The Role of Testosterone Therapy in Men's Health

Blake K. Smith, MSN, BSN, BS, RN[a,b,c],
Michael Ward, MSN, APRN, AGACNP-BC[d,*]

KEYWORDS

• Low T • Testosterone • Men's health • Testosterone replacement therapy

KEY POINTS

- It is essential to understand thorough, efficient, and cost-effective assessment and diagnosis of low testosterone.
- Low testosterone can manifest based on comorbid conditions or contribute to other disorders/conditions if not treated.
- There is a continuation of the inconsistency of standardization of guidelines around the globe on best practices for low testosterone treatment.
- To achieve the best treatment outcomes, the provider must consider laboratory assays and the presentation of signs and symptoms.

INTRODUCTION

Charles Édouard Brown-Séquard injected himself with a mixture containing liquid extracted from the testicles of dogs or guinea pigs in 1889 (Video 1). The therapy was injected 10 times over 3 weeks. Brown-Séquard observed physical changes: an increase in his forearm flexor strength, a more forceful urinary stream, the ability to defecate more efficiently, and a subjective improvement in his cognitive abilities. The once-proclaimed "Elixir of Life," *testosterone* (T), has many well-studied anabolic, metabolic, and developmental properties that affect target organs in men and women. The potential uses of this compound prompted several teams of biochemists to race for isolation of the testicular hormone in the early twentieth century.[1] The surge of athletes hoping to benefit from the anabolic effects of T began in the first half of the twentieth century. It was not until researchers controlled for exercise routines and protein intake that it was identified that testosterone leads to increases in strength, fat-free

[a] American Association for Men in Nursing, Wisconsin Rapids, WI, USA; [b] Clinical Documentation Sr. Analyst, Enterprise Applications, Nebraska Medicine, Omaha, NE, USA; [c] Accelerated Program Student Success Coach, School of Nursing, Nebraska Methodist College, Omaha, NE, USA; [d] Critical Care Nurse Practitioner, Cardiovascular ICU, Medical ICU, Texas Health Huguley Hospital, 11801 South Freeway, Burleson, TX 76028, USA
* Corresponding author. 214 NE Wilshire Boulevard, Burleson, TX 76028.
E-mail address: Brandonw.rn@gmail.com

Nurs Clin N Am 58 (2023) 525–539
https://doi.org/10.1016/j.cnur.2023.07.001 **nursing.theclinics.com**

mass, and overall muscle mass in exercising men.[2] *Testosterone replacement therapy* (TTh), as it has become known, has proved to be an effective treatment strategy for improving the quality of life for hypogonadal men around the globe.

Low levels of circulating serum T characterize *hypogonadism* due to interference or malfunction of the hypothalamic-pituitary-gonadal axis (HPGA). It is estimated to affect 2 to 4 million men annually in North America alone. An estimated 1 in 10 men older than 60 years has a *testosterone deficiency* (TD) and 1 in 3 has diabetes.[3] By 2025, an estimated 6.5 million American men will be affected.[4]

T is a pleiotropic hormone that plays an essential role in the human body. Through its conversion to estrogen, T affects bone health and density. Male hypogonadism is the clinical condition representing symptoms and gonadal dysfunction of Leydig cells, resulting in decreased T, Sertoli cell/germ cells, and decreased sperm production.[5] There has been a renewed interest recently in the systemic role of T in pain, well-being, and cardiovascular function in both women and men.[2]

Therapeutic T levels are linked to improved sexual function, physical performance, strength, lean body mass, and cognitive function and have some cardiovascular benefits.[6,7] Low T levels can lead to sarcopenia, increased adiposity, fatigue, lack of motivation, cardiovascular diseases, cancer, and all-cause mortality.[4,8] Androgen deficiency signs and symptoms take time to manifest clinically in adolescents and young men, given the numerous pathways within the HPGA and reduced efficiency changes to hormonal levels.[5] Experts have debated using TTh in men who might benefit from replacing declining hormone levels.[2] With the recent prolongation of life expectancy, especially in men, the question concerning T replacement in older men has become more important.[9]

Considerations of Testosterone

Testosterone production

Androgen synthesis in the gonads of men and women is regulated by the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, releasing luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland.[2] The HPGA plays a significant role in male hormonal balance maturation, development, and sustainability. The pulsatile secretion of GnRH by the hypothalamus stimulates LH and FSH production and secretion by the anterior pituitary gland. LH stimulates T production from the interstitial Leydig cells of the testes. Male internal and external reproductive organ development requires T production, resulting in the differentiation of secondary human sexual characteristics. FSH, in turn, sustains testicular function via Sertoli cells through spermatogenesis.[10] Ninety-five percent of the synthesis of serum T in men is produced by the Leydig cells of the testis under the influence of LH secreted from the pituitary gland.[5] Evidence from genetic studies of fetal testicular tissue has shown that adrenocorticotropic hormone can stimulate fetal Leydig cells to produce steroids, reinforcing the link between adrenal and testicular tissue.[2]

Dehydroepiandrosterone (DHEA) and DHEA-S are prohormone substrates for forming potent androgens such as T and dihydrotestosterone (DHT) by peripheral conversion. Free T and DHT then bind the intracellular androgen receptor, enabling the complex to bind DNA regions and exert androgenic effects.[2] T can also be converted to estrogen via aromatase, a cytochrome P450 enzyme family member, in target areas, including neural tissue, adipose, liver, and bone. In men, estrogen from this reaction is essential for the maturation of sperm and libido maintenance.[11] Albumin-bound T is also biologically active, given the low affinity of T for the protein.[2]

