Testosterone and Sexual Function

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Abstract and Introduction

Abstract

Purpose of review: Testosterone therapy has been advocated in the treatment of symptoms that may represent normal aging. We briefly review randomized clinical trials on the effects of testosterone therapy on sexual function.

Recent findings: About half of clinical trials showed no benefit of testosterone therapy on any aspect of sexual function. In those studies showing a benefit on some aspect of sexual function, most sexual function domains were not improved. Testosterone therapy has been disappointing in the treatment of erectile dysfunction. Potential risks of therapy include an increase in thromboembolic and other cardiovascular diseases.

Summary: The limited and inconsistent benefits of testosterone therapy for sexual function argue against use of this therapy in aging men, including those with 'low testosterone'.

Introduction

The hope that testosterone treatment could combat symptoms of aging is rapidly fading. The reluctantly aging have always been a profitable market. In the 1920s, implanting testicle slices from animals or executed prisoners into scrotal sacs was briefly popular.[1] Of course, those grafts would not have survived, but the procedure thrived for a while, fueled by pictures of rejuvenated men. Testosterone patches, gels, and injections are the modern version of testicular implants, marketed as youth-restoring tonics. The market for testosterone took off after topical gel formulations became available. AndroGel (Abbvie, North Chicago, IL) sales exceeded $1.1 billion in 2012 but then fell after the food and drug administration revised the labeling and lawsuits over adverse effects emerged; in 2016, AndroGel sales were $675 million.[2] Testosterone lawsuits have been consolidated in multidistrict litigation, and the first cases were scheduled to go to court in summer 2017.

Hypogonadism or Normal Aging?

Documents from a whistleblower lawsuit against Solvay (which first developed AndroGel; the company was later bought by Abbott Park, IL) showed that Solvay planned to 'expand the testosterone market by 36.5 percentage, particularly by pushing the drug to primary care physicians'. The company wanted to '… help write a new paradigm. One that captures both the andropausal male, as well as the hypogonadal male'. Drug reps were told to ask physicians to determine how far a patient's testosterone levels were 'from the top of the normal range, rather than how close he is to the bottom of it'.[3]

Testosterone concentrations, however, change hour-to-hour, day-to-day, and seasonally and are affected by glucose ingestion, triglyceride concentrations, exercise, sexual activity, job status, and competition.[4] Even the expectation of competition matters: soccer fans had higher testosterone levels on the day of the World Cup than other days.[5] There is a wide range of normal testosterone concentrations at all ages, and we lack age-adjusted
or ethnicity-adjusted normal testosterone concentration ranges.\[6\] There is no agreement on what concentration of testosterone constitutes a 'low' level; the definition of low ranges from 200 to 350 ng/dl (6.9–12.2 nmol/l). Some men are treated for testosterone deficiency without the benefit of lab tests. Direct-to-consumer advertising (DTCA) fueled this trend; a 2017 study found that DTCA was associated with more testosterone testing, more new prescriptions, and more initiation of therapy without recent testing of testosterone concentrations.\[7\]

The symptoms purportedly associated with Low-T (decreased energy, increased body fat, and reduced sex drive) are nonspecific and include symptoms associated with normal aging. A systematic review of 40 studies found only weak associations between low testosterone and any symptoms.\[8\]

### Sex and Testosterone

Sexual function is one area in which most people believe testosterone helps. But does it? Testosterone has never been approved by a regulatory authority for erectile dysfunction, libido enhancement, or any other aspect of sexual function, so all such uses are off-label.

Testosterone concentrations do not correlate with sexual function; even eunuchs can have erections. Eunuchs live longer, too. Eunuchs in the Imperial Korean court lived, on average, to age 70 years, which was 14–19 years longer than concurrent intact males of similar socioeconomic backgrounds.\[9\]

Our systematic review of 156 randomized controlled trials of testosterone conducted between 1950 and 2016 included 47 studies that looked at sexual function in normal men, men identified by study authors as 'hypogonadal', and men with erectile dysfunction.\[10\] Men with various chronic diseases were included. Half of the studies found no benefit of testosterone over placebo on any sexual function endpoint. Although almost half of the remainder found a benefit on at least one endpoint, most sexual endpoints showed no improvement with testosterone therapy.\[10\]

We identified 31 studies that evaluated erectile function. Half of the studies found no improvement with testosterone therapy and half reported a benefit. One study was reported as positive for both testosterone and placebo compared with baseline; however, our analysis did not show a difference between treatment groups. In our analysis, among the 17 studies that had Jadad scores of 4 or 5, indicating good study quality, nine showed a beneficial effect of testosterone therapy and eight did not.

