

A Matter of Opinion

Should you prescribe testosterone replacement, and when is it warranted?

If you are like many physicians in this field, you've likely pondered the testosterone (T) debate.

Many of us can espouse the theory behind testosterone replacement. Both cross-sectional and longitudinal evaluations show serum testosterone level decrease an average of 1 percent to 2 percent a year after age 30.¹³ We also know that aging men, as a group, experi-

ence the same signs and symptoms as young men with acquired hypogonadism from trauma.

These men experience changes in body composition with decreased muscle mass, strength, bone mass and libido, as well as increased fat mass, impaired red cell production and erectile dysfunction.¹⁵ Studies show that replacing T can abate these symptoms in men who have lower T levels.

But how do you determine which older men merit T therapy and what makes them clinically "androgen defi-

cient?" In practice, the decision is often influenced, in part, by philosophy and, in part, by science.

Guidelines for T Replacement

The Endocrine Society recently published clinical guidelines for adult men, outlining diagnosis and treatment recommendations for T replacement, making special note of other confounding issues that might affect T levels.⁶

To warrant diagnosis, men with consistent symptoms and signs of androgen deficiency should have unequivocally

KYLE MELINSKI



About 1 million men are turning to testosterone therapy in hopes of restoring vitality and slowing the aging process. By age 60, about one in five men have testosterone levels lower than what's normal for younger men, although no one knows whether these levels are low for men their age.

Source: Harvard Health Publications

low serum T levels, the task force recommends. The Endocrine Society defined these levels as those clearly below the lower limit of normal for healthy, young men.

The reality of clinical practice is many older men have symptoms and signs of deficiency. In addition, treating only those symptomatic patients in the very low limits of normal would leave out a significant number of people we can help.

In my opinion, this approach doesn't stress the benefits that patients value in favor of purported risk. Now, increasingly, clinical experience with T supplementation is showing greater safety. In fact, some research indicates there may be no risk at all of prostate cancer.^{2,8} Another study shows that men with low T levels have an 88 percent increase in risk of death compared with those who had normal levels.⁹

It is becoming more difficult for the clinician to avoid the issue and retreat to the old standbys: "Not enough is known about safety" and "first, do no harm." In my opinion, the choice not to treat could be more harmful than treatment.

Patient Assessment

That being said, it is illegal to prescribe androgens for sports performance or cosmetic muscle enhancement. Thus, we need to document the diagnosis of hypogonadism and list those symptoms and signs that support the diagnosis.

The decision to treat with T is not an easy one. In fact, many psychological and physiological processes affect all of the signs and symptoms of hypogonadism. These processes could be the sole cause of the problem.¹⁰

For example, an obese sedentary man with poor nutrition could present with sarcopenia (e.g., decreased muscle mass), muscle weakness, increased body fat, insulin resistance, metabolic syndrome, osteopenia, impaired cognitive function and decreased libido.

An older man with these symptoms likely would have low serum T, predictable, in part, because of his age alone. All of these changes have been demonstrated to improve with T, yet all of these changes could be simply a consequence of fitness and nutrition issues. All could be improved with changes in fitness and nutrition, without using hormones.

In addition, clinical manifestations of hypogonadism are sometimes a result of other causes. Low serum T itself can be

a result of several medical conditions, including diabetes mellitus, liver disease, hemochromatosis and obesity, especially with increased abdominal fat. Lower T levels also have been associated with several medications, including ketoconazole, cimetidine and glucocorticoids. Smoking and chronic alcohol use lower T levels. These confounding issues of cause often combine and are not easy to extrapolate.

Heavy alcohol use, for example, is independently associated with bone demineralization, and thus, can influence body composition, nutrition, erectile function and mood. In addition, excessive alcohol affects testicular production of T. Obviously, restoring T levels without addressing alcoholism would fail to address the fundamental cause of the imbalance.

However, in both of these patient examples, T could, with lifestyle changes, accelerate the improvement. Ideally, one would like to know what imbalances in male hormones look like clinically and how to assess them (key indicators), as well as where they come from (genetics, diet, nutrition, environmental toxins, stress). In reality, this is not possible for the majority of patients because causes and indicators overlap.

Thus, clinicians need to understand the patient as a whole person, not as a series of parameters. To come to a diagnosis, physicians should measure morning total T levels with a reliable assay, according to the Endocrine Society. The society also recommends retesting patients who are borderline low, since these levels may change.⁷

It's important to consider that all T measures are not the same. T is nearly all bound to sex hormone binding globulin (SHBG) and more loosely bound to albumin. However, some tests calculate free T based on a measure of bioavailable T, serum albumin and SHBG.

Genetic variations in SHBG allow for tight or loose binding of T, which can result in less or more bioactive T. Calculated values do not take these variations into account, rendering them less accurate. Many labs will offer a platform-based test, but I recommend spending more on the LC/MS/MS test, which means liquid chromatography followed by mass spectroscopy, and then again run through mass spectroscopy. This is the gold standard because it measures the free T most reliably and limits cross-reaction contamination.¹¹

LAB VALUES TO NOTE

When prescribing T therapy, you need to consider the following hormones:

Testosterone. When measuring testosterone (T) levels, you should document the time since the last dose. This will help you interpret a given serum hormone level. If the patient takes T cream twice daily, for example, he should hold his morning dose and have the blood drawn in the morning, about 12 hours from the last dose.

