*Case in Point*

# Testosterone Replacement Therapy: Playing Catch-up With Patients

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As patients seek treatment for low testosterone, it is important for primary care providers to understand the risks and benefits of the therapy and the off-label promotions of its advocates.

The objective of this article is to help primary care providers (PCPs) council patients regarding testosterone replacement therapy (TRT). This case will present a patient who initiated TRT at a community-based alternative medicine clinic. The case will be followed by a discussion regarding the standard diagnosis of hypogonadism, the potential benefits and risks of TRT, and a review of the current clinical guideline recommendations. Examples of information being disseminated to the general public by the complementary and alternative medicine (CAM) providers will be briefly reviewed for an increased awareness of the questions patients may pose regarding TRT.

## BACKGROUND

From 2000 to 2011, total testosterone sales increased 12-fold globally.[1] Possible causes for the increase involved the aging population, newer options for TRT administration, and increased direct-to-consumer advertising. A low testosterone level (sometimes referred to as low T in consumer marketing materials) is associated with a variety of medical conditions (ie, low mood, increased body fat, declining athletic performance, and decreased sexual performance) that have become increasingly prevalent among middle aged and older men.[2] It has also received attention as an intervention to reverse frailty and sarcopenia.[3]

Testosterone replacement therapy options include injectable solutions, transdermal gels and patches, pellet implants, or buccal tablets. The ease of administration of transdermal testosterone comes at a relatively high cost. Injectable testosterone preparations are generally the least expensive option, and many patients choose injections for this reason.

Testosterone prescriptions were most frequently written by PCPs with 36% coming from family practitioners and 20.1% from internal medicine practices, according to a Kaiser Permanente study.[4] Endocrinologists (13.5%) and urologists (6.6%) were less likely to have written the prescriptions for patients.

Due, in part, to direct-to-consumer advertising and to the availability of online medical information, many men now present to their PCP questioning whether they might have low T. Others may have already started therapy at a CAM, integrative medicine, or anti-aging clinic.

Confusing the issue further, some CAM providers promote a variety of off-label medications and nutritional supplements for the treatment of low T, which seems to have struck a chord in the baby boomer generation. No other age group in history has tried to work so intensely on its physical condition and appearance.[5] Much of the information marketed to consumers emphasizes that many traditionally trained physicians are not educated in the treatment of low T.

## CASE REPORT

Mr. C. is a 65-year-old man who was seen in the primary care clinic for the first time. He was accompanied by his much younger fiancée. She reported that Mr. C.'s energy and sexual interest were declining, and the patient reported his "get up and go had gotten up and left." They sought medical advice from a CAM provider who or-

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dered blood work and then explained that the symptoms were due to low testosterone. For the past 6 months he had been visiting the clinic weekly for testosterone injections.

Mr. C. reported feeling as good as a "40 year old." He also reported that he started working with a personal trainer and had given up most junk food and alcohol. He had no symptoms of chest pain, erectile dysfunction, or significant urinary urgency, frequency, or nocturia.

The visits to a CAM provider had been an out-of-pocket expense, and he was hoping to transfer his treatment to the VA so the costs could be covered. Mr. C. failed to bring medical records from the other provider but remembered being told that all his tests were "fine" except for the low testosterone level.

His past history was notable for controlled type 2 diabetes mellitus for 8 years, hypertension, hyperlipidemia, and spinal stenosis. He had no history of benign prostatic hyperplasia or prostate cancer.

In addition to the testosterone (100 mg intramuscular injection weekly), his medication regimen included metoprolol 25 mg twice daily, atorvastatin 20 mg daily, acetaminophen 650 mg 3 times daily as needed, aspirin 81 mg daily, metformin 500 mg twice daily, vitamin D 2,000 IU daily, vitamin B12 1,000 mg daily, and Co-Q10 200 mg daily.

On physical examination, Mr. C.'s vitals were stable and his body mass index was in the overweight range at 29.8 kg/m$^2$. His cardiopulmonary examination was normal. There was increased central obesity without palpable organomegaly. There was no gynecomastia, and he had normal amounts of axillary and pubic hair. There was no peripheral edema; his genitourinary examination included normal-sized testicles, and the prostate was smooth without nodules.

