Diagnosing and managing low serum testosterone

Ana Marcella Rivas, MD, Zachary Mulkey, MD, Joaquin Lado-Abeal, MD, PhD, and Shannon Yarbrough, MD

Measuring testosterone levels became easier in the 1970s, and it wasn't long before levels were being checked in men across all age groups. At that time, several authors reported an age-associated decline of serum testosterone levels beginning in the fourth or fifth decades of life. Other studies found that the decline in testosterone with age might be more related to comorbidities that develop in many aging men. Aggressive marketing campaigns by pharmaceutical companies have led to increased awareness of this topic, and primary care physicians are seeing more patients who are concerned about "low T." Unfortunately, testosterone replacement therapy has not been straightforward. Many men with low testosterone levels have no symptoms, and many men with symptoms who receive treatment and reach goal testosterone levels have no improvement in their symptoms. The actual prevalence of hypogonadism has been estimated to be 39% in men aged 45 years or older presenting to primary care offices in the United States. As the US population ages, this number is likely to increase. This article, targeted to primary care physicians, reviews the concept of late-onset hypogonadism, describes how to determine the patients who might benefit from therapy, and offers recommendations regarding the workup and initiation of treatment.

A 56-year-old overweight man with symptoms of low energy, daytime sleepiness, and decreased libido happens to be watching a golf tournament on TV from his favorite recliner and suddenly a commercial appears. This patient is in your office the following Monday and asks you, "Is it low T?"

Aggressive marketing campaigns by pharmaceutical companies have led to increased awareness of hypogonadism among men, who may then present to the clinic requesting testing or treatment (1). As a result, primary care physicians are seeing more patients like the one described above. The physiological age-related decrease in testosterone production should be differentiated from late-onset hypogonadism (LOH), defined as the presence of three sexual symptoms and low testosterone (low T) in aging men (2). This definition was proposed to help clinicians identify aging men with low testosterone who could potentially benefit from hormonal replacement therapy. The purpose of this article is to review the data on LOH, also known as low T, and present the most recent evidence and recommendations regarding the approach to the patient from our case scenario.

PHYSIOLOGY AND DEFINITIONS

Male reproductive endocrine physiology involves the hypothalamic-pituitary-target organ and feedback model. Disruptions at different levels of this pathway can lead to disturbed androgenic effects: primary disorders of the testes (primary hypogonadism), disorders of the pituitary or hypothalamus (secondary hypogonadism), and disorders of androgen action on target tissue or androgen resistance. Other less common entities that manifest as androgen deficiency include chronic stress (by suppressing gonadotropin-releasing hormone secretion) and exogenous glucocorticoids, which can theoretically block the effects of testosterone on its target tissues (3).

In men, testosterone levels increase from puberty to adulthood and then progressively decline starting by the fourth or fifth decade of life (4). Multiple studies have raised the question of whether or not the declining T level seen in aging men is a natural age-related process or is caused by the accumulation of multiple chronic medical illnesses that virtually all aging men experience. One small study investigated this question by looking at groups of men across different age groups who were in "very good or excellent health" (5). The authors found no statistically significant difference in serum total testosterone levels across the cohorts grouped by decades of age. Their data support the idea that "the decline in serum T with male ageing is a non-specific effect of the common co-morbidities that accumulate during ageing" (5). Despite this novel study's results, the fact remains that most aging men seen in primary care offices are very likely to have at least two chronic medical illnesses (6) and are dissimilar from the study population. It would be helpful if health care professionals could identify men with low serum testosterone levels who are likely experiencing symptoms purely from androgen deficiency and would therefore benefit from treatment.

From the Departments of Internal Medicine (Rivas, Mulkey, Yarbrough) and Endocrinology (Lado-Abeal), Texas Tech University Health Science Center, Lubbock, Texas.

Corresponding author: Ana Marcella Rivas, MD, Department of Internal Medicine, Texas Tech University Health Science Center, 3601 4th Street, Lubbock, TX 79430 (e-mail: Marcella.Rivas@ttuhsc.edu).