Measuring testosterone

The diagnosis of TD requires the presence of characteristic symptoms and signs in combination with decreased serum concentration of T.[12] Although sensitive, screening questionnaires or structured interviews on male symptomatic TD have low specificity.[13] Morley and colleagues compared the most used questionnaires in 148 men using bioavailable testosterone to diagnose TD. They found the sensitivity to be 97% for the ADAM (Androgen Deficiency in the Aging Male questionnaire), 83% for the AMS (Aging Male's Symptoms scale), and 60% for the MMAS (Massachusetts Male Aging Study questionnaire). Specificity was 30% for the ADAM, 59% for the MMAS, and 39% for the AMS.[14] Although other extensive face-to-face comparisons are lacking, more recently, a large systematic review including 40 studies concluded that a specific structured interview, ANDROTEST, for detecting hypogonadism-related symptoms and signs, showed both the most favorable positive and negative likelihood ratio for detecting low T.[13] A 12-item version of the interview (ANDROTEST) had a sensitivity and specificity of 68% and 65% in detecting low total T (<10.4 nmol/L) and 71% and 65% in the screening for low free T (<37 pmol/L).[15] Given this specificity compared with the ADAM questionnaire, the structured interview hypogonadism screening questionnaires, including the ANDROTEST, may not be as economic and efficient as the ADAM questionnaire as a first-line screening test for hypogonadism.[16] Fig. 1 is an example of the ADAM Questionnaire developed by Saint Louis University in 2000.

The expected morning T range for men is between 300 and 1000 ng/dL, and *hypogonadism* is defined as a total T less than 300 ng/dL by the Endocrine Society clinical practice guidelines.[17,18] Threshold, along with various others defining low total T set from 250 to 300 ng/dL by other societies such as the American Urological Association, have been established regardless of age following many large-scale population studies.[10] T secretion follows a circadian rhythm in young and aging men, with the highest levels generally occurring in the early morning; therefore, it is recommended that blood samples for T should ideally be drawn in the morning to assess patients'

Questions Used as Part of the Saint Louis University ADAM Questionnaire

1. Do you have a decrease in libido (sex drive)?

2. Do you have a lack of energy?

3. Do you have a decrease in strength and/or endurance?

4. Have you lost height?

5. Have you noticed a decreased "enjoyment of life"?

6. Are you sad and/or grumpy?

7. Are your erections less strong?

8. Have you noted a recent deterioration in your ability to play sports?

9. Are you falling asleep after dinner?

10. Has there been a recent deterioration in your work performance?

NOTE. A positive questionnaire result is defined as a "yes" answer to questions 1 or 7 or any 3 other questions.

Fig. 1. Androgen Deficiency in Adult Males (A.D.A.M.) Questionnaire

androgen status properly.[2] Free and albumin-bound T is a relatively accurate measure of a patient's clinical and hormonal composition, more so than total hormone levels.[2] Following confirmation of low serum T levels and concomitant signs and symptoms of hypogonadism, clinicians should use serum LH and FSH in conjunction with T to differentiate between primary and secondary hypogonadism.[5] Measuring T levels is challenging; it is essential to appreciate androgen production and regulation.[2]

T assays play a vital role in the workup and diagnosis of many endocrine disorders. Assays in men are used to diagnose clinical *hypogonadism* in patients with prostate cancer (PCa) treated with GnRH analogues and in children to monitor signs and symptoms of advanced and delayed puberty.[2] Sertoli cell assessment is needed to diagnose *hypogonadism* in prepubertal populations.[5] Clinicians should be cognizant that varying measurements between laboratories may be consequences of the method used rather than a reflection of actual changes in T levels. One proposed solution is to measure free rather than serum T, which can be measured by equilibrium dialysis. Free T passes through a membrane into a dialysate solution in this method, but protein-bound testosterone does not.[2]

Age/environmental factors

A distinction should be made because *hypogonadism* has been defined more so based on adults, children, and adolescents. If not occurring together in *hypogonadism* as hypoandrogenism (Leydig cell dysfunction), other testicular cell populations, germ cells, or Sertoli cells are considered for possible dysfunction.[5] Approximately 70% of children with *hypogonadism* are misdiagnosed based on serum gonadotropin measurement.[19] Male adolescents may present with few typical signs of adult *hypogonadism*, and biochemical androgen levels must be followed-up in the younger cohorts of men so effective clinical research strategies can be recommended.[5] Diagnosing hypoandrogenism in healthy adolescents can be challenging, as the symptoms correlating with a decreased T level are different than in the elderly population. In a recent study, hypogonadal symptoms in men younger than 40 years were associated with a total T level of less than 400 ng/dL. Of the hypogonadal symptoms evaluated with the Aging Male (ADAM) questionnaire, "lack of energy" seems to be the most acute symptom that predicts a total T level of less than 400 ng/dL in men younger than 40 as opposed to erectile dysfunction and decreased libido, which were more frequent complaints in the elderly population.[20] Symptoms of fatigue and lack of energy may be more specific in the younger adult cohort than sexual symptoms. There is increasing evidence that anti-Mullerian and inhibin B levels can improve the sensitivity and result in earlier diagnosis, ultimately allowing treatment to start at a younger age.[5]

