% reduction** in cardiovascular events in men with total testosterone above **550 ng/dL**, the researchers exclusively used a **mass spectrometry**-based technique that provides a more accurate assessment of testosterone status than testing methods used in previous studies. The more obvious flaw, however, relates to the large number of **independent risk factors** involved in the development of atherosclerosis, thrombosis and subsequent heart attack and stroke. While some of these other risk factors are sometimes factored in, no study on testosterone has included all of them and they all rely on outdated reference ranges for artery-damaging factors such as glucose and hypertension.

## How Testosterone Protects Against Heart Attacks

Most people know that higher blood levels of HDL protect against atherosclerosis and subsequent heart attack. What few understand is the critical role that testosterone plays in enabling HDL to remove built-up cholesterol from the arterial wall.

HDL removes cholesterol from the arterial wall and returns it to the liver for safe disposal via a process known as **reverse cholesterol transport**. Testosterone enhances HDL-induced reverse cholesterol transport from the arterial wall.<sup>9</sup> That is one of testosterone's unique and lifesaving anti-atherosclerotic effects.

While a person can reduce their arterial wall exposure to cholesterol through healthier diets and by taking certain drugs, the average person still synthesizes about **750 mg** every day of cholesterol in their peripheral tissues (outside of the liver). If there is any distortion in the HDL-mediated removal of cholesterol (i.e. reverse cholesterol transport) from the arterial wall, the consequence is atherosclerosis.<sup>54</sup> Said differently, testosterone is required for optimal transport of excess cholesterol from our tissues and blood vessels to our liver for processing and disposal. In the testosterone-deficient state, **reverse cholesterol transport** is compromised, and excess cholesterol cannot be removed from the arterial wall.<sup>55-57</sup>

HDL and testosterone levels often plummet in aging humans.<sup>59,60</sup> The combination of low HDL and low testosterone virtually guarantees an explosion in demand for vascular stents and drugs that earn tens of billions of dollars in profits each year for pharmaceutical behemoths.

Under optimal circumstances, HDL efficiently removes cholesterol from arterial walls and then transports it (via reverse cholesterol transport) to the liver for elimination (mostly through the bile duct into the intestines). When there is a deficiency of testosterone, HDL is less efficient in removing debris from the arterial wall and the liver is less efficient in breaking down cholesterol-laden HDL from the blood-stream. Armed with this knowledge, you can now see past the charade perpetrated by the medical establishment that still questions the value of testosterone supplementation. Numerous well-controlled human studies show that higher testosterone levels play a critical role in maintaining healthy blood flow throughout the body by accelerating **reverse cholesterol transport**— thereby helping to prevent atherosclerosis.<sup>61,62</sup>

- Testosterone elevates the hepatic lipase enzyme that the liver needs to safely clear the body of excess cholesterol.
- The liver contains a receptor called scavenger receptor B1 that acts to stimulate cholesterol uptake for processing and disposal. Testosterone beneficially increases scavenger receptor B1.<sup>9</sup>
- Furthermore, a liver enzyme called hepatic lipase functions to remove phospholipids from the surface of HDL and helps enhance the uptake of these HDL-derived lipids by scavenger receptor B1.<sup>9,10,58</sup>
- Testosterone increases the activity of hepatic lipase.<sup>10</sup>
- By increasing both scavenger receptor B1 and hepatic lipase activities, testosterone facilitates an increase in reverse cholesterol transport, a process that removes excess cholesterol from the tissues and carries it to the liver for processing and disposal.<sup>9,10</sup>
- The important take home point is the critical role of reverse cholesterol transport in enabling HDL to protect against atherosclerosis.

## Low Testosterone Sharply Increases Coronary Artery Disease Risk

The relationship between low testosterone and increased coronary artery disease incidence has been the featured topic of several covers of *Life Extension Magazine*® over the past two decades. One study evaluated men under age 45 who presented with coronary artery disease compared with an age matched control group. The findings revealed that even moderately reduced **free testosterone** blood levels (below **17.3pg/mL** of blood) in these younger men resulted in a **3.3-fold** greater risk of developing premature coronary artery disease compared with men who had values above **17.3 pg/mL**.<sup>70</sup>

To put this testosterone blood reading in perspective, aging men who don't use testosterone-boosting nutrients or drugs often have very low free testosterone blood levels (less than **10 pg/mL** of blood). These same men often have low HDL blood test readings in the danger zone (less than **40-50 mg/dL**). More recent studies confirm low blood levels of free testosterone **increase** cardiovascular mortality in men.<sup>71,72</sup> Is it any wonder that despite aggressive use of statin drugs and other advances in cardiac medicine, heart attack and stroke are still today's leading killers?

