Controversies and Advances With Testosterone Therapy: A 40-Year Perspective

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Testosterone therapy (TTh) has become highly controversial. There are important health consequences of testosterone deficiency, and meaningful benefits with treatment. There is level 1 evidence that TTh improves sexual function and desire, body composition, and bone density. Concerns regarding cardiovascular risk were based on two deeply flawed retrospective studies and are contradicted by dozens of studies showing cardiovascular benefits of TTh or higher endogenous testosterone, including placebo-controlled studies in men with known heart disease (angina, heart failure). Prostate cancer should no longer be considered a risk of TTh. Testosterone is neither scourge nor panacea—it is just good medicine. UROLOGY 89: 27–32, 2016. © 2016 Elsevier Inc.

"We must seek the truth like a lost child seeks its mother"
Old rabbinical saying

After nearly 40 years working with testosterone (T)—first, as a basic science researcher and, for the last 27 years, as a clinician and investigator—I have been a witness to a considerable number of advances and controversies in the diagnosis and management of testosterone deficiency (TD), also known as hypogonadism. I have been honored to be able to contribute to the field, particularly in the understanding of the biological relationship of androgens to prostate cancer (PCa). As physicians and the public have come to increasingly recognize the benefits of testosterone therapy (TTh), there has also developed a powerful backlash against the use of TTh. Today, the topic of TTh generates as much passion as any other topic in medicine.

Unfortunately, passion makes dispassionate analysis impossible. Today, there is a dominant narrative that the benefits of TTh are unproven, the risks are substantial, and TTh is abused and overused because of physicians yielding to unwarranted demand by misguided patients who are unwilling to accept normal aging. Although there is no evidence to support this position, and considerable evidence to the contrary, this narrative has trumped the facts within the public media. The impact of this vilification of TTh has been substantial, discouraging symptomatic patients from accepting a potentially beneficial treatment, and generating suspicion of physicians offering TTh by their colleagues, for questionable medical practices. This is unfair to patients and physicians alike.

Once a narrative is established, it influences how we view new information.[1] For example, it has been reported that rates of absent T testing prior to receiving a T prescription are approximately 25%.[2] This high rate of absent testing has been interpreted to indicate that there is widespread prescription of TTh that is inappropriate. However, the same methodology also revealed absent testing prior to TTh prescription by nearly 20% of endocrinologists, based on computerized data without a single medical chart being examined.[3] It is not credible that this high value is accurate because endocrinologists are trained to evaluate patients based on serum hormone levels, and testosterone blood tests are easily available throughout the US, yet we willingly accept the unlikely conclusion of inappropriate T prescribing because we have been predisposed to believe it is true. We must recognize our own biases in order to objectively assess evidence. Below, I present information regarding several of the key topics in TTh today.

TERMINOLOGY

TD is now increasingly preferred over the older term, hypogonadism, to describe the clinical syndrome in which low levels of testosterone lead to clinical signs and symptoms. Hypogonadism technically refers also to the impaired testicular production of sperm, which is not of immediate relevance to most men with low testosterone levels. For this reason, TD is considered simpler and more accurate than hypogonadism and is the terminology used in this review. TTh is preferred over testosterone replacement therapy for similar reasons, as testosterone is not "replaced" in men, unlike hormone replacement therapy in women.

Financial Disclosure: *Abraham Morgentaler, M.D., has received payments for consulting, scientific advisory boards, research grants, or lecture honoraria from AbbVie, Bayer, Clarus, Endo, Eli Lilly, and Pfizer.*

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Submitted: October 18, 2015, accepted (with revisions): November 30, 2015

HISTORY

Testosterone was first synthesized in the mid-1930s, and underwent a brief golden period, being described in *New England Journal of Medicine* in several papers in the late 1930s and early 1940s as a potent treatment for impotence, lassitude, muscle strength, restoration of secondary sexual characteristics, and mood among hypogonadal men, and also as a successful treatment for angina.[4,5] However, concerns that testosterone "activated" prostate cancer soon trumped this early enthusiasm.[6] By the time that I began my urological practice in 1988, the use of TTh was rare and restricted to the most severe cases, such as men with pituitary tumors or anorchia.

