REVIEWS IN UROLOGY

Contemporary Management of Male Hypogonadism

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Abstract

Background: Male hypogonadism affects up to 40% of men and is becoming more prominent because of increasingly prevalent medical comorbidities. Because various forms of treatment are available today, physicians should discuss drug efficacy and safety while simultaneously ensuring that therapy forms are in alignment with patient preferences. Treatment adherence is critical to sustaining patient health outcomes.

Methods: A database search was conducted in PubMed using a sensitive search approach. Abstracts were assessed for relevance, and papers were read in depth if more details were required to collect current data about the search topic. Relevant results were further researched in the US Food and Drug Administration's product classification database for label and approval information.

Results: Exogenous testosterone replacement therapy is the most common treatment for male hypogonadism and includes injectables, nasal gels, topical therapy, subcutaneous pellets, and oral medications. Injectables are widely available and cost-effective and remain the most popular option, though they have a higher rate of adverse effects. Topical testosterone replacement therapy offers a no-pain solution, but absorption and clinic outcomes can vary, and the risk of transference remains high. Oral medications are a promising newer option that may provide convenience and efficacy while minimizing the risk for adverse effects.

Conclusion: Various routes of administration provide patients with a multitude of treatment options, potentially increasing adherence rates. Physicians should discuss the risks and benefits of each form of testosterone replacement therapy with each patient while considering pharmacokinetics, dose response, side effect profiles, and patient preference factors.

KEYWORDS:
Hypogonadism; testosterone deficiency; hormone replacement therapy

Male hypogonadism refers to a reduction in the functioning of the male gonads, which decreases the output of the sex hormone testosterone.[1,2] Commonly identified as testosterone deficiency (TD), male hypogonadism is characterized by serum testosterone levels below the normal range. Testosterone is responsible for the development of many characteristically masculine traits: the production of sperm, male hair growth patterns, fertility, libido, and the development of muscle mass.[3] According to the American Urological Association (AUA), TD is defined by serum testosterone levels below 300 ng/dL.[4]

Age has long been identified as an important parameter associated with TD, but male hypogonadism has further been linked to dietary patterns, metabolic syndrome, sleep disturbances, and increasing rates of obesity.[5] Male hypogonadism is therefore of growing medical interest and currently affects 10% to 40% of men, depending on diagnostic criteria.[6] As TD becomes more prevalent, it is important to understand the various treatments

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available to address the clinical presentation of male hypogonadism while accommodating patients by offering multiple therapy options, thus promoting better treatment adherence and health outcomes.

Diagnostic Evaluation

Prominent guidelines available for diagnosing TD include those provided by the Endocrine Society and the AUA. The guidelines encourage testing high-risk patients based on various comorbid factors such as type 2 diabetes, sleep apnea, and obesity.[4] The presence of symptoms is also a necessary diagnostic criterion, though many symptoms of male hypogonadism, including erectile dysfunction, low libido, and fatigue, are nonspecific and can have an array of etiologies, necessitate additional testing and potentially delaying diagnosis and treatment. The Endocrine Society stresses the evaluation of patients who present with consistent symptoms associated with male hypogonadism and whose testosterone levels prove to be consistently low.[4]

Diagnostic findings in physical examinations might pertain to comorbidities such as high body mass index, obesity, and osteoporosis, but they are generally nonspecific. Patients who have been diagnosed with TD should undergo further evaluation to determine the root cause and type of male hypogonadism as well as the location of the dysfunction (hypothalamic, pituitary, or testicular).[4] Measuring serum levels of pituitary hormones such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH) can help discriminate between primary and secondary hypogonadism, a relevant distinction when identifying the best form of treatment for patients.

The primary diagnostic criterion for male hypogonadism remains a laboratory assessment of the patient's morning total serum testosterone levels—which should be repeated at least once to confirm the patient's diagnosis—along with the presence of symptoms. The AUA considers 300 ng/dL a realistic threshold for the diagnosis of low testosterone, and this measurement should be viewed as a guide for clinicians.[4] Different sources in the literature provide varying definitions of what constitutes a "normal range," though, prompting physicians to take many factors into account, including age, stress level, and concomitant medications. Most commonly, this transitional range can be anywhere from 280 mg/dL to 350 mg/dL.[7]

The higher prevalence of TD has led to an increase in the number of testosterone prescriptions. From 2007 to 2014, the number of testosterone prescriptions among Medicare patients increased by an