Of 12 studies that included men with erectile dysfunction, eight found no benefit of testosterone over placebo, and four found a benefit. One negative study found that testosterone reduced erectile function when compared with placebo; however, there was no change when each group was compared with its baseline.

Of 23 studies that specifically reported changes in libido, 13 found that testosterone treatment increased libido, eight found no effect, one found an effect after 3 but not 6 months of treatment, and one found that testosterone improved sexual desire only in men with initial testosterone 8.0 nmol/l or less. Most (10/13) but not all of the studies on libido or desire with a Jadad score of 4 or 5 found a benefit.

Since our systematic review, three additional studies on testosterone and sexual function were identified. One treated 199 diabetic men with severe or mild hypogonadism with 30 weeks of long-acting testosterone undecanoate or placebo. Men with mild hypogonadism experienced no effect on sexual endpoints. Men with severe hypogonadism had more sexual desire and intercourse satisfaction after 6, 18, and 30 weeks of treatment; erectile dysfunction showed no improvement at 6 or 18 weeks but improved at 30 weeks.\[11\]
A study of 88 men with testosterone less than 10.4 nmol/l and erectile dysfunction treated with intramuscular testosterone undecanoate for 12 months found that, compared with baseline, erectile function improved at 6 and 12 months. Nocturnal penile tumescence (including frequency and duration of rigidity) also improved.[12]

The sexual portion of the Testosterone Trials, a set of seven trials that tested testosterone treatment in men over 65 with testosterone concentrations less than 275 ng/dl, was reported in two journals, the same year, with consistent improvement (characterized as moderate) in sexual function but not in assessments of vitality or walking distance.[13,14]

**Adverse Effects**

Concern about adverse effects of treatment should be balanced against the inconsistent findings of testosterone benefits for what may be normal manifestations of aging. Testosterone has been linked to thromboembolic events, especially in those with thrombophilia-hypofibrinolysis.[15] The risk of venous thromboembolism appears to be highest in the first 6 months of use.[16] Testosterone probably increases cardiovascular risks, especially soon after treatment initiation.[17–19] A 2017 study found that testosterone gel administered to older men with low testosterone and symptoms for a year was associated with a greater increase in coronary artery plaque volume compared with placebo.[20] Adverse effects of supplemental testosterone on subclinical prostate cancer remain at least a theoretical concern, although empiric confirmation has been lacking.

**Comments**

Enthusiasm for testosterone therapy is reminiscent of the enthusiasm for estrogen in the treatment of aging women, in spite of estrogen therapy having been shown to be ineffective for many of the benefits once put forward by its advocates. As is the case for estrogen therapy, testosterone therapy defenders suggest reasons why the studies are mixed in their outcomes. Perhaps testosterone therapy does not increase serum or tissue concentrations adequately in all men, perhaps not all men convert testosterone as effectively to 17β-estradiol, perhaps testosterone therapy is effective primarily in subgroups of men with particular characteristics. We cannot exclude these possibilities, but suggest that absent consistent evidence of testosterone effectiveness in defined populations, androgen therapy be withheld in favor of clearly effective treatments of erectile dysfunction and clearly beneficial approaches to aging including weight control, exercise, and avoidance of tobacco and excessive ethanol.

**Sidebar**

*Key Points*

- Testosterone concentrations are not associated with sexual function.
- Testosterone may increase libido, but there are not consistent effects on erectile dysfunction and other measures of sexual function.
- For erectile dysfunction, effective drugs such as phosphodiesterase Type 5 inhibitors are preferred over testosterone.
- Testosterone has adverse effects and can cause thromboembolic events and cardiovascular events.
- Testosterone should not be used to treat sexual dysfunction or aging-related symptoms.
References

* A systematic review of 40 studies found wide variation in estimated prevalence, from 2 to 77%. There were only weak correlations between signs, symptoms, and testosterone levels.
* In a UK study of 19 215 patients with confirmed venous thromboembolism, the risk of venous thromboembolism was 1.25 [95% confidence interval (CI) 0.94–1.66] for current users of testosterone compared with nonusers. The risk was highest in the first 6 months of testosterone treatment: the rate ratio of venous thromboembolism was 1.63 (95% CI 1.12–2.37). There was no significant increase in risk after more than 6 months' treatment.
   *A randomized controlled trial in 170 older men with symptomatic hypogonadism enrolled in the Testosterone Trials found that testosterone gel for 1 year was associated with a significantly greater increase in coronary artery noncalcified plaque volume.

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