Low Testosterone Associated With High Mortality in Men With CHD

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October 22, 2010 (Sheffield, United Kingdom)— Among men who have coronary heart disease, mortality was doubled in those with low testosterone levels compared with those who had normal levels, a new observational study has shown. **Dr Chris J Malkin** (Royal Hallamshire Hospital, Sheffield, UK) and colleagues report their findings in *Heart*.

"This is the fourth epidemiologic study to have shown that low testosterone is a marker of early mortality," senior author **Dr Kevin S Channer** (Royal Hallamshire Hospital, Sheffield, UK) told **heart*wire*** . "But most crucially, it is the first in men with vascular disease; all of the other epidemiologic follow-up studies of testosterone have excluded this patient population."

In an accompanying editorial, **Drs Ronald CW Ma** and **Peter CY Tong** (Prince of Wales Hospital, Shatin, Hong Kong) describe the history of studies on testosterone and cardiovascular disease and say the new trial "adds to the emerging picture" by making it clear that the link between reduced testosterone and increased mortality extends to subjects with established cardiovascular disease.

Channer says a long-term (5 to 10 years) prospective randomized placebo-controlled trial of testosterone replacement therapy is now needed in patients with heart disease, to assess its effects on mortality: "If you replace the testosterone, can you push that Kaplan-Meier survival curve back to the normal line?"

The editorialists agree. While Ma and Tong say there are some risks from testosterone--it might increase the risk of prostatic diseases and erythrocytosis, and exacerbate sleep apnea--overall, "The encouraging results from clinical studies so far support investigating the effects of testosterone supplementation on cardiovascular disease in larger clinical trials."

20% of Men Were Testosterone-Deficient

To examine the effect of testosterone levels on survival, Malkin et al followed 930 consecutive men with coronary disease referred for angiography for a two-year period from June 2000, with a mean follow-up of almost seven years. The main variables were all-cause and vascular mortality and the presence of testosterone deficiency.

The overall prevalence of biochemical testosterone deficiency was 20.9% using a measure of bioavailable testosterone <2.6 nmol/L; 16.9% using total testosterone <8.1 nmol/L; and using either measure it was 24%.

Adjusted all-cause and vascular mortality was more than doubled among those with low bioavailable testosterone (hazard ratio [HR] 2.2. $p<0.0001$ for all-cause mortality; HR 2.2, $p=0.007$ for vascular mortality) compared with those who had normal levels of the hormone.

Low serum testosterone was one of only four variables found to influence time to all-cause and vascular mortality in multivariate analyses (HR 2.27), along with the presence of left ventricular dysfunction (HR 3.85), aspirin therapy (HR 0.63), and beta-blocker therapy (HR 0.45).

"In patients with coronary disease, testosterone deficiency is common and impacts negatively on survival. Prospective trials of testosterone replacement are needed to assess the effect of treatment on survival," the authors conclude.

Testosterone Not Like Female HRT, No Money for a Big Trial

Channer explains that testosterone replacement therapy can be given in a number of ways. Testosterone is not suitable for oral therapy, because "It undergoes high first-pass metabolism through the liver," he explains. But it is available in slow-release injection formulations, as a three-month depot injection, as transdermal patches, and as a gel. He says his team has had some problems with the skin patch because it causes a rash and men tend not to like it, but they have had more success with the three-month depot injections, which they have been able to keep people on for a year. However, "We desperately need some other formulations," he says.

He is keen to stress that testosterone is a whole different ballgame from female hormone replacement therapy: "Men are given testosterone, the same hormone as they make themselves, and we monitor levels and titrate to physiologic levels. This is not like female hormones, where women were given doses of a drug and the physicians didn't know whether they were physiological, super-physiological, or what; it's totally different."

But he does not hold his breath when it comes to a big trial. He and his colleagues have had every request for funding for such a large study turned down, he says, adding: "The problem is that none of the drug companies that make testosterone are big enough to fund such a study, because it would cost millions."

Concerns Dismissed: Testosterone "Like Thyroid Hormone"

Channer also doesn't understand what he sees as reticence from some quarters when testosterone as a potential therapy is discussed. "I've struggled to understand why endocrinologists don't just accept that replacing testosterone is the same as replacing thyroid hormone, for example, what's the matter with that?"

And he dismisses any concerns arising from a US **National Institutes of Health** study in elderly men, which was stopped early because testosterone treatment was associated with an increased risk of cardiovascular events; the paper was published in the *New England Journal of Medicine* earlier this year.

"We were very surprised that NEJM published that paper. The end points were very soft indeed," he comments. "Yes, there were a few more deaths, but these were elderly men and you wouldn't expect in the duration of that study for the testosterone to have had that kind of effect. We've been doing studies for 15 years with testosterone in men with known heart disease, angina, and heart failure, and we haven't had any [serious] adverse reactions."

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