ABBREVIATIONS

AUA	American Urology Association
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
hCG	human chorionic gonadotropin
IM	intramuscular
LH	luteinizing hormone
TD	testosterone deficiency
TRT	testosterone replacement therapy
TU	testosterone undecanoate

SUMMARY OF MAIN POINTS

- Testosterone deficiency is increasing in prevalence, likely as a result of the concurrent increase in comorbid conditions such as obesity, type 2 diabetes, and sleep apnea. Testosterone prescriptions have increased wildly in the last 15 years. Though some medications are used off-label to promote endogenous testosterone production, all FDA-approved therapies for TD rely on exogenous testosterone replacement.
- Cost-effective injectable testosterone (cypionate and enanthate) remains the most commonly prescribed form of TRT, but these formulations also have the highest rates of secondary erythrocytosis. They can also lead to supraphysiologic and subphysiologic levels of serum testosterone throughout the dose interval, which can be reflected in symptomatic changes.
- Topical testosterone is a pain-free alternative to injection therapy, with many products available, ranging from gels to transdermal patches. The risk of transference to women and children and inconsistent absorption rates remain concerns.
- Oral testosterone is the newest form of TRT, with its first formulation, Jatenzo, approved in the United States in 2019. Two more TU formulations have been approved since then: Tlando and Kyzatrex. Oral TU is taken twice daily with food and has the potential to be a convenient, pain-free, and easy-to-administer alternative when compared with traditional TRT methods.

average of 15.5% annually. From 2016 to 2019, the number of testosterone prescribers increased a mean of 8.89% annually.[8] Testosterone therapy has therefore garnered substantial interest among clinicians of varying specialties, suggesting a need for greater clarity about the forms of therapy available today.

Disease Management

For patients who have been diagnosed with male hypogonadism, initial disease management should include lifestyle modifications such as dietary, weight-loss, and muscle-building interventions. Poor diet can contribute to increased visceral fat and a higher body mass index and can fuel comorbidities such as obesity, increasing a patient's chances of developing male hypogonadism.[5] Lifestyle modification should therefore remain an important part of treatment, even when patients undergo active testosterone therapy. Depending on an array of variables, such as the etiology of a case of hypogonadism and the patient's desire for future fertility, disease management options mainly consist of (1) increasing the endogenous production of testosterone and (2) exogenously replacing testosterone. Testosterone replacement therapy (TRT) includes treatment with most forms of testosterone and is available through various routes of administration, including oral medications, injectables, topical agents, and pellets surgically inserted near the hip.

RESTORING ENDOGENOUS PRODUCTION OF TESTOSTERONE

The primary reason for stimulating the internal testosterone production system is to preserve fertility in patients diagnosed with male hypogonadism. Endogenous therapy promotes the increase of testosterone production by the body itself, either through increased secretion from the testes or by preventing testosterone aromatization into estrogen. A variety of medications are commonly used for this purpose in an off-label manner.

Clomiphene citrate, a selective estrogen receptor modulator, acts on the pituitary gland to increase the secretion of LH and FSH, thereby increasing testosterone levels and promoting spermatogenesis.[9] Clomiphene has long been used as an off-label treatment for male hypogonadism and male infertility because of this effect, but a large percentage of patients who take clomiphene do not report substantial symptom improvement, despite numerical increases in total serum testosterone. An alternative is human chorionic gonadotropin (hCG), a form of injection therapy that has been studied in patients with male hypogonadism, which acts similarly to LH. In its role in treating anabolic steroid–induced hypogonadism by limiting side effects such as testicular atrophy and as an adjunct to TRT, hCG can also be used to boost endogenous testosterone production.[10] The limitations of hCG include its relatively high financial cost and the fact that hCG regimens usually involve multiple injections per week.

Aromatase inhibitors, such as anastrozole and letrozole, can also be used to increase endogenous testosterone levels. Aromatase is an enzyme that transforms testosterone into estradiol.[11] By suppressing the conversion of testosterone to estradiol, aromatase inhibitors generate higher levels of endogenously produced testosterone, which is especially useful in men with obesity because aromatase is found in adipose tissue. Men must be cautioned, however, that estrogen remains a critical hormone responsible for their sexual libido and bone density and that oversuppression of estradiol can cause deleterious side effects in the long run.