The PCP informed Mr. C. that he was familiar with the evaluation and management of testosterone therapy. He was advised that additional evaluation would be needed before determining whether the clinical benefit of TRT outweighed the potential risks.

## ANDROPAUSE

Testosterone levels in men are known to decline at a rate of 1% per year after aged 30 years.[6] About 20% of men aged ≥ 60 years and 50% of men aged ≥ 80 years have low (hypogonadal) total testosterone levels.[7] The clinical diagnosis of hypogonadism, however, is made on the basis of signs and symptoms consistent with androgen deficiency and a low serum morning testosterone level measured on serum on multiple occasions.[8]

Specific clinical signs and symptoms ("A" list) consistent with androgen deficiency include low libido and sexual activity; diminished spontaneous erections; gynecomastia; reduced facial, axillary, or pubic hair; small (≤ 5 mL) testes; inability to father children; loss of height, fractures, or other signs of bone loss; and hot flashes and night sweats.[9]

Less specific signs and symptoms ("B" list) of androgen deficiency include a decrease in energy or motivation, feelings of sadness or depression, poor concentration or memory, trouble sleeping, increased sleepiness, mild anemia, reduced muscle bulk or strength, increased body fat, and diminished physical performance.[9]

Making the clinical diagnosis of hypogonadism is challenging, because the clinical symptoms have a high prevalence in the older male population and overlap with many nonendocrine diseases. Testosterone replacement therapy has been associated weakly, but consistently, with improved sexual function,[10-12] bone mineral density,[13,14] fat free mass,[13,14] strength,[15,16] lipid profiles,[17,18] insulin resistance,[17,18] and with an increased time to ST segment depression during stress testing.[19,20]

### Laboratory Evaluation

Serum total testosterone circulates in 3 forms: free testosterone, sex hormone-binding globulin (SHBG)-bound testosterone, and albumin-bound testosterone. Free testosterone is the most bio-available testosterone but represents only 2% to 3% of total testosterone.[21] Whether total testosterone or free testosterone measurements most closely correlate with symptomatic androgen deficiency is a matter of debate.[21] A total testosterone level is an appropriate screening test in young, healthy, and lean men for whom SHBG levels are presumably normal. However, a free or bioavailable testosterone level should be considered for men when there is a high likelihood of conditions that can affect SHBG levels.

Conditions that can decrease SHBG (and may result in a low total testosterone reading even when the free fraction may be normal) include obesity, metabolic syndrome, type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, chronic glucocorticoid use, and the use of progestins and anabolic steroids.[21] Conditions that can increase SHBG (and may result in a normal total testosterone level in patients with hypogonadism, as they have low levels of free testosterone) include aging, cirrhosis, anticonvulsant use, hyperthyroidism, catabolic conditions, and HIV.[21]

Serum testosterone levels generally peak in the early morning, followed by a progressive decline over the course of the day until they reach a nadir in the evening.[21] Although it has been debated that morning

testosterone levels are not necessary in older men due to a blunting of the circadian rhythm, many men aged 65 to 80 years who have low T in the afternoon will have normal testosterone levels when retested in the morning.[22,23] Readings below a reference range of 280 ng/dL to 300 ng/dL on at least 2 different occasions support a diagnosis of hypogonadism.[9]

Follicle stimulating hormone (FSH) and luteinizing hormone (LH) laboratory tests may be ordered following confirmation of a low testosterone level. Prolactin levels and iron saturation can help evaluate for the presence of hyperprolactinemia and hemochromatosis, respectively. Primary hypogonadism due to testicular failure is diagnosed with high FSH, high LH, and low testosterone levels. Secondary hypogonadism due to hypothalamic or pituitary failure is diagnosed with low FSH, low LH, and low testosterone levels.

