Dealing with the "T" (testosterone)

Over the past few years, TV viewers have been inundated with commercials and infomercials extolling the value of testosterone supplementation for men with "low T" and various symptoms. So there is no surprise that during clinic visits questions arise regarding the need for testosterone level testing or concerns with empiric supplementation.

Testosterone levels (free and total) decrease in many men, seemingly as part of the normal aging process, but more markedly in men taking certain medications and in men with obesity, sleep disturbances, and several chronic diseases. Low testosterone levels have been variably associated with erectile dysfunction, fatigue, sarcopenia, depression, low libido, anemia, decreased bone density, and a host of other symptoms. Association of course is not equivalent to causation. The implication of that statement is that testosterone supplementation will not necessarily ameliorate all these conditions.

Shumaker et al[1] in this issue of the *Journal* concisely review the urologic perspective on the appropriate diagnosis of testosterone deficiency and potential therapeutic value of testosterone supplementation. They emphasize from the outset that the diagnosis of testosterone deficiency demands the presence of both clinical signs and appropriate laboratory evidence of low testosterone. Intrinsic to that statement is a challenge that presents itself in the primary care physician's and subspecialist's office: when to attribute nonspecific symptoms to low testosterone vs normal aging or comorbid medical conditions. This can be difficult even in the setting of low total testosterone (< 300 ng/dL per the American Urological Association).

An interesting question to me is whether there is a physiologic need for testosterone levels to decrease with male aging. If there is, supplementation with exogenous testosterone to attain the "normal" levels of a young male would not necessarily exert a major beneficial effect and might even be counter to other physiologic functions. To date, however, major adverse effects of testosterone supplementation in aging men with low or, in some short-term studies, normal levels have not been observed, the caveat being that large long-term studies do not exist. The recent TRAVERSE (Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men) study[2] designed to address part of this question found no significant increase in major cardiovascular adverse events resulting from testosterone supplementation in middle-aged and older men with increased cardiovascular risk, low testosterone (< 300 ng/dL), and at least 1 symptom of hypogonadism. They did observe an increased occurrence of arrhythmias, including atrial fibrillation and thromboembolic events. The modestly low rate of volunteer adherence to the full protocol and a lower than anticipated rise in serum testosterone in the treated group are of note. Nonetheless, this and other randomized studies (reviewed by Diem et al[3]) provide some comfort that there is not likely a major risk of serious adverse effects in reasonably dosed, selected patients with hypogonadism at baseline.

The pragmatic clinical questions remain as to how much benefit is provided by testosterone supplementation, and for which symptoms. As noted by Shumaker et al,[1] there are some

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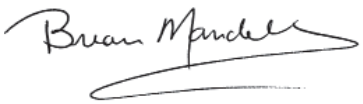
evidence-based benefits of testosterone supplementation, and it is reasonable to offer this treatment to select symptomatic men with documented hypogonadism and sexual dysfunction. Importantly, they discuss how hypogonadism must be appropriately confirmed. Despite admonitions in the literature to document hypogonadism prior to offering testosterone supplementation, this is not always adhered to in the real world. An ongoing challenge is to mesh patients' expectations of success, which have been ginned up by multiple TV advertisements and online tributes to various "T supplements," with randomized trial data. In 2020 the American College of Physicians[4] published a grounded clinical guideline, informed by randomized trial data,[3] addressing testosterone treatment of men with age-related hypogonadism.

The recommendations and conclusions from the evidence expressed in that guideline are few and succinct. The authors concluded that there is evidence for a modest effect size improvement in components of sexual dysfunction with testosterone supplementation (with "low-certainty evidence"), and that the perceived benefit should be reevaluated in patient discussions within a year of treatment initiation. Perhaps what should have greater impact on real-world practice (and patient expectations) is their recommendation[4] that clinicians "*not* initiate testosterone treatment in men with age-related low testosterone to improve energy, vitality, physical function, or cognition (… low-certainty evidence) [emphasis added]."

But randomized trials can sometimes offer surprises; even well-designed trials may not always reflect the complete "truth." Testosterone has previously been shown to increase bone density in men with hypogonadism,[5] and in practice, low testosterone is a sought cause of decreased bone density in men with unexplained osteoporosis. So it was an unexpected observation in a subtrial analysis[6] looking at fractures in participants of the TRAVERSE study[2] that the men with hypogonadism receiving testosterone supplementation actually had a numerically higher incidence of fractures than those receiving placebo. The fracture rate was low, the study may not have been long enough, the post-treatment testosterone level may not have reached the desired level, and bone densities in the participants before and after entry were not reported. The results were surprising nonetheless. This is consistent with other observations suggesting that testosterone may have many effects, but they may be modest enough to require large-scale, protracted clinical trials that include only participants with truly low testosterone levels to unequivocally demonstrate clinical effects.

Randomized testosterone clinical trials have demonstrated some benefits and other mixed results. In the real world, if a patient feels better taking testosterone supplementation, is it the "T" or is it a placebo effect? *If* supplementation is truly safe, does it matter? So the question of whether it has been demonstrated with certainty that long-term testosterone supplementation for the patient with age-associated hypogonadism (without complicating comorbidities) is benign remains relevant.



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1. **Shumaker AD, Leelani N, Roth B, et al.** Does my patient have testosterone deficiency? Clev Clin J Med 2024; 91(2):93–95. doi:10.3949/ccjm.91a.23064
2. **Lincoff AM, Bhasin S, Flevaris P, et al.** Cardiovascular safety of testosterone-replacement therapy. N Eng J Med 2023; 389(2):107–117. doi:10.1056/NEJMoa2215025
3. **Diem SJ, Greer NL, MacDonald R, et al.** Efficacy and safety of testosterone treatment in men: an evidence report for a clinical practice guideline by the American College of Physicians. Ann Intern Med 2020; 172(2):105–118. doi:10.7326/M19-0830
4. **Quaseem A, Horwitch CA, Vijan S, et al.** Testosterone treatment in adult men with age-related low testosterone: a clinical guideline from the American College of Physicians. Ann Intern Med 2020; 172(2):126–133. doi:10.7326/M19-0882
5. **Snyder PJ, Kopperdahl DL, Stephens-Shields AJ, et al.** Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone: a controlled clinical trial. JAMA Intern Med 2017: 177(4):471–479. doi:10.1001/jamainternmed.2016.9539 Erratum in: JAMA Intern Med 2017; 177(4):600. Erratum in: JAMA Intern Med 2019; 179(3):457.
6. **Snyder PJ, Bauer DC, Ellenberg SS, et al.** Testosterone treatment and fractures in men with hypogonadism. N Eng J Med 2024; 390(3):203–211. doi:10.1056/NEJMoa2308836