LATE-ONSET HYPOGONADISM

Symptoms of hypogonadism are highly nonspecific and include decreased libido, erectile dysfunction, decreased volume of ejaculate, loss of body and facial hair, decreased bone density, decreased lean body mass, increased body fat, fatigue, weakness, increased anxiety, profuse sweating, and anemia (7). It is challenging to differentiate these symptoms from those that result from aging per se, and this was one of the reasons why the concept of LOH was introduced.

LOH is defined as a total testosterone level <300 ng/dL combined with the presence of three sexual symptoms:

- Decreased frequency of morning erection
- Erectile dysfunction
- Decreased frequency of sexual thoughts

Sexual symptoms have been found to be more strongly associated with androgen deficiency and are therefore specified in the definition of LOH (8). This syndromic approach involving clinical and biochemical criteria allows physicians to identify patients who are symptomatic from androgen deficiency and separate them from those with isolated biochemical hypogonadism and nonspecific symptoms from aging. Further research by the European Male Aging Study has found an association between LOH and end-organ deficits compatible with androgen deficiency, specifically low hemoglobin, reduced bone mineral density, and reduced muscle mass (2).

Data on the prevalence of low T are highly variable due to the different cutoffs used to define low testosterone and the clinical syndrome of LOH (3, 9, 10). The Massachusetts Male Aging Study (10), an observational cohort study conducted on healthy men aged 40 to 70 years from the Boston area, estimated that the prevalence of androgen deficiency (total testosterone <400 ng/dL) in men in this age group was 25.3% to 39.3%, but when considering the presence of at least three signs or symptoms of low T (the definition of LOH), the prevalence dropped to 6% to 12%.

DIAGNOSIS

Guidelines, including the most recent guidelines published by the Endocrine Society in 2010, recommend against screening asymptomatic patients and against case finding with tools such as the ADAM (Androgen Deficiency in the Aging Male) questionnaire. Guidelines do recommend considering case detection, which involves testing specific groups of patients that may be at higher risk of androgen deficiency due to certain comorbid diseases (type 2 diabetes mellitus, moderate to severe chronic obstructive pulmonary disease, obesity, etc.) (11).

Symptoms are mostly nonspecific. Even the sexual symptoms can be due to many other conditions, including vascular disease, chronic alcohol use, and depressive disorders. Thus, many men are seeking solutions for these bothersome symptoms, which may involve indiscriminant testing and possible overtreatment.

The physical exam also is generally nonspecific. Typical exam or diagnostic findings include obesity, loss of body hair, gynecomastia, mild anemia, and osteoporosis. Testicular volume may be decreased (normal volume 15 to 30 mL, equivalent to the size of a quarter dollar coin). In addition to size determination, the testes should be palpated to rule out the presence of a mass, which may represent a benign or malignant tumor. A pituitary mass may cause visual field deficits, and prolactinomas specifically can cause galactorrhea (11, 12).

The diagnostic approach to hypogonadism is illustrated in *Figure 1*. Normal values for testosterone levels vary among different sources (2, 11, 12). The most common cutoff transitioning from normal to low ranges from 280 ng/dL to 320 ng/dL; the guidelines recommend using 300 ng/dL as the cutoff (11). Serum testosterone levels exhibit ultradian and circadian variation, providing physiologic sources of biologic variability. Ultradian fluctuations (rhythmic fluctuations of less than a 24-hour period but more than 1 hour) are more pronounced in older men, while circadian variation in testosterone is blunted, but still present, in older men (12). Therefore, except in older men, a morning (7 to 11 AM) serum total testosterone should be checked initially, if testing is necessary. There is some evidence that a glucose load can significantly decrease testosterone levels for a short time, so conducting this test in the fasting state may result in improved accuracy (13). If initial test results are low, repeat measurements are recommended in 2 to 3 weeks, since repeat levels may be within the normal range in up to 30% of cases. Additionally, at this point it is prudent to consider outside influences on sex hormone production and address these issues first if appropriate. Such issues include use of corticosteroids or opiates, malnutrition, acute illness, alcoholism, and cirrhosis