I was curious about the role of T based on research I had performed in the American chameleon, *Anolis carolinensis*, beginning in the mid-1970s.[7] Those experiments demonstrated that T had important activity in the brain that was sufficient to restore sexual behavior in the castrated male. I therefore began routinely obtaining testosterone levels in my patients with sexual or reproductive issues, and was surprised at the high prevalence of low T levels in these men. I was even more surprised when a large majority of these men responded well to T injections, not only with improved or resolved sexual complaints but also with reports of improved energy, decreased fatigue, and improved mood and sense of well-being. TTh became a standard part of my treatment for T-deficient men with sexual dysfunction in the early 1990s, at a time when research was focused nearly entirely on vascular etiologies and treatments for erectile dysfunction (ED).

The approval of the first topical gel, AndroGel, in 2000, exposed a much broader physician population to the potential benefits of TTh. This coincided with public interest in quality of life and a wish to minimize symptoms that had previously been considered inevitable consequences of aging. Today, there are 21 approved T formulations in the US. As use has gone up, so has the level of scrutiny and the number of critical media stories. Many of these have been anchored by reports of increased cardiovascular (CV) risk that were published approximately 2 years ago.[8,9]

BENEFITS OF TTh

The frequently stated assertion that the benefits of TTh are unproven is simply false. There is level 1 evidence that TTh improves erection quality, libido, sexual frequency; increased lean mass and bone density; improves lipid parameters; causes reduced fat mass; and improves glycemic control.[10,11]

The sexual benefits of TTh are of particular importance because the chief presenting complaint that drives men with TD to see medical attention is sexual dysfunction. In a meta-analysis of randomized control trials (RCTs), TTh was shown to significantly improve libido in men with TT <8 nm/L (approximately 240 ng/dl) and TT <12 nm/L (approximately 350 ng/dl). Improvement in erection was also noted for these men with baseline T values below these same thresholds.[11] Importantly, eugonadal men did not demonstrate increased libido or erectile function. Significant improvements in frequency of sexual activity and orgasm were also noted.

There are mixed results for the use of TTh in addition to phosphodiesterase type 5 (PDE5) inhibitors for the treatment of ED. Improvement in erection was noted in uncontrolled studies but not in placebo-controlled studies.[11] This discrepancy may not only be due to the limitations of uncontrolled studies, but may also be related to the methodology of RCTs. For example, in the RCT by Spitzer et al, T-deficient men with ED were first treated with an interval of sildenafil, followed by the addition of a T gel.[12] Erections improved significantly during the PDE5i period, without additional benefit from TTh. However, the improvement in erection was so robust with PDE5i alone that there was little opportunity to demonstrate additional benefit from TTh. Studies of this type are unable to answer the important clinical question whether TTh offers benefits for those men who fail PDE5i's. Anecdotally, in our practice we routinely offer TTh to men who fail PDE5i's, and often see positive responses.

WHO IS A CANDIDATE FOR TTh?

There is consensus that candidates for treatment with TTh should have signs or symptoms of TD combined with biochemical evidence of low T levels.[13] The challenge, however, is deciding what T level is considered low. For the first 40 years after the commercial availability of T products, the diagnosis was made entirely on clinical presentation. With the introduction of readily available testing with the development of radioimmunoassays in the 1970s, the emphasis shifted to documentation of low blood levels. Today, it is becoming increasingly clear that symptoms and clinical presentation should once again take priority,[13] with blood test results an important, yet secondary confirmation.

The difficulty with arriving at a reasonable threshold value for biochemical confirmation of TD is underscored by the wide range of recommended thresholds offered by various professional groups and experts, ranging from 200 ng/dl (approximately 7 nmol/l) to 400 ng/dl (approximately 14 nmol/l).[13] This confusing situation is worsened by the recommendation by the Endocrine Society in 2010 to follow reference ranges provided by the laboratory performing the testosterone testing,[14] because there is so much variation in reference ranges across laboratories that one survey revealed that 17 of 25 laboratories had different reference ranges.[15] This means that the same test result may be categorized as normal by one laboratory and low by another.

The explanation for the wide range in threshold recommendations is that there is no specific T value that reliably separates men who may benefit from treatment from those who will not.[14] Threshold recommendations are therefore arbitrary. The application of lower thresholds means that a higher rate of treated men are likely to experience benefits, but at the cost of denying treatment to many men who may also benefit. Higher thresholds allow for inclusion of more candidates who may benefit, yet overall response rates may be lower.[16] Moreover, there is a substantial