

## Treating Aging with Testosterone

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Although some off-label medication use is justified, the use of testosterone for nonspecific symptoms of aging is not. Using testosterone to treat older men with decreased energy, decreased strength, low libido, erectile dysfunction, mood disorders, sleep disorders, or poor memory is inappropriate because symptoms do not correlate with testosterone levels, testosterone supplementation is unimpressive in clinical trials, and inappropriate testosterone therapy is not safe.

Many nonspecific symptoms treated with testosterone are due to normal aging or pathologies for which there are more effective, safer therapies. For example, depression should be treated with antidepressants, not testosterone, and erectile dysfunction is appropriately treated with phosphodiesterase inhibitors. A systematic review of 40 studies found only weak correlations between low testosterone and any symptoms.<sup>1</sup> Symptoms associated with low testosterone are also associated with chronic disease, psychogenic factors, and substance use. Erectile dysfunction, for example, is associated with diabetes mellitus, vascular dysfunction, and neurologic impairment—all of which are common in older men.

Although there are more than 100 trials of testosterone therapy, there is little evidence that testosterone works for any symptoms. Evidence from randomized controlled trials<sup>2</sup> and a systematic review conducted by our team<sup>3</sup> found that testosterone does not benefit physical function, mood, cognition, or cardiovascular health. A recent set of testosterone studies that included men 65 years or older with a serum testosterone level less than 275 ng per mL (9.5 nmol per L) found that topical testosterone therapy over one

year improved bone density<sup>4</sup> and anemia<sup>5</sup> but had no effect on age-associated memory impairment.<sup>6</sup>

Evidence on sexual function is mixed. Out of 47 studies, 24 found no benefit of testosterone over placebo on any sexual function end point. Although 23 studies found a benefit on at least one end point, most end points were negative.<sup>3</sup> About one-half (16 out of 31) of erectile dysfunction studies found a benefit.<sup>3</sup>

Testosterone levels vary hourly, daily, weekly, and seasonally.<sup>7</sup> There is no reliable evidence that raising testosterone levels prevents or treats any disease. Although many persons with chronic diseases have low testosterone levels,<sup>8</sup> it is much more likely to be an effect rather than a cause of chronic disease. Our systematic review found no evidence of benefit for any clinical end points of cardiovascular disease. Although trials have occasionally found a benefit for a marker of cardiovascular disease, clinical end points are more important, and evidence must be considered as a whole.<sup>3</sup>

Adverse effects of testosterone therapy are a concern. Testosterone may increase prostate cancer rates, and it is also linked to thromboembolic events, especially in those with thrombophilia-hypofibrinolysis.<sup>9</sup> Testosterone probably increases cardiovascular risks, especially soon after treatment commences.<sup>10-12</sup> It bears noting that long-term observational studies showing no increased cardiovascular risk censored short-term events.<sup>13,14</sup> All prevalence studies will have this bias; it is vital to study new users prospectively, and in the case of testosterone therapy, long-term prospective trials would contribute to a more accurate understanding of all-cause adverse effects.

Studies of testosterone and cardiovascular risk have received attention recently. One trial found that in a subset of 170 men (mean age of 71.2 years; one-half with severe atherosclerosis), testosterone treatment significantly increased noncalcified plaque volume over a year compared with placebo, ►

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as measured by coronary computed tomographic angiography.<sup>15</sup> This is not a good sign, possibly indicating increased future cardiovascular risk.

On the other hand, a recent retrospective cohort study within an integrated health care delivery system found that men older than 40 years with androgen deficiency who were ever prescribed any form of testosterone had a reduced risk of cardiovascular events (a composite end point of acute myocardial infarction, coronary revascularization, unstable angina, stroke, transient ischemic attack, and sudden cardiac death) over a median follow-up of 3.4 years.<sup>16</sup> However, this was not a randomized trial, and benefit cannot be proven in observational studies. It may be that physicians prescribed testosterone to healthier men, or avoided prescribing testosterone in men with comorbidities. There is precedent for this with menopausal hormone therapy—dozens of observational studies seemed to show that hormones decreased cardiovascular risk, but the Women's Health Initiative, a definitive, long-term, federally-funded, randomized controlled trial, showed that hormone therapy actually increased cardiovascular risk.<sup>17</sup>

The labeling of normal older men as “hypogonadal” and in need of hormone treatment closely parallels the social construction of menopause as a disease in the latter part of the 20th century. Estrogen manufacturers paid physicians to convince their peers that all menopausal women were in a state of hormonal deficiency. The concept that all menopausal women should take estrogen lasted for decades and was harmful to many patients. Hormone prescriptions plummeted after the Women's Health Initiative found that risks outweighed benefits in 2002, and breast cancer rates subsequently dropped in every country with a breast cancer registry.<sup>18</sup>

True testosterone deficiency should be treated with testosterone. Klinefelter syndrome, pituitary or hypothalamic disease, hyperprolactinemia, or radiation exposure can cause incomplete sexual development, low-trauma fractures, infertility, and hot flashes. However, most patients on testosterone are being treated for normal symptoms of aging. Given that the diagnostics are questionable and the benefits are unconvincing, the risks of testosterone, some of which may be life-threatening, are not worth taking.

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Author disclosure: In 2015, Dr. Fugh-Berman was a paid consultant to attorneys in litigation involving testosterone therapy. In addition, she has periodically done expert witness work in litigation involving pharmaceutical marketing practices.

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