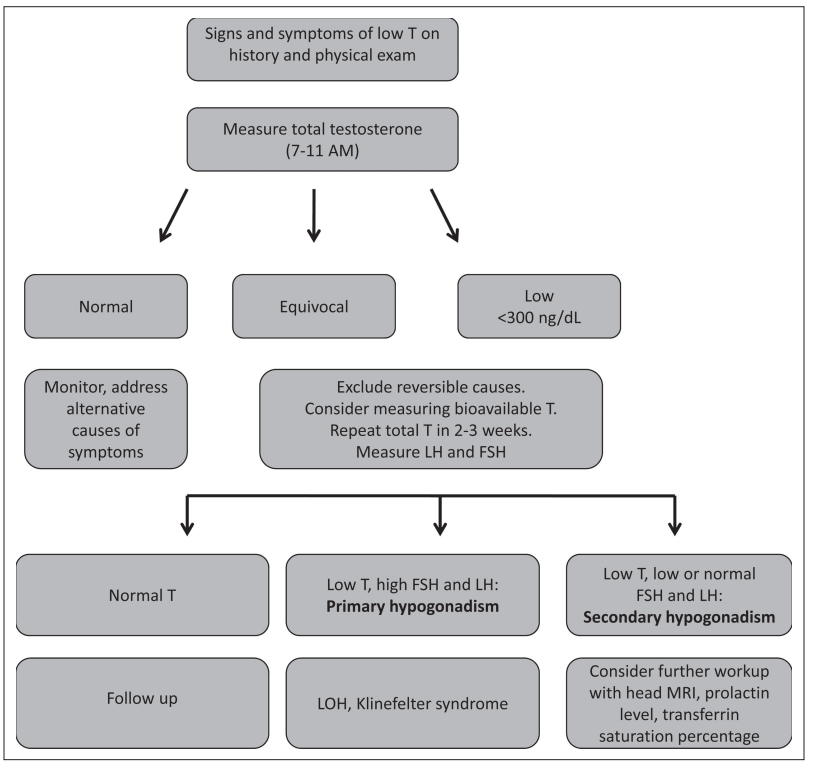

Figure 1. Diagnostic approach for patients suspected of having hypogonadism.

(5, 11, 12). If the testosterone levels are equivocal, consider checking a free or bioavailable testosterone level. It is important to note that there is an age-associated increase of sex hormone binding globulin levels by about 1.2% per year, so the decrease of free testosterone is larger than that of total serum testosterone in older patients.

If testosterone is confirmed to be low, it is recommended to categorize the hypogonadism as primary or secondary by checking levels of luteinizing hormone and follicle-stimulating hormone. Elevated levels of these hormones would indicate primary testicular failure. Causes include LOH, Klinefelter syndrome, and infectious diseases such as chlamydia- and gonorrhea-associated epididymo-orchitis and mumps. If luteinizing hormone and follicle-stimulating hormone levels are low (or inappropriately normal), secondary hypogonadism is diagnosed and hypothalamic/pituitary pathologies should be considered (11, 12) depending on the patient's presentation.

TREATMENT

Once the diagnosis of LOH is confirmed, testosterone replacement therapy (TRT) should be considered with the goals of improving secondary sexual characteristics, sexual function, sense of well-being, and bone mineral density. During the initial workup, if a clear treatable condition that explains androgen deficiency is diagnosed, it should be addressed first (11, 14).

In obese individuals, several studies have demonstrated that intense lifestyle intervention and weight loss are associated with a rise in testosterone levels. Androgen rise has been found to be greater in those patients who lose more weight (14, 15). It is therefore important to recommend weight loss either prior to or concomitant with TRT in obese patients. Obese patients should also be assessed for obstructive sleep apnea, which is also an important cause of low T (16).

TRT in older men with low testosterone concentrations has been associated with improved libido, sexual function, mood, and possibly muscle strength (12, 17). Improvement in bone mineral density has been reported, but no studies exist that determine whether the risk of fractures in these patients decreases when receiving TRT (11, 12, 18).