Hypothalamic or pituitary suppression from a nonendocrine condition may result in functional hypogonadotropic hypogonadism (FHH), which can be identified with low (or normal) FSH; low (or normal) LH; and low testosterone levels. Hypogonadotropic hypogonadism has been associated with depression, obesity, stress, and physical exertion; and FHH may also be associated with the use of multiple drugs and drug classes (spironolactone, anabolic and corticosteroids, ketoconazole, ethanol, anticonvulsants, immunosuppressants, tricyclic antidepressants, selective serotonin reuptake inhibitors, antipsychotics, and opioids).[24,25] Even statin therapy has been associated with FHH.[26,27] Testosterone levels will often recover if or when modifiable factors for FHH are corrected.[28]

Although there is no consensus on an absolute number that defines a low testosterone level, concern exists that there are economic incentives to raise the bar for normal and thereby increase the potential market for testosterone-raising products.[29] Many commercial avenues for the treatment of low T do not follow the standards of the established medical community. Some websites suggest screening for low T with total and free testosterone levels for all men aged > 40 years. Others advise men to consider TRT if they have a total testosterone level of < 500 ng/dL or a free testosterone level that is not in the upper one-third range for men aged 21 to 49 years.[30] Of even greater concern, Baillargeon and colleagues reported that 25% of all new androgen users had not had their testosterone levels measured in the 12 months before starting treatment.[31] In another study, 40% of men who initiated TRT did not have a baseline measurement.[32]

## TREATMENTS

Before considering TRT, physicians need to emphasize lifestyle modifications as first-line treatment for hypogonadism. The most important modifications include weight loss, tobacco cessation, and moderation in alcohol use.

Patients need to be advised of possible adverse events (AEs) of TRT, which may include gynecomastia, polycythemia, sleep apnea, decreased high-density lipoprotein cholesterol, benign prostatic hypertrophy, infertility, testicular atrophy, and abnormal liver function tests. More recently, several studies have shown an association between TRT and an increase in cardiovascular complications, such as stroke, heart attacks, and death.

Prior to considering TRT, a careful history and physical examination, including a clinical prostate examination, should be performed. Minimum additional tests should include hematocrit, fasting lipid profile (FLP), complete metabolic profile (CMP), and prostate-specific antigen (PSA). Initiation of TRT is not recommended for patients with metastatic prostate cancer; breast cancer; an unevaluated prostate nodule; a PSA > 4 ng/mL (or > 3 ng/mL in African Americans or men with a first-degree relative with prostate cancer); hematocrit > 50%; untreated severe obstructive sleep apnea; uncontrolled or poorly controlled congestive heart failure; or an International Prostate Symptoms Score (IPSS) > 19.[9]

A past history of prostate cancer had previously been a contraindication for the use of TRT. However, more recent studies have shown that TRT can be used in those who have no evidence of active or metastatic disease and who are under the close supervision of a physician.[33-35]

Widespread screening is not recommended, and population-based surveys can be unreliable. Fifteen percent of healthy young men, for example, will have a low serum testosterone level in a given 24-hour period.[9] Thirty percent of men with an initial testosterone level in the mildly hypogonadal range will have a normal testosterone level when retested; moreover the threshold below which AEs occur remains unknown.[9]

The goal of TRT is to achieve a total testosterone level in the 400 ng/mL to 700 ng/mL range with improved clinical signs and symptoms.[9] Laboratory tests should be conducted at 3 months, 6 months, and then annually. These tests include hematocrit, PSA, and a testosterone level.[32] Testing for CMP and FLP should also be considered. If, during therapy, the hematocrit is > 54%, the patient should be assessed for hypoxia and sleep apnea, and treatment should resume at a lower dose only when the hematocrit returns to baseline.[9] A digital examination

of the prostate is recommended for men with a PSA of > 0.6 ng/mL. A urologic consultation should be obtained for an increase in the PSA of > 1.4 ng/mL over 12 months, a PSA velocity of > 0.4 ng/mL per year (using the PSA after 6 months as a reference), or for an IPPS of > 19.[9]

### Emerging Cardiovascular Concerns

The Testosterone for Older Men study, a randomized, placebo-controlled clinical trial of testosterone therapy in men with a high prevalence of cardiovascular disease, showed significantly greater improvements in leg-press, chest-press, and stair-climbing exercises while carrying a load compared with that in the placebo group.[36] However, the study was stopped early due to an increased risk of cardiovascular AEs in those who received testosterone gel.

