



EDITORIAL

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Will Testosterone Replacement Therapy Kill Your Patient?

At first it seems to be a fairly straightforward proposition. The older gentleman you are seeing in the clinic reports that he has been running rather low on energy in recent weeks, and he also mentions that there's not much lead in his pencil these days. As a conscientious clinician, you immediately entertain the possibility that hypogonadism might explain some of his symptoms. You dutifully order up a total testosterone level, and then a free testosterone level when the total comes back low, recognizing that binding protein abnormalities might produce a low total even when the clinically relevant free level is still normal. Both levels do come back well below the age-adjusted lower limits of normal, which gives you some transient level of satisfaction that you have identified a very significant factor contributing to your patient's difficulties.

You have confirmed a deficiency of a major hormone, and it seems logical that you would want to restore the hormone level to normal in this particular patient. But before you reach for your prescription pad (or your mouse), a fundamental question hangs uneasily in the air. Are you going to be doing more harm than good by prescribing testosterone replacement therapy (TRT) to this rather trusting older fellow? In light of recent studies, might you actually increase this patient's chances of a heart attack or a stroke? That would not be a nice thing to do to this pleas-

ant older gentleman. (As a newly minted senior citizen, I pray mightily that my own caregivers adhere rigorously to Hippocrates' hoary admonition to, above all, do no harm.)

I'm not going to be able to resolve this clinical conundrum definitively in this editorial. (Please don't stop reading just yet!) But maybe a review of the pros and cons for testosterone replacement therapy can help you faithful readers gain just a little bit better sense of the operative risk/benefit considerations at play here.

Let's look first at the case for prescribing TRT when the laboratory test values show definitive evidence of low testosterone levels. I don't want to delve into the distracting issue of which form of testosterone replacement to consider, which pits injections vs gels vs patches vs pills (don't use the potentially hepatotoxic methyltestosterone pills passed out like candy by some urologists). Apart from the possibly relevant issue of peaks and troughs seen with injection therapy, the same risk/benefit considerations pretty much apply to all forms of TRT.

The benefits of TRT clearly include an increase in lean muscle mass, an increase in red blood cell concentration due to the hematopoietic effects of the male hormone, and a reduction in both the total amount and the percentage of body fat. A number of studies have shown that testosterone enhances insulin sensitivity—surely a good thing given the massive number of older patients with either pre-

diabetes or full-blown type 2 diabetes. Some men also report a significant increase in their hard-to-define-but-still important sense of manliness, and sometimes a major improvement in their ability to perform in the sack. The latter effects, though, are often very modest and of considerably less potency (sorry, pun intended) than seen with sildenafil or one of the other PDE-5 inhibitors. In spite of all these seemingly positive effects, the clear majority of men report that they really don't feel much different after starting on TRT, and many discontinue it on their own after relatively short periods, especially those enduring intramuscular injections every 2 weeks.

So the benefits derived from TRT are not really very impressive in many patients. What about the downside of giving testosterone? Surely there can't be any problems associated with simply replacing an important hormone that has fallen to low levels? After all, we don't hesitate to give thyroid hormone to hypothyroid patients, to give growth hormone to children with low levels of this critical hormone, or to give insulin to diabetic patients whose pancreases are not producing enough of that life-saving hormone.

For a very long time the risk/benefit arguments over whether or not to give TRT were almost entirely theoretical. Those in favor cited the several aforementioned benefits, and those in opposition decried replacement therapy as a perverse form of tinkering with nature by trying to

alter the natural decline in the levels of certain hormones that were part and parcel of the natural aging process.

Then along came 3 rather worrisome studies in fairly rapid-fire succession, which seemed collectively to deliver a true body blow to TRT. However, a closer examination of these studies reveals that each is so severely flawed that no meaningful conclusions can be derived from any of them.

The Testosterone in Older Men with Sarcopenia (TOM) trial was a randomized trial of TRT vs placebo in older men (mean age 74 years) with mobility limitations (sarcopenia, after all, means decreased muscle bulk) and a high prevalence of chronic disease.¹ The trial was stopped early because of a much higher occurrence of self-reported cardiovascular-related adverse events. However, these adverse events were extremely disparate and were all self-reported; none had been prespecified outcomes. Any objective observer would have to conclude that the study was poorly designed and that no meaningful conclusions can be drawn from its premature termination.

The second trial that seemed to cast doubt on the safety of TRT suffered from an even worse design. It was a retrospective cohort study of 8,709 veterans aged 60 to 64 years with low testosterone levels who were undergoing coronary artery angiography. The authors reported in the *Journal of the American Medical Association* that those receiving testosterone therapy had a higher risk of experiencing a composite outcome of all-cause mortality, myocardial infarction (MI), or cerebrovascular accident than did those who had not received testosterone therapy (hazard ratio [HR] = 1.29; 95% confidence inter-

val [CI]: 1.04-1.58).² Right off the bat, you should be very wary of any HR emanating from a retrospective study that shows a small increase in risk of 29%; it's only when a HR is 2.0 or more that it's likely you're looking at a real phenomenon. But to add insult to injury, the percentage of actual adverse outcomes was actually SMALLER in those taking testosterone than in those who did not get any! The authors had used such an incredibly tortured series of risk adjustments for a variety of comorbidities that they actually managed to stand the raw numbers on their head.

The third study, which had seemed at first blush to demonstrate cardiovascular toxicity of TRT, was a much larger retrospective cohort study of 55,793 men who had received replacement testosterone.³ The authors reported an increase in the relative risk of MI in the first 3 months after starting testosterone compared with the risk of MI in the same men in the prior year (relative risk [RR] = 1.36). However, the much more important absolute risk increase was very, very low, with only an additional 1.25 cases of MI seen over 1,000 patient-years. Apart from the fact that a RR of 1.36 is most unimpressive in a retrospective study, the simple fact that the men were older by a few months after TRT is probably more than adequate to explain this tiny increase in apparent risk.

The FDA has monitored these studies closely and has chosen not to make a determination that there is an increased risk of cardiovascular events associated with TRT. That is not at all the same as saying that it has been proven to be completely free of cardiovascular risk; rather it is a common-sense acknowledgment that there is not any

convincing evidence to date of such a risk.

Thus, the conscientious clinician is left to conclude that TRT is a reasonable option in symptomatic patients who have been shown to have low levels of free testosterone. It has not been conclusively demonstrated that TRT will have significant beneficial effects, but neither has it been proven to have any true cardiovascular toxicity. It is a therapy worth trying in those symptomatic patients who understand that they will be receiving therapy of uncertain benefit, if any, and with the possibility of uncertain risk, if any. ●

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