## 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 an interesting report, 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.<sup>73</sup> 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.<sup>73</sup>

A landmark study analyzed the relationship of natural hormones (free testosterone, DHEA, and insulin like growth factor-1 [IGF-1]) to death rates in men suffering from chronic heart failure.<sup>63</sup> The findings from this study are tabulated on the chart in this box. As one can see, more men die when any of these hormones are deficient. This same chart shows catastrophic mortality when two or more of these hormones are deficient.<sup>63</sup>

A large number of studies reveal that higher testosterone or dehydroepiandrosterone (DHEA) levels are associated with reduced heart disease risk.<sup>64-69</sup>

## Testosterone and Stroke Risk

One way to evaluate one's risk for a stroke is to undergo an ultrasound test 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, ultrasounds 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.”* 21

## Doctors Overlook Lethal Impact of Estrogen Imbalance

When **Life Extension®** started offering comprehensive **blood test** panels back in 1996, men did not understand why we were checking their **estrogen** levels. Back in those days, estrogen was considered a hormone of importance only to women. We tested estrogen based on published data indicating that when estrogen levels are unbalanced, the risk of degenerative disease in aging men skyrockets.<sup>38,47-52</sup> Of concern to us 16 years ago were reports showing that excess estrogen contributes to the development of **atherosclerosis**.<sup>74,75</sup> Human clinical studies conducted more than a decade later confirmed our suspicions. Men with even slightly elevated estrogen levels doubled their risk of **stroke** and had far higher incidences of **coronary artery disease**.<sup>43,76,77</sup> Our early observations also revealed that men presenting with **benign prostate enlargement** or **prostate cancer** had higher blood estrogen levels (and often low free testosterone blood levels).<sup>78-81</sup> Subsequent clinical studies help confirm our early observations.<sup>82-86</sup> Insufficient estrogen, on the other hand, predisposes men to **osteoporosis** and **bone fracture**.<sup>87,88</sup>

The fact that **99%** of men today have no idea what their blood **estrogen levels** are helps explain the epidemic of **age-related disease** that is bankrupting this nation's medical system. A study published in the **Journal of the American Medical Association** (JAMA) measured blood estradiol (a dominant estrogen) in **501** men with chronic heart failure. Compared to men in the balanced estrogen quintile, men in the lowest estradiol quintile were **217%** more likely to die during a 3-year follow-up, while men in the highest estradiol quintile were **133%** more likely to die.<sup>39</sup>

The men in the balanced quintile—with the fewest deaths—had serum **estradiol** levels between **21.80** and **30.11 pg/mL**. This is virtually the ideal range that **Life Extension** has long recommended male members strive for. The men in the highest quintile who suffered **133%** increased death rates had serum estradiol levels of **37.40 pg/mL** or above. The lowest estradiol group that suffered a **217%** increased death rate had serum estradiol levels under **12.90pg/mL**.

The dramatic increase in mortality in men with unbalanced estrogen (i.e., estradiol levels either too high or too low) is nothing short of astounding. It uncovers a gaping hole in conventional cardiology practice that is easily correctable and explains why clinical trials on aging men that fail to measure estradiol have serious shortcomings. This study revealing the lethal dangers of estrogen imbalance was published in conventional medicine's Bastille of knowledge—the **Journal of the American Medical Association**, yet doctors continue to design clinical trials on aging men that measure total and/or free testosterone levels, but fail to account for estradiol, which can sharply **increase** when large doses of testosterone are administered.

## Low Testosterone Increases Prostate Cancer Risk

Fear of prostate cancer is the leading reason why aging men have shied away from restoring their free testosterone to youthful ranges. To dispel this concern, **Life Extension** long ago analyzed every published study and found there is no basis for asserting that testosterone causes prostate cancer.<sup>89-94</sup>

Our observations from the thousands of blood tests we perform each year for members confirm this. What we found is that men with low testosterone appear to be more likely to contract prostate cancer. In the landmark book, **Testosterone for Life** (McGraw-Hill, 2008), Harvard professor Abraham Morgentaler thoroughly discredited the notion that testosterone causes prostate cancer.<sup>95</sup> What came as a bombshell to the medical establishment was the compilation by Dr. Morgentaler of scientific facts showing that men with low testosterone levels have an increased percentage of prostate cancer-positive biopsies.<sup>96,97</sup> To further help dispel the myth that higher testosterone levels increase PSA levels (and presumably prostate cancer risk), the two charts (on the next page) compiled from our blood test analysis clearly show that as free testosterone levels decline in aging men, their PSA levels sharply increase.

## What are Optimal Free Testosterone Levels?

The number of men who suffer testosterone deficiency is so high that laboratory reference ranges accept ridiculously low levels as “normal.” We at **Life Extension** suggest that men maintain their free testosterone in the range of **20** to **25 pg/mL** of blood.<sup>98</sup> Others with expertise in this area believe free testosterone as low as **15 pg/mL** is adequate.<sup>70</sup> Conventional blood labs, on the other hand, say aging men are alright with as little as **6.6 pg/mL** of free testosterone in their blood—an absurdly low level!