Older men have been known to have had declines in serum T levels for some time. However, researchers disputed whether this process naturally occurred or if it was secondary to concurrent comorbidities and related factors.[2] The age-related decrease in T reflects general age-related cellular degeneration, reduced number of functional Leydig cells, and atherosclerosis of testicular arterioles.[21] Increasing age also brought about gradual decreases in free and total T, with increases in gonadotropins, LH, and FSH.[2] The difference between the decline of total T and free T during aging is an age-related increase in the circulating concentration of sex hormone–binding globulin (SHBG), reducing free T proportion.[22]

In the developing world, several increasing conditions may be shifting the prevalence of *hypogonadism* to a younger age, including diabetes, obesity, and increasing rates of opioid use.[23] With the increasing epidemic of adolescent and young adult obesity and type II diabetes, it is plausible that these conditions, in isolation or

tandem, may explain lower-than-average androgen levels in patients aged 20 to 40 years.[5] Opioid-induced androgen deficiency has increased dramatically in the last 10 to 15 years. Sexual dysfunction is reported in 85% of heroin addicts and 81% on a stable methadone maintenance regimen, although this might be due to additional factors.[24] Chronic opioid use disrupts the HPGA creating secondary *hypogonadism*. Opioid receptors μ (MOR), δ (DOR), and κ (KOR) are present in the hypothalamus and the pituitary, with activation leading to a suppressed HPGA and subsequent decrease in serum T within hours of opioid administration.[25] Exposure to several environmental toxins may also contribute to *hypogonadism*, notably Sertoli and germ cell dysfunction. Tobacco smoke contains highly carcinogenic nitrosamines, polycyclic aromatic hydrocarbons (benzopyrene), and volatile organic compounds (benzene).[5] Increased seminal levels of reactive oxygen species from smoking impair sperm function, and data show that nicotine and its metabolites can cross the blood-testis barrier.[26]

Understanding Hypogonadism

TD occurring during adulthood (ie, late-onset *hypogonadism* [LOH]) is a common condition, representing the main endocrine concern in the aging men.[27] Signs and symptoms of low androgen levels include reduced sexual desire and activity, erectile dysfunction, decreased spontaneous erections, incomplete or delayed sexual development, small testes, gynecomastia, loss of body hair/reduced shaving, subfertility, and reduced bone mass. Less specific symptoms and signs are decreased energy and motivation, reduced physical performance, depressed mood, poor concentration and memory, sleep disturbances, anemia, reduced muscle mass, and increased body fat.[5] The benefits of T concerning mental health, mood, cognition, bone density, and pain control should be considered.[2] Clinicians should consider the overlap of TD and chronic conditions when performing the diagnostic workup for *hypogonadism*.[27]

Hypogonadism can result from multifactorial conditions, and finding an ideal therapy cannot be a one-size-fits-all approach.[5] Chronic diseases could impair sexual functioning but do not affect sexual motivation, as TD does. Chronic illnesses and TD can be considered overlapping conditions, often sharing the same phenotype and hormonal alterations.[27] There are weak associations between signs and symptoms and serum T levels in aging men. The unimpressive positive likelihood ratios may be because many symptoms and signs of low T are nonspecific—resulting from other comorbid conditions commonly occurring in older men.[28] The condition of primary testicular dysfunction (lower total and free T and high gonadotropins) and its related symptoms (higher ANDROTEST score) are often present in subjects with chronic morbidities. Because hypogonadal symptoms, including the sexual ones and penile blood flow, are known to be affected by T levels, the relative weight and mutual effect of the Chronic Disease Score and total T on these associations were evaluated.[27] Low T level has implications for metabolic health in both men and women and can be a risk factor because it correlates with metabolic syndrome and all-cause mortality.[29] Men with TD not receiving TTh experience a significant increase in body weight, waist size, and deterioration in glycemic control over time. Being overweight or obese underscores the importance of also considering the risks of untreated TD.[30] Many causes of hypoandrogenism in adolescents may be transient, which will resolve low androgen levels once the underlying condition is improved or resolved. **Fig. 2** lists the known disorders of congenital or acquired means of the testicular (primary *hypogonadism*) or HPGA (secondary *hypogonadism*) conditions leading to androgen deficiency.[10]

Fig. 2. Causes of hypogonadism.

Presentation

Cardiovascular

The bidirectional role of T and cardiovascular risk is confounding. Some studies claim that TTh increases cardiovascular (CV) risk. Conversely, some studies demonstrate that low T is a CV risk marker, which improves with normalizing T levels after exogenous T administration. This potential CV risk has resulted in the Food and Drug Administration (FDA) releasing a statement about the potential risk associated with TRT.[31] In a large retrospective study with extended follow-up of more than 83,000 male veterans, normalizing T levels after TTh significantly reduced all-cause mortality, myocardial infarction, and stroke.[32] A meta-analysis of observational studies from 1988 to 2017, which consisted of 43,041 men with an average age of 63.5 years, demonstrated that low T in aging men is a marker of CV risk.[33] The lack of adequately powered and long-term randomized control trials on the efficacy and safety of TTh has not helped. However, in 2018 the Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and efficacy ResponSE in hypogonadal men (TRAVERSE) trial became underway. The TRAVERSE study was a double-blind placebo, parallel-group, noninferiority, multicentered controlled trial that randomized approximately 6000 men, ages 45 to 80 years, with baseline serum T less than 300 with hypogonadal symptoms and preexisting CV disease or increased CV risk. The men were randomized to a 1.62% T or placebo gel.[7] The trial was completed on Jan 7, 2023, with results currently being compiled. The required reporting date is Jan 19, 2024.[34]