Vigen and colleagues examined a cohort of veterans who underwent coronary angiography and had a low serum testosterone level.[37] The use of TRT in this cohort was also associated with an increased risk of adverse cardiovascular outcomes. This study generated several letters and a recent article in response that vigorously questioned the validity of the methods used and the conclusions reached.[38-44] Prior clinical studies of TRT had not detected cardiac AEs, but these trials were generally of short duration and not powered for clinical endpoints.[37]

A FDA Safety Announcement as well as a VA National Pharmacy Benefits Management bulletin were based on the results of these studies.[45] The FDA did not conclude that TRT increased the risk of stroke, heart attack, or death, but health care providers were asked to consider whether the benefits of TRT are likely to exceed the potential risk of treatment.

### Direct-to-Consumer Marketing

Some direct-to-consumer marketing promotes the use of aromatase inhibitors, such as anastrozole. This class of medications prevents the conversion of endogenous and exogenous testosterone to estrogen by the aromatase enzyme, which is found predominately in abdominal adipose tissue. There is no evidence that naturally occurring elevations in estrogen cause low testosterone or that treatment of elevated estrogen with an aromatase inhibitor during TRT has any significant clinical benefit in terms of male sexuality.[46] Nevertheless, some CAM providers now hypothesize that the increase in cardiovascular AEs with TRT noted in the recent studies may have been due to the increase in estrogen that is associated with TRT.[46]

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The off-label use of clomiphene citrate to block the negative feedback of estrogen on the production of LH has been promoted as another potential treatment to increase testosterone levels. Luteinizing hormone is the pituitary analog of human chorionic gonadotropin (HCG). Many CAM providers also prescribe HCG to increase the testicles' testosterone production.

Some consumer-focused media insist that the use of either clomiphene citrate or HCG will increase testosterone production and does not cause testicular atrophy, a known TRT-associated AE. This seems to increase the motivation of many men to try these off-label medications.

Some sources even posit a "conspiracy theory" that the FDA and pharmaceutical companies conspire to keep the price of transdermal TRT options high. Men are told that testosterone creams made at compounding pharmacies are much less expensive than are the transdermal pharmaceuticals, and they are urged to see a CAM provider to obtain a prescription for the compounded testosterone. In some cases, a sample prescription is included.[47]

Many supplements are available that claim to boost testosterone or suppress estrogen. Chrysin, for example, is a bioflavonoid that is marketed as having the potential to act as a natural aromatase inhibitor. Although studies have suggested the potential for chrysin to work in such a manner, the effectiveness may be attenuated by its low bioavailability in supplements.[48] Long-term studies have not been conducted.[49] Nettle root is a plant-derived compound that is stated to increase free testosterone levels by binding to SHBG, in place of testosterone, and by inhibiting the enzyme that converts testosterone to dihydrotestosterone. The clinical evidence of effectiveness is based on many open studies, and the significance and magnitude of the effect still needs more rigorous evaluation.[50]

## CONCLUSIONS

Patients today are barraged with medical information through television, print advertising, radio, and the Internet. A recent study of online sources of herbal product information found that only 10.5% recommended a consultation with a health care

professional and < 3% cited scientific literature to accompany their claims.[51] Many patients present to their PCP with questions about TRT or have already started an intervention for low T. Complementary and alternative medicine providers of TRT have been able to capture a segment of the population that often has the motivation and disposable income to pursue nontraditional therapies.

All nutritional supplements contain a standard warning from the FDA: "The above statements have not been evaluated by the FDA. This product is not intended to diagnose, treat, cure or prevent any disease." Providers should remind patients of the statement and point out the contradictions between the statement and the benefits touted by the supplement marketing literature.

Finally, despite the well-established role of testosterone in enhancing libido, its definitive role in erectile function had been controversial until evidence substantiated a key function for this hormone.[52] Testosterone may facilitate erection by acting as a vasodilator of the penile arterioles and cavernous sinusoids and may ameliorate the response to the phosphodiesterase-5 inhibitors in hypogonadal men.[53] Testosterone replacement alone in hypogonadal men can restore erectile dysfunction.[51] However, hypogonadism is not a common finding in those with erectile dysfunction, only occurring in about 5% of cases.[53]

Allopathic providers are concerned about the vitality and sexual health of their aging male patients, but their enthusiasm for anti-aging treatments is often tempered by evidence-based studies that have shown a lack of efficacy or potentially serious health care risks. Unfortunately, many patients remain unaware of the controversies regarding TRT. For those patients who receive treatment through CAM providers and are convinced of the efficacy of their low-T treatment regimen, it is important to keep lines of communication open. ●

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