Controversy exists about the long-term safety of TRT. Although several studies have reported a significant reduction of carotid intima media thickness; decreases in fat mass, blood pressure, fasting glucose, and insulin resistance; and increases in high-density lipoprotein cholesterol (12, 19), the effect of TRT on cardiovascular risk is still uncertain. One study in men older than 65 years of age with limitations in mobility and a high prevalence of chronic disease concluded that the application of a testosterone gel was associated with an increased risk of cardiovascular adverse events (20). Many argue that the investigators used higher dosages of testosterone than recommended by the guidelines or that the results might have been associated with increased hematocrit in the treatment group. In contrast, other studies have found increased cardiovascular mortality in patients with testosterone deficiency (19). Further studies are needed to determine the exact role of testosterone and TRT in cardiovascular risk. This is an issue patients should be aware of when considering TRT. Debate also surrounds to what extent metastatic prostate cancer and breast cancer may be stimulated during testosterone treatment. For this reason, all men should be assessed for risk of breast and prostate cancer prior to treatment. Other potential side effects of TRT include fluid retention, acne, sleep apnea, gynecomastia, and infertility (11). The 2010 guidelines list the following contraindications to TRT: breast cancer, severe lower urinary tract symptoms, and poorly controlled heart failure.

The different testosterone preparations available include intramuscular formulations, topical gels, solutions, and skin patches. Tablets and implanted subcutaneous pellet formulations are less commonly used options. Each preparation has advantages and disadvantages and should be presented as an option to the patient *(Table 1)*. Intramuscular injections are administered every 2 to 3 weeks and trade the inconvenience of bimonthly injection visits with the avoidance of possible medication contact

Table 1. Therapeutic options for testosterone replacement therapy

Preparation	Route	Advantage	Disadvantage
Testosterone cypionate, Testosterone enanthate	Intramuscular	Effective, avoids daily administration	Requires intramuscular injection of oily solution
Patch	Transdermal	Relatively convenient, stable serum concentrations	Daily application, rash in up to 30%, unavailable in some countries
Gels	Transdermal	Consistent serum levels	Daily application, theoretical transfer to others upon skin contact
Injection (pellets)	Subcutaneous fat implants	Only needed every 3–6 months	Requires surgical implantation
Fluoxymesterone, Methyltestosterone	Oral	Convenience	Up to 4 daily doses may be needed, potentially significant hepatic effects and first-pass metabolism leading to ineffective therapy
Testosterone undecanoate	Oral	Convenience	Same as other orals but possibly fewer hepatic effects; available in Canada and Europe, not USA
Buccal testosterone	Oral (patch that adheres to buccal mucosa)	Convenience	Some dropout in trials due to discomfort due to patch

with other household members. A disadvantage of the injections is the fluctuation in serum testosterone concentration that can cause fluctuating libido, energy level, and mood. Transdermal forms offer more stable concentrations (13), but they can cause rash in the applied area.

MONITORING AND FOLLOW-UP

The general target level for testosterone ranges from 350 to 750 ng/dL, which is roughly the range for healthy, androgen-sufficient adult men. Testosterone levels should be monitored 3 to 6 months after initiation of treatment. Patients receiving the intramuscular testosterone enanthate or cypionate should have levels checked midway between injections, and levels should be checked 3 to 12 hours after application in the case of transdermal patches (11, 13).

The recommended duration of testosterone administration is uncertain. A hematocrit test is recommended prior to therapy initiation to establish a baseline for future monitoring. Hematocrit and prostate-specific antigen (PSA) levels should be measured 3 to 6 months after treatment initiation and then annually. TRT should be reconsidered in patients with a hematocrit >50%. An increase in PSA of more than 1.4 ng/mL within a 12-month period of testosterone treatment or an International Prostate Symptom Score above 19 should prompt urological evaluation. On the other hand, what should a clinician do with a PSA value that increases to a lesser degree *per year* but is steadily increasing every time it is checked? This can be managed using the concept of PSA velocity. Any PSA velocity >0.4 ng/mL per year should also prompt urological evaluation (at least 2 years of measurements are needed, based on PSA values measured at least 6 months after initiating therapy). For example, PSA levels of 1.5 ng/mL, 2.3 ng/mL, and 3.3 ng/mL over 3 years do not meet the first indication for urology referral (more than 1.4 ng/mL over a year's time) but show an average PSA velocity of 0.9 ng/mL and require referral based on that criterion (11).

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