Sexual function

Sexual symptoms are the most related explicitly to androgen deficiency.[35] The loss of sexual desire seems as the most genuine hallmark of TD. The presence of a specific association between sexual symptoms and TD is not enough to establish the direction of the relationship; in fact, TD may be responsible for causing the symptoms or the other way around. Symptoms of LOH encompass various domains, including psychological, physical, and sexual disturbances.[27] Studies related to the sexual domain (ie, reduced libido and reduced spontaneous or sexual-related erections) show a syndromic association with TD. Therefore, they could represent a valuable correlate to

define a symptomatic LOH.[21] When TD is suspected in men with chronic illnesses, hypoactive sexual desire could help outline an androgen deficiency–related clinical phenotype. Hypoactive sexual desire is more severe in hypogonadal groups irrespective of health status, thus strengthening the concept that sexual desire depends on T with limited influence of chronic conditions.[27]

Musculoskeletal strength

Lower levels of androgens contributed to decreased lean muscle mass, strength, and size.[36] Sex hormones play a critical role in the maintenance and growth of bone in both men and women. Androgen receptors manifest in chondrocytes in growth plates, osteoblasts, and osteocytes.[2] The most acute effects of testosterone on bone are its aromatization to estradiol, which activates bone α and β estrogen receptors, decreasing bone resorption, and increasing bone mineral density.[37] Bone mineral density of the vertebral bone with idiopathic osteoporosis in men increases with TTh. T has also been shown to have associations with vitamin D, which plays a vital role in calcium homeostasis.[2]

The development and progression of chronic diseases are correlated with low T levels and inflammatory biomarkers, but their mechanisms remain poorly understood.[38] A low T level is correlated with a high level of adipokines and inflammation, and T therapy is necessary to restore the physiologic and hormonal levels.[38] Androgen therapy in older men with T deficiency improves physical efficiency and reduces the risk of rehospitalization.[39] Musculoskeletal benefits do not persist after cessation of TTh. Lean body mass decreases within 6 months after discontinuing TTh, although it remains higher than baseline. Strength training in older men with low to normal T levels improved muscle function but not lean body mass. Combined with TTh, strength training led to increased muscle function and mass. In this study, TTh alone did not improve function or mass over the study period.[2]

Obesity/insulin efficiency

Obesity is a decisive risk factor for TD, which further increases fat accumulation, insulin resistance, and deterioration of glycemic control, creating a vicious circle.[40] The obesity-related decline of T levels is multifactorial.[20] These body composition changes from T have metabolic effects.[41] It can be associated with decreased SHBG or an increased conversion of T to estrogen by peripheral adipose tissue.[20] T and estradiol levels interact to increase muscle mass and decrease body fat.[36] T benefits affect lean muscle mass and body fat.[2] It is well documented that TTh consistently results in a significant reduction in fat mass and an increase in lean mass.[42] This body composition changes from T have metabolic effects.[41] Men with low T are suspectable to increased insulin resistance.[43] Low T is associated with insulin resistance even in young nonobese men.[43] The underlying cause of *hypogonadism* in young obese men is the possibility of a concurrent diagnosis of type 2 diabetes mellitus, which has been increasing at a yearly rate of 4.8% compared with 1.8% for type 1.[44] Seventy-three percent of men with reduced T were overweight or obese, and serum T in men with a body mass index (BMI) greater than 30 kg/m^2 was 5 nmol/L lower than those with average weight.[45]

Cognition/mood

Aging is associated with cognitive decline, including verbal and visual memory, executive function, and spatial ability.[46–48] Aging in men is also associated with reduced serum T, raising the possibility that reduced circulating T concentration may contribute to age-related cognitive decline. Support for this hypothesis comes from studies of clinical conditions that cause low T levels, epidemiological investigations,

and small randomized trials showing improved memory with T supplementation. Among psychological traits, depressive symptoms were the most specific to low T, associated with it independently of comorbidities.[27] A meta-analysis explicitly focusing on the effects of TTh on mood found an improvement in T-treated men, which was maintained independently of a chronic condition.[5]

Prostate cancer

In healthy men, the androgen T and its derivative DHT are essential for cell survival and function of the prostate.[49] Low serum T was associated with a higher risk of poorly differentiated PCa, albeit BMI was not considered in the data analysis.[49] PCa cells exhibit excess activation of the androgen signaling pathway, resulting in the uncontrolled proliferation of tumor cells.[50] Almost all PCa tumors will initially respond to androgen deprivation therapy (ADT). However, with long-term T suppression, some cell populations become refractory, and eliminating T production from the testes is no longer sufficient to suppress tumor cell growth entirely.[51] This growth is called castration-resistant PCa, which an increasing prostate-specific antigen determines in an environment where T levels are castrated. There is increasing evidence that deficient nadir T levels, particularly during the first few months of ADT, and the absence of micro-surges and escapes in T may be associated with improved clinical outcomes, including survival.[52] This low T environment seems to promote the development of a less differentiated, aggressive cancer phenotype.[53]

