

# Are Higher Testosterone Levels Associated with Greater Heart Risk?

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Potential benefits of testosterone replacement for men with low levels and symptoms include a reduction in frailty and associated risks for falls and fractures; improved cognitive function and mood; increased libido; and a greater sense of well-being. New research aims to better gauge benefits and risks.

Testosterone in men has become a hot health topic. New studies, including one by UCSF researchers, now are sparking a controversy over the role of testosterone in heart disease.

If naturally high or low <u>testosterone</u> levels prove to be significantly associated with <u>heart disease</u> risk, it might then make sense to weigh testosterone levels along with other risk factors in making decisions about screening and preventive strategies. But even basic facts about



how much testosterone is normal or healthy are not quite nailed down, and what's normal and healthy may vary among individuals.

Testosterone levels in men generally decline slowly from middle age onward. In cases where testosterone is thought to be too low, US physicians may prescribe injections, gels or patches.

Already physicians write more than one million prescriptions for testosterone each year. With <u>baby boomers</u> becoming elderly this number is likely to trend upward.

The indication for treatment approved by the US <u>Food and Drug</u> <u>Administration</u> is a condition known as hypogonadism - low testosterone accompanied by at least two other symptoms, such as low libido, fatigue, depression, bone thinning, erectile dysfunction, or dwindling muscle strength.

While these symptoms are not uncommon among <u>older men</u>, in the past they were more often accepted as part of normal aging.

## Heart Benefits, Risks of Testosterone Are Now Unclear

Several studies in recent years have reported that older men with naturally higher testosterone levels tend to have less heart disease. But two new research findings make it clear that the nature of the hearthormone connection remains an open question.

In June at the annual meeting of the Endocrine Society in San Diego, UCSF resident Kristen Sueoka, MD, discussed research on nearly 700 men aged 65 and older. Those whose testosterone levels placed them among the top 25 percent of study participants were 2.2 times as likely



to experience a heart attack or other event related to heart disease over four years compared to men whose testosterone levels were in the bottom 25 percent.

Sueoka has been working with her faculty mentor, UCSF internist Douglas Bauer, MD, on research associated with the multi-center Osteoporotic Fractures in Men Study. The research team measured testosterone levels and heart disease risk factors once at the start of the study. They continued to survey each man periodically and monitored hospital records for heart attacks, coronary artery surgery and heart failure due to blocked arteries. A cardiologist reviewed electrocardiograms, lab findings and physician notes to confirm whether or not participants had in fact had experienced a medical event due to heart disease.

The findings contrast with the results of similar prospective studies conducted earlier, including some that were larger. A handful of these studies found that heart disease mortality was associated with low levels of testosterone, not high levels.

Sueoka noted that in these other studies, outcomes were not monitored as closely. In some cases low testosterone levels in those studies might have been a result of a chronic disease process, she says. "We looked at heart disease itself, not simply at reported causes of death."

Testosterone can dilate blood vessels, which may help keep blood flowing. On the other hand it can increase the number of blood platelet cells, causing blood to clot more easily and increasing stroke risk. Similarly, testosterone affects fat metabolism, the immune system and other endocrine systems in ways that might significantly increase or decrease a man's risk for heart disease - no one knows for certain.

Sueoka acknowledges that the findings are controversial and that they



must be regarded as preliminary, as they are not yet published in a peerreviewed scientific journal.

In Sueoka's study, total testosterone levels in the men in the top quartile were at least 495 nanograms per deciliter (ng/dL). Testosterone levels in men in the bottom quartile were no more than 308 ng/dL.

Treatment guidelines differ somewhat on the cutoff for low testosterone. A total testosterone level below 200 ng/dL is considered a clear indicator. In men whose blood levels are between that cutoff and 300 ng/dL, physicians may order additional tests to measure "free" testosterone, the fraction that is actually available to act hormonally.

Controversial though they may be, Sueoka's results now have company. A different study - this one a clinical trial on testosterone treatment via a topical gel - was halted due to an unexpected increase in heart attacks among the treatment group. Frail men age 65 and older whose natural testosterone levels were less than 350 ng/dL were treated with a skin gel to bring levels up to between 500ng/dL and 1,000 ng/dL.