If he takes only one dose every 24 hours, be sure to consistently check the level at the same time. Be aware that comparing T levels from blood drawn 24, 12 or sometimes one hour after cream application can cause big changes in the serum level.

Estradiol. These measures before and after therapy can indicate the conversion from T to estradiol. This is important because it indicates the activity of the patient's aromatase enzyme. Still, measurements of estradiol in men require a sensitive accurate measure for low concentrations.

Too much estrogen can mediate the effects of T, and low levels of estrogen can affect neurons and bone and may lead to loss of teeth. In my experience, lowering the T dosages usually still delivers benefits, while limiting the potential adverse effects of using another medication to solve the problem.

DHT. T is converted to dihydrotestosterone (DHT) by the enzyme 5 alpha-reductase. DHT blood levels are about one-tenth of T levels, but the potency of DHT in bio-assays is at least twice that of T. In some patients who start T supplementation, DHT rises dramatically and disproportionately to T. Thus, we monitor DHT levels to ensure proper prostate differentiation and function.

If DHT levels rise, make sure the patient isn't applying T near the groin. He shouldn't apply the topical anywhere from the waist to the knees. Having excluded that issue, patients with high DHT levels and perhaps any patient at risk of benign prostatic hypertrophy, could use saw palmetto or finasteride. Both inhibit 5 alpha-reductase enzymes.

—Dan Cosgrove, MD

Applications for T Replacement

T is not available orally except as modified compounds that are hepatotoxic. Oral troches and buccal patches are being investigated and are available from some compounding pharmacies.

Medical professionals have prescribed testosterone or cypionate injections for decades to replace T, but I find that patients may have difficulty with the injections, the marked swing of serum level peaks and troughs, as well as tissue damage, with potential fibrosis from repeat injections.

T application is also available in a patch. One of the first was a scrotal patch. However, T application near the groin usually results in unwanted higher DHT levels, apparently due to an increased concentration of the 5-alpha reductase enzyme subcutaneously near the groin. Now, physicians recommend patients apply patches to the upper torso.

Patches are not my first choice for treatment because they can lose their adhesion and irritate the skin. Patches also are limited for titration of the dose. I prefer using T gel as a delivery method in most cases and often turn to reliable compounding

pharmacies for my prescription. Compounding pharmacies often provide a less expensive alternative to the branded gels.

I typically recommend 50 mg T per gram of cream. I generally recommend patients apply 1 gram twice daily. If men prefer to take a single dose, we can double the concentration.

Follow-up and Reassessment

Once men begin using T gel, they return in two weeks for a review of potential adverse effects, such as aggression. As physicians, we should discuss perceived benefits, such as libido, desire to exercise or any change in fatigue and energy.

We draw lab tests at two weeks, just to be certain the dose is correct. We may notice the level remains low at 200-300 ng/dl, which is common. However, we can check back in six to 12 months for more accurate clinical and lab evaluation. By this time, men should feel maintained subjective changes in mood, well-being, libido and erectile function. Body composition, weight and changes in muscle strength provide more objective measures.

At six months, we also obtain a PSA to determine risk of prostate cancer. We consider PSA that increases to more than 0.6 a rapid rise. Although PSA reference ranges are often less than 4, we add a serum free PSA if the level is greater than 2.5. This offers greater sensitivity in early detection of prostate cancer.

Some experts believe there's no association between T and cancer, but one study did show that a small portion of those who took T got a more aggressive prostate cancer.⁵ Thus, it's always good to be vigilant.

We also monitor hemoglobin change. Many men on T have hemoglobin creep up from 15 grams to nearly 20 grams since T stimulates erythropoiesis. At 17 grams, I encourage patients to donate blood to lower iron levels. T therapy is not a contraindication for most blood banks. If the patient has a strong hematopoietic response to T, he may need to give a unit of blood once or twice annually.

I have seen iron deficiency in patients, but most men do not have this problem. Because iron is a potent oxidant, lowering the iron level through blood donation is an added benefit.

I also recommend ordering baseline serum total and free T, DHT, estradiol and DHEA-S. Some cost-sensitive patients may not want to measure all these hormones in follow-up. Mostly, I'm looking for high or low amounts of conversion of T to estradiol or DHT. (See sidebar on previous page.)

Hormones are potent and increase various cellular processes. When those processes are imbalanced, increasing hormone activity may magnify the imbalance and do more harm than good.

Thus, the cavalier prescription for a potent hormone without follow-up invites trouble. At my clinic, we insist on a protocol that requires baseline screening tests and the patient's commitment for follow-up. In this way, we can document the degree of response to therapy. ■

For a list of references, go to www.advanceweb.com/healthyaging and click on the references toolbar.

DAN COSGROVE, MD, is an internist in private practice at WellMax, a destination medical clinic in La Quinta Calif.

Disclosure: Dr. Cosgrove indicates he has no affiliations with any commercial entities, directly or indirectly referenced in this article.