Treatment

There is much to consider by both the patient and the provider when initiating TTh. Historically, TTh has been the most used option in treating primary and *secondary hypogonadism*.[54] However, for *secondary hypogonadism*, there are very effective additional treatment options available that have been used off-label for some time. As mentioned previously, *secondary hypogonadism* results in an interruption in T production due to the HPGA. This interruption could include *age-related hypogonadism*, *obesity-related hypogonadism, opioid-induced hypogonadism*, metabolic syndrome, and type 2 diabetes mellitus.[55]

Various formulations of TTh exist, offering options with different pharmacologic profiles, delivery methods, and half-lives. T formulations with shorter half-lives are more consistent with endogenous T production but often result in nonadherence due to the multiple-day dosing.[56] Longer-acting formulations have proved much more feasible for patients, with some preparations only requiring weekly and even monthly administration. One delivery method is implanted under the skin once every 2 to 4 months. However, there are drawbacks to the more prolonged duration preparations. The longer the half-life, the higher the likelihood of adverse effects, for example, impaired sperm parameters.[56]

DELIVERY METHODS

As mentioned earlier, there are various routes of delivery and formulations available on the market today. Each delivery route brings advantages and disadvantages. In short-acting formulations, the advantage is convenience and painless application. Short-acting delivery methods include intranasal sprays; transdermal applications such as a gel, cream, or patch; and oral formulations in capsules and troches.

Natesto intranasal is a nasal spray used daily. Some of the adverse effects associated with its use include mucosal dryness, rhinorrhea, epistaxis, and even upper respiratory tract infections. Although, these adverse reactions occur in less than 9% of those who use them.[56] *Fortesta Gel*, *AndroGel*, and *Testim Gel* are topical compounds

applied under the arm or behind the knee daily. The most common adverse reaction reported was skin irritation.[56] An important consideration with gels and creams is the risk of transference if one should contact another person. *Androderm* patches are transdermal patches applied to the skin daily. Gurayah and colleagues[56] cite a study demonstrating that up to 18.8% of patients who used *Androderm* patches experienced administration site reactions, that is, pruritis and erythema. *Jatenzo* and *Tlando* are daily oral capsules. With *Jatenzo*, elevated hematocrit was higher than all other formulations and resulted in higher blood pressure in a few participants.[56] *Tlando* resulted in elevated levels of prolactin and weight gain.[56]

Long-acting formulations also bring with them their advantages and disadvantages. Longer-acting formulations require fewer administrations throughout the month. These formulations come in the form of injectable T and subcutaneous pellets. Injectable T has been used since the late 1930s and has proved to maintain T levels.[3] The first T injectable was called testosterone propionate. With a half-life of 1 to 2 days, testosterone propionate was discontinued due to other formulations with longer half-lives. Testosterone cypionate and enanthate are the gold standards for injectable TTh. They both have similar half-lives of approximately 8 days. Risks of injectable T include bleeding and discomfort. Testosterone undecanoate is administered every 10 to 12 weeks. Unlike testosterone cypionate and enanthate, testosterone undecanoate must be administered by a health care professional due to its ability to cause microembolism and anaphylaxis.[3] Testosterone cypionate and enanthate can be self-administered at home.

Subcutaneous T pellets are inserted under the skin into the soft tissue every 2 to 4 months. Some providers will insert pellets for up to 6 months. Each subcutaneous pellet contains 75 mg of T. The number of pellets inserted depends on the BMI of the patient. A person with a BMI greater than 25 can have up to 12 pellets inserted. The risks associated with subcutaneous pellets include rejection, injection site infection, hemorrhage, fibrosis, or scarring with prolonged use of T pellets. In addition, if one's laboratory result values do not reflect optimal dosing after insertion, another incision is required to insert additional pellets.

POTENTIAL ALTERNATIVE USES

Exogenous T has demonstrated many benefits regarding sexual health in men, including enhanced libido and improved erection quality. However, exogenous T is known to interfere with the HPGA, resulting in decreased production of LH and FSH. The following result is testicular atrophy and oligospermia. There is a contraindication for TTh in men who have inclinations of having children soon. However, there are other options available for men in this demographic. Gonadotropins, aromatase inhibitors, and selective estrogen receptor modulators (SERMS) effectively treat secondary hypogonadism while maintaining fertility.[3,8]

Exogenous gonadotropins, similar to human chorionic gonadotropin, stimulate the Leydig cells to produce T because of their similarity to LH and have been effectively used in men with oligospermia or azoospermia.[3] These medications are administered intramuscularly or subcutaneously. Aromatase inhibitors, such as anastrazole, preserve T levels by inhibiting the aromatization of T to estradiol. Aromatase inhibitors can maintain therapeutic T levels without affecting sperm counts. However, over time, these medications can cause deficient estrogen levels, resulting in decreased bone density and increased risk of fractures.