Many of the 209 men in the study had known heart disease risks, including hypertension, high blood lipids, obesity and diabetes. According to a July research report, <u>muscle strength</u> increased among treated men, but the study was stopped early after 10 men in the treatment group versus just one man in the control group suffered a cardiac event. Some researchers have pointed out that even larger studies have found no such association, and have suggested that the study results are an anomaly, due to chance.

The National Institutes of Health (NIH) is sponsoring an ongoing, multicenter trial of testosterone replacement of 800 men. The study started last year and is still enrolling men.



At least when it comes to natural testosterone levels, the results of studies to date might not be incompatible, Sueoka says. She speculates that there might be a happy medium for testosterone levels. Biological mechanisms that come into play when levels are low may differ from those that become important when levels are high.

"There may in fact be some kind of sweet spot, where if you have too much it's bad, or it's too little is bad," she says.

### **Testosterone Replacement**

Physicians have offered testosterone replacement since the 1940s. However, there have been relatively few scientific studies in subsequent decades, and they have tended to be small.

A 2003 report from the Institute of Medicine - based on a review of 31 modern, high-quality clinical trials - concluded that possible benefits of testosterone replacement - including better sexual function; reductions in frailty, falls, fractures and disability; improved cognitive performance; and improvements in vitality, well-being and quality of life - merited more study.

Many leading urologists say that insisting on clear evidence from future, placebo-controlled, double-blinded clinical trials in older men discounts what they are confident they have already learned from less-than-perfectly controlled studies and from their own practices - for many men, benefits are real.

UCSF urologist James Smith has no doubt that testosterone prescribed for hypogonadism can greatly benefit many, but not all men with the condition. He is careful to watch for significant side effects.

"One common side effect is that testosterone can stimulate the kidney to



make erythropoietin," he notes. Erythropoietin is a protein that spurs the proliferation of oxygen-carrying red blood cells and of platelets - a component of blood that plays an important role in forming blood clots.

In addition, Smith says, "Testosterone treatment can worsen sleep apnea," a temporary cessation of breathing, that afflicts many men, especially obese men. "It can worsen benign prostatic hyperplasia - an enlarged prostate. It can even cause hot flashes and irritability, especially when injected." Skin patches and gels can also cause rashes, Smith says.

A testosterone pill has been approved for the treatment of hypogonadism in Europe but has not been approved by the FDA. There are concerns that it may be toxic to the liver.

Smith doesn't dismiss Sueoka's study results, and notes the close monitoring of participants as a strength of the study, but the study appears to be an outlier, compared to other studies in the literature, he says.

#### **Estrogen Studies in Women Are a Precedent**

If an accumulation of research results were to eventually overturn earlier evidence for an inverse association between <u>testosterone levels</u> and heart health, it would not be unprecedented. A similar sea change resulted from ongoing studies of estrogen replacement in women.

Early studies of estrogen pointed to biological mechanisms promoting heart health. As clinical trials began and grew larger, conflicting results emerged. UCSF epidemiologists Deborah Grady, MD, MPH, and Stephen Hulley, MD, MPH, were among the first to conduct a large clinical trial, called HERS, with results that seriously challenged the idea that hormone therapy provides heart benefits for postmenopausal women.



As a result of one of the largest studies ever - the Women's Health Initiative - hormone replacement therapy that combines estrogen and progestin now is known to increase a woman's risk for <u>heart attack</u>. This combination therapy was adopted decades ago after treatment with estrogen alone was shown to increase a woman's risk for uterine cancer.

Compared to the new, 800-man NIH study, the Women's Health Initiative prospective clinical trial conducted to gauge health risks of treatment combining estrogen and progestin was huge - 16,608 women participated.

"We just need more studies, with more people," Sueoka says. Testosterone's effects on heart disease risk might take many years or decades to have a measurable impact. "It would be worthwhile to look at younger men, if you're going to look for a causal association, she says.

#### More information:

-- NIH-Supported Trial to Study Testosterone Therapy in Older Men, National Institute on Aging, November 2, 2009.
<u>www.nia.nih.gov/NewsAndEvents/ ... 102-Testosterone.htm</u>
-- Testosterone Deficiency and Replacement in Older Men, New England Journal of Medicine, July 8, 2010.
<u>www.nejm.org/doi/full/10.1056/NEJMe1006197</u>
-- Estrogen Plus Progestin and the Risk for Coronary Heart Disease, New England Journal of Medicine, August 7, 2003.
<u>www.nejm.org/doi/full/10.1056/NEJMoa030808</u>

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