Mainstream medicine's ignorance regarding the need to maintain free testosterone in the higher ranges is a significant cause of premature disability and death in aging men. When Life Extension conducted a study of its members free testosterone blood levels two years ago, a startling **86%** of the men had less than **15 pg/mL of free testosterone**, placing them at high risk for virtually every age-related disease. Free testosterone is the biologically active form of this hormone measured in the blood. When looking at **total testosterone** blood levels, one should strive for a moderately youthful range of **700-900 ng/dL**, though conventional reference ranges state that levels as low as **193 ng/dL** are sufficient, a range that we at Life Extension believe is woefully inadequate.

## Low Estradiol and Testosterone Predict Mortality in Aging Men

Sales of testosterone replacement drugs have surged more than 20-fold in response to studies linking low testosterone to a host of common maladies. In a study of **3,014** men aged 69-80 years, serum levels of testosterone and estradiol were measured during a mean follow-up of 4.5 years. Men with low testosterone had **65%** greater all cause mortality, while men with low estradiol suffered **54%** more deaths.<sup>40</sup> Those men low in estradiol and testosterone were almost twice as likely to die (a **96%** increase in mortality) compared to men in the optimal ranges.<sup>40</sup> This large study of aged men corroborates prior published reports linking **imbalances** of testosterone and/or estradiol with greater incidences of degenerative disease and death.<sup>6,7,13-18</sup>

## How Aging Men Can Control Their Estrogen Levels

An epidemic problem we at **Life Extension** observe in aging male members is insufficient free testosterone, i.e., less than **15-20 pg/mL** of serum. When accompanied by excess estradiol (over **30 pg/mL** of serum), this can signal excess aromatase enzyme activity. Excess aromatase robs men of their testosterone while exposing them to higher than desirable estradiol.<sup>99</sup> Aromatase can be suppressed with absorbable forms of chrysin (a plant flavonoid) and/or lignans such as those extracted from the Norway spruce tree (HMRlignan™).<sup>100-104</sup> If these nutrients fail to reduce estradiol adequately, then we suggest that men ask their doctor to prescribe a low-cost generic aromatase-inhibiting drug like **anastrozole** in doses as low as **0.5 mg** twice a week. When aromatase is properly suppressed, estradiol levels are reduced to safe ranges, while free testosterone often increases, since less testosterone is being aromatized into estradiol.

## Testosterone Decline and Aging

**Aging** is accompanied by reduced levels of **hormones** required to sustain life. As **testosterone** levels **decline** in **men**, their risk of dying markedly **increases**.<sup>105-107</sup> **Heart disease**,<sup>7,19,63,73,108</sup> **osteoporosis**,<sup>109-111</sup> and **muscle wasting**<sup>112-114</sup> are strongly linked to **testosterone** deficiency, as are **chronic inflammatory** <sup>13,115</sup> and **neurodegenerative** disorders.<sup>18,116</sup> Most doctors are surprised to learn that men with low testosterone show an increased incidence of **prostate cancer**.<sup>117-121</sup> Long before life prematurely ends, testosterone deficit can manifest in the form of psychological disturbances such as depression,<sup>122-125</sup> reduced **sexual** desire,<sup>126-129</sup> and a loss of **sense of well-being**.<sup>125,130</sup> The encouraging news is that restoring testosterone to youthful ranges can easily be accomplished at minimal cost.

As this article was being finalized, the findings from a brand new study were released that measured **free testosterone** and **25-hydroxyvitamin D** blood levels in a large group (2,069) men who were referred for coronary angiography.<sup>131</sup> The results were nothing short of **startling** for those who fail to maintain optimal blood ranges of **vitamin D** and **testosterone**. The researchers conducting this study carefully adjusted for confounding factors like age, body-mass index, active smoking, physical activity, diabetes, C-reactive protein, prevalent coronary artery disease, serum calcium, and parathyroid hormone.

After study researchers corrected for these confounding factors, they found that in comparison with people having higher levels of 25-hydroxy- vitamin D and free testosterone in the body:

☐ Deficiencies of either **free testosterone** or **25-hydroxyvitamin D** resulted in a **40% increased risk** for **all-cause mortality** (p=0.002);

☐ Deficiencies of **free testosterone** and **25-hydroxyvitamin D** resulted in a **111% increased risk** for **all-cause mortality** (p<0.001).

☐ Deficiencies of **free testosterone** and **25-hydroxyvitamin D** resulted in a **77% increased risk** for **cardiovascular mortality** (p<0.001);

☐ Deficiencies of either **free testosterone** or **25-hydroxyvitamin D** resulted in a **60% increased risk** for **non-cardiovascular mortality** (p=0.011);

☐ Deficiencies of **free testosterone** and **25-hydroxyvitamin D** resulted in a **133% increased risk** for **non-cardiovascular mortality** (p<0.001).

These sharp increases in mortality in response to deficiencies of **testosterone** and/or **vitamin D** reveal how far behind mainstream cardiologists are in treating patients with coronary artery disease. This study makes it abundantly clear that aging

men should strive to achieve optimal **blood levels** of **vitamin D** and **free testosterone**, something that many Life Extension male members have been doing for the past three decades.

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