SERMS show the most promise. In addition to maintaining fertility and increasing baseline T levels, SERMs are not shown to cause supratherapeutic T levels.[54]

Clomiphene citrate, also known as Clomid, was introduced in the 1960s for women and is the most widely used SERM for treating *hypogonadism* in men wishing to have children. Ide and colleagues reviewed 5 randomized controlled trials on the use of SERMs for hypogonadal men. In one study, out of 400 men treated with clomiphene citrate for 25.5 months, only 8% reported side effects. The most common side effects were mood changes, blurred vision, breast tenderness, and weight gain. These side effects were a result of elevated estradiol levels. Another study of 46 men treated for more than 12 months reported no side effects. Despite not being FDA approved for use in men or patients with *hypogonadism*, the extensively researched use of this "off-label" indication proves to effectively treat men for this purpose.[8] However, despite its known safety and efficacy, more research is needed.

Clomiphene citrate consists of 2 isomers, enclomiphene, the trans-isomer, and zuclomiphene, the cis-isomer. Enclomiphene is an estrogen antagonist, whereas zuclomiphene is an estrogen agonist. This distinction is why clomiphene citrate has caused elevated estradiol levels in some.[57] Enclomiphene is more potent than clomiphene, causing more significant increases in serum T levels while, in some studies, significantly raising sperm counts.[57] Enclomiphene is well tolerated and causes mild side effects in a low percentage of those studied. The most concerning adverse effect of SERMs is the increased risk of venous thromboembolism. According to Earl and Kim,[57] this incidence has been very low. Other side effects include headache 3.3%, nausea 2.1%, diarrhea 1.9%, nasopharyngitis 1,7%, hot flashes 1.7%, arthralgia 1.2%, and dizziness 1%.[57] Enclomiphene demonstrates significant effectiveness in raising baseline T levels while preserving fertility and without raising estrogen levels. However, the FDA did not approve the drug because the lack of data indicates improvement in clinical symptoms; this is an area of research that should be explored. Much more could be discussed here, but it is beyond the scope of this article.

REPLACEMENT THERAPY VERSUS OPTIMIZATION

TTh is a T treatment regimen that results in therapeutic serum T levels. T optimization refers to optimizing T levels for maximum benefit and well-being without achieving supratherapeutic levels well above the established reference ranges. The US serum T reference ranges from 264 to 916 ng/dL for healthy, nonobese men. Many providers will not initiate T treatment if the total serum T is less than 264, despite having symptoms consistent with *hypogonadism*.

The Endocrine Society's stance on T optimization is that TTh, when initiated, should raise serum total T only up to the mid-normal range, which is approximately 426 ng/dL.[28] They also recommend that it should only be initiated when multiple unequivocal tests demonstrate low levels of serum total testosterone paired with signs and symptoms of TD. However, as recognized by the American Urological Association, there are men with total T levels greater than 300 ng/dL who exhibit conclusive and significant signs and symptoms of *hypogonadism* and have experienced symptomatic improvement with TTh. Thus, TTh aimed at raising serum total T to optimized therapeutic levels should be considered in those cases. The use of sound clinical judgment and discussing risks versus benefits with the patient is strongly encouraged.

Many studies demonstrating little or no benefit when initiating TTh provide little information about the maximum serum T levels attained in the men tested. Are the subject's serum total T levels at the low standard or mid-standard value? More research should be conducted on the impact of optimized serum T levels on symptomatic hypogonadal men.

DISCUSSION

T, once touted as "the Elixir of Life," is a hormone found in both men and women. In men, most T is produced by the Leydig cells in the testicles when stimulated by the LH. T has been shown to improve bone health and density. Therapeutic levels of T also increase sexual function and libido, physical performance, strength, lean body mass, and cognitive function. However, supratherapeutic levels can cause mood swings, increased sebum production resulting in acne, elevated estradiol levels, erythrocytosis, increased incidence of male pattern baldness, and can worsen sleep apnea.

Over the last 3 decades, there has been increased interest in TTh. This trend results from increasing obesity rates, an aging population, and endocrine disruptors in our foods and environment. In addition, there has been a surge in Men's Health clinics and online direct-to-consumer Web sites, making TTh much more readily accessible. The potential risks associated with supratherapeutic levels of T have created conflicting guidelines and treatment strategies for many organizations across the globe for diagnosing and prescribing *hypogonadism*. The inconsistency of standards has led to confusion and uncertainty among prescribers. Much of the confusion lies wherein the total serum T is in the low normal range, but signs and symptoms of *hypogonadism* still exist. T optimization should be considered within this realm with close follow-up and reevaluation of signs and symptoms after initiating TTh. Clinical judgment and provider-patient discussions about risk versus benefit are necessary.

These days there are many T delivery methods to consider. Longer-acting T injections, including T cypionate and enanthate, provide more patient advantages due to convenience and effectiveness. Other delivery forms include shorter-acting formulations in the form of daily gels, creams, transdermal patches, and daily capsules. Lastly, subcutaneously inserted T pellets last up to 4 to 6 months. In men considering having children, the contraindication of T is due to its negative effect on spermatogenesis, in these men. SERMs such as enclomiphene citrate provide normalization of T levels while having positive effects on sperm counts. Although these medications have proved effective and well tolerated, SERMs are not FDA approved for treating hypogonadal men and have long been used off-label.

SUMMARY

As more men seek to increase their T levels, more long-term random control studies are needed to gain better insight into T optimization to support the anecdotal observation commonly experienced in the practice setting. In addition, studies evaluating the risks and benefits of effective off-label treatment options such as SERMs should be considered. Lastly, an ever-growing number of women are turning to TTh. In this population, there lies tremendous opportunity for research focused on T optimization and those undergoing gender transitional care.

Video content accompanies this article at http://www.nursing.theclinics.com.

CLINICS CARE POINTS

- The use of screening tools, like the Androgen Deficiency Men (A.D.A.M Questionnaire), is useful at the beginning of treatment and when reassessing effectiveness of treatment.
- LH and FSH are useful lab tests in determining whether someone has been primary or secondary hypogonadism and should always be included initially.

- Despite a seemingly limitless number of delivery methods for Testosterone Therapy, Injectable testosterone has remained as the most consistent and reliable.
- Because of the negative effect of testosterone on spermatogenesis, it is strongly recommended to verify full understanding by both the patient and the partner before initiating therapy.

DISCLOSURE

The authors of this article do not have any commercial or financial conflicts of interest in addition to not having any funding sources.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.cnur.2023.07.001.

REFERENCES

1. Brown-Séquard CE. Note on the effects produced on man by subcutaneous injections of a liquid obtained from the testicles of animals. Lancet 1889;134:105–7.
2. Tyagi V, Scordo M, Yoon RS, et al. Revisiting the role of testosterone: are we missing something? Rev Urol 2017;19(1):16.
3. Ugo-Neff G, Rizzolo D. Hypogonadism in men: updates and treatments. Jaapa 2022;35(5):28–34.
4. Lopez DS, Qiu X, Advani S, et al. Double trouble: co-occurrence of testosterone deficiency and body fatness associated with all-cause mortality in US men. Clin Endocrinol 2018;88(1):58–65.
5. Cohen J, Nassau DE, Patel P, et al. Low testosterone in adolescents & young adults. Front Endocrinol 2020;10:916.
6. Khera M, Adaikan G, Buvat J, et al. Diagnosis and treatment of testosterone deficiency: recommendations from the Fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med 2016;13(12):1787–804.
7. Bhasin S, Lincoff AM, Basaria S, et al, TRAVERSE Study Investigators. Effects of long-term testosterone treatment on cardiovascular outcomes in men with hypogonadism: rationale and design of the TRAVERSE study. Am Heart J 2022;245:41–50.
8. Ros CTD, Ros LUD, Ros JPUD. The role of clomiphene citrate in late onset male hypogonadism. Int Braz J Urol 2022;48:850–6.
9. Bain J, Brock G, Kuzmarov I. International consulting group canadian society for the study of the aging male: response to Health Canada's position paper on testosterone treatment. J Sex Med 2007;4:558–66.
10. Salonia A, Rastrelli G, Hackett G, et al. Pediatric and adult onset hypogonadism. Nat Rev 2019;5:1–21.
11. Simpson ER, Mahendroo MS, Means GD. Aromatase cytochrome P450, the enzyme responsible for estrogen biosynthesis. Endocr Rev 1994;15:342–55.
12. Corona G, Mannucci E, Petrone L, et al. ANDROTEST: a structured interview for the screening of hypogonadism in patients with sexual dysfunction. J Sex Med 2006;3(4):706–15.
13. Morley JE, Perry HM, Kevorkian RT, et al. Comparison of screening questionnaires for the diagnosis of hypogonadism. Maturitas 2006;53(4):424–9.

14. Chen W, Liu ZY, Wang LH, et al. Are the aging male's symptoms (AMS) scale and the androgen deficiency in the aging male (ADAM) questionnaire suitable for the screening of late-onset hypogonadism in aging Chinese men? Aging Male 2013; 16(3):92–6.
15. Bernie AM, Scovell JM, Ramasamy R. Comparison of questionnaires used for screening and symptom identification in hypogonadal men. The Ageing Male 2014;17(4):195–8.
16. Crawford ED, Heidenreich A, Lawrentschuk N, et al. Androgen-targeted therapy in men with prostate cancer: evolving practice and future considerations. Prostate Cancer Prostatic Dis 2019;22(1):24–38.
17. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2006;91:1995–2010.
18. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2018;103:1715–44.
19. Grinspon RP, Freire AV, Rey RA. Hypogondism in pediatric health: adult medicine concepts fail. Trends Endocrinol Metab 2019;30:879–90.
20. Scovell JM, Ramasamy R, Wilken N, et al. Hypogonadal symptoms in young men are associated with a serum total testosterone threshold of 400 ng/dL. BJU Int 2015;116:142–6.
21. Rastrelli G, O'Neill TW, Ahern T, et al. Symptomatic androgen deficiency develops only when both total and free testosterone decline in obese men who may have incident biochemical secondary hypogonadism: prospective results from the EMAS. Clin Endocrinol 2018;18:459–69.
22. Varimo T, Miettinen PJ, Känsäkoski J, et al. Congenital hypogonadotropic hypogonadism, functional hypogonadotropism or constitutional delay of growth and puberty? An analysis of a large patient series from a single tertiary center. Hum Reprod 2016;32:147–53.
23. Shi Z, Araujo AB, Martin S, et al. Longitudinal changes in testosterone over five years in community-dwelling men. J Clin Endocrinol Metab 2013;98:3289–97.
24. Vowles KE, McEntee ML, Julnes PS, et al. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain 2015; 156:569–76.
25. Grover S, Mattoo SK, Pendharkar S, et al. Sexual dysfunction in patients with alcohol and opioid dependence. Indian J Psychol Med 2014;36:355–65.
26. Durairajanayagam D. Lifestyle causes of male infertility. Arab J Urol 2018;16: 10–20.
27. Rastrelli G, Corona G, Maggi M. Both comorbidity burden and low testosterone can explain symptoms and signs of testosterone deficiency in men consulting for sexual dysfunction. Asian J Androl 2020;22(3):265.
28. Millar AC, Lau AN, Tomlinson G, et al. Predicting low testosterone in aging men: a systematic review. CMAJ (Can Med Assoc J) 2016;188(13):E321–30.
29. Bianchi V. Metabolic syndrome, obesity paradox and testosterone level. Endocrinol Metab Syndr 2015;4(172):1–16.
30. Hackett G, Cole N, Mulay A, et al. Long-term testosterone therapy in type 2 diabetes is associated with decreasing waist circumference and improving erectile function. World J Mens Health 2020;38:68–77.
31. Gagliano-Jucá T, Basaria S. Testosterone replacement therapy and cardiovascular risk. Nat Rev Cardiol 2019;16(9):555–74.

32. Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J 2015;36(40):2706–15.
33. Corona G, Rastrelli G, Di Pasquale G, et al. Endogenous testosterone levels and cardiovascular risk: meta-analysis of observational studies. J Sex Med 2018; 15(9):1260–71.
34. FDAA Trials Tracker retrieved from. Available at: https://fdaaa.trialstracker.net/trial/NCT03518034/. Accessed March 1, 2023.
35. Rastrelli G, Corona G, Tarocchi M, et al. How to define hypogonadism? Results from a population of men consulting for sexual dysfunction. J Endocrinol Invest 2016;39:473–84.
36. Finkelstein JS, Lee H, Burnett-Bowie SA, et al. Gonadal steroids and body composition, strength, and sexual function in men. N Engl J Med 2013;369: 1011–22.
37. Kalb S, Mahan MA, Elhadi AM, et al. Pharmacophysiology of bone and spinal fusion. Spine J 2013;13:1359–69.
38. Bianchi VE. The anti-inflammatory effects of testosterone. Journal of the Endocrine Society 2019;3(1):91–107.
39. Baillargeon J, Deer RR, Kuo YF, et al. Androgen therapy and rehospitalization in older men with testosterone deficiency. Mayo Clin Proc 2016;91(No. 5):587–95. Elsevier.
40. Caliber M, Saad F. Testosterone therapy for prevention and reversal of type 2 diabetes in men with low testosterone. Curr Opin Pharmacol 2021;58:83–9.
41. Dandona P, Dhindsa S, Ghanim H, et al. Mechanisms underlying the metabolic actions of testosterone in humans: a narrative review. Diabetes Obes Metab 2021;23:18–28.
42. Skinner JW, Otzel DM, Bowser A, et al. Muscular responses to testosterone replacement vary by administration route: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle 2018;9:465–81.
43. Contreras PH, Serrano FG, Salgado AM, et al. Insulin sensitivity and testicular function in a cohort of adult males suspected of being insulin-resistant. Front Med 2018;5:190.
44. Levine H, Jørgensen N, Martino-Andrade A, et al. Temporal trends in sperm count: a systematic review and meta-regression analysis. Hum Reprod Update 2017;23:646–59.
45. Poobalan A, Aucott L. Obesity among young adults in developing countries: a systematic overview. Curr Obes Rep 2016;5:2–13.
46. Cherrier MM, Asthana S, Plymate S, et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. Neurology 2001;57(1):80–8.
47. Amanatkar HR, Chibnall JT, Seo BW, et al. Impact of exogenous testosterone on mood: a systematic review and meta-analysis of randomized placebo-controlled trials. Ann Clin Psychiatry 2014;26:19–32.
48. Culig Z, Santer FR. Androgen receptor signaling in prostate cancer. Cancer Metastas- Rev. 2014;33:413–27.
49. Price L, Said K, Haaland KY. Age-associated memory impairment of logical memory and visual reproduction. J Clin Exp Neuropsychol 2004;26(4):531–8.
50. Ceder Y, Bjartell A, Culig Z, et al. The molecular evolution of castration-resistant prostate cancer. Eur Urol Focus 2016;2:506–13.
51. Parimi V, Goyal R, Poropatich K, et al. Neuroendocrine differentiation of prostate cancer: a review. Am J Clin Exp Urol 2014;2:273–85.

52. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology 2007;132:2208–25.
53. Weng H, Li S, Huang JY, et al. Androgen receptor gene polymorphisms and risk of prostate cancer: a meta-analysis. Sci Rep 2017;7:40554.
54. Ide V, Vanderschueren D, Antonio L. Treatment of men with central hypogonadism: alternatives for testosterone replacement therapy. Int J Mol Sci 2020;22(1):21.
55. Rodriguez KM, Pastuszak AW, Lipshultz LI. Enclomiphene citrate for the treatment of secondary male hypogonadism. Expet Opin Pharmacother 2016; 17(11):1561–7.
56. Gurayah AA, Dullea A, Weber A, et al. Long vs short acting testosterone treatments: a look at the risks. Urology 2023;172:5–12.
57. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metabol 2018;103(5):1715–44.