TESTOSTERONE REPLACEMENT THERAPY

Most forms of therapy for male hypogonadism involve exogenous replacement and can be administered through varying routes, including as a topical gel or a transdermal patch, as injections, intranasally, as pellets implanted into the hip area, or orally. The most traditional form of TRT is testosterone injection, which has been available since the 1950s. Each form of TRT comes with risks and benefits and can potentially affect the secretion of FSH and LH from the pituitary gland. Side effects and the extent of relief achieved can substantially contribute to treatment adherence and ultimately to treatment success.

Topical TRT

Topical forms of testosterone, including gels, solutions, and transdermal patches, are commonly used as first-line therapies by many physicians. The pharmacokinetics of topical agents tend to result in a lower peak-to-trough variance in testosterone levels than injections because they are applied daily.[12] Despite their benefits, topical agents can cause application site reactions and are often incapable of reaching serum levels high enough for some patients to have satisfactory symptomatic outcomes. Though testosterone gels are less likely than injectables to cause erythrocytosis, they present a risk of transference, yielding adverse effects in women and children after skin-to-skin contact. Transference can occur even hours after application or with a barrier in between the patient's skin and the skin of another person.[12] Though generally considered effective for most patients, real-world clinical experience often shows high rates of patient dissatisfaction and discontinuation as absorption and efficacy vary widely among individuals.[13]

AndroGel (AbbVie Inc) was approved by the US Food and Drug Administration (FDA) in 2000 as the first transdermal testosterone gel to become commercially available for TRT.[14] It is available in 1% and 1.62% concentrations and can be prescribed as metered-dose pumps as well as packets. AndroGel is available in 4 doses: 20.25 mg, 40.5 mg, 60.75 mg, and 81 mg. Dosage generally starts at 40.5 mg daily. AndroGel should be applied to the upper arm or shoulder area in the morning.

Testim 1% (Auxilium Pharmaceuticals) is a translucent 50-mg testosterone gel available in 5-g tubes. An emollient added to Testim 1% promotes testosterone absorption as it prevents the skin from drying out.[15] Treatment over a 12-month period showed increases in bone mineral density, proposing that Testim 1% may help prevent osteoporosis.[15]

Axiron (Lilly USA, LLC) is a testosterone solution available for use in each axilla and is indicated for primary and hypogonadotropic hypogonadism. The starting dose is 60 mg, administered as 30 mg in each axilla as 1 pump or 1 twist actuation each, going up to 4 pumps or 4 twist actuations.[16] Dose adjustments should be made following a laboratory assessment for serum testosterone levels 2 to 8 hours after application and at least 2 weeks after treatment initiation or previous dose adjustment.[16]

Fortesta (Endo Pharmaceuticals Inc), another testosterone gel formulation, is only available as a metered-dose pump, with every pump actuation providing 10 mg testosterone. The starting dose of 40 mg is applied to the thighs every morning, with a maximum dose of 70 mg.[17] Dose titration is essential, and serum testosterone levels should be assessed 2 hours after application 14 days to 35 days after treatment initiation or dose adjustment.[17]

The testosterone market is also widely saturated with the use of compounded topical products. These products can vary widely in their concentration, with some offering concentrations as high as 200 mg testosterone per pump. The AUA generally does not advise the use of these products, but they are used with high frequency in community practice given the sometimes arduous task of getting testosterone approved through traditional insurance channels.

Nasal TRT

Natesto (Trimel Biopharma SRL) is the only intranasal testosterone gel available and was approved by the FDA in 2014. It is supplied as a metered-dose pump, with each pump providing 5.5 mg testosterone. The recommended dosage is 11 mg 3 times per day, which equals 2 pump actuations (1 per nostril) 3 times a day. Intranasal testosterone is short acting and reaches peak serum levels quickly. This form of administration does not appear to fully suppress endogenous pituitary hormone production and maintains some amounts of FSH and LH as well as spermatogenesis.[18] Natesto has been shown to improve hypogonadal symptoms such as mood, erectile function, and bone density, with infrequent adverse events.[19] Despite its efficacy and fertility-preserving ability, the application of Natesto can be messy, and because of its short-acting nature, it requires application 3 times daily, which can inconvenience patients and lead to treatment nonadherence.

Injectable Testosterone Cypionate

Developed in the 1950s, testosterone cypionate has been studied in great detail. With a half-life of approximately 8 days and administered as an intramuscular (IM) or subcutaneous injection, it is the most widely used form of TRT overall. Testosterone cypionate is generally available in a 200-mg/mL concentration and supplied in cottonseed oil for extended absorption. The FDA recommends the administration of 50 to 400 mg testosterone cypionate every 2 to 4 weeks, although weekly or even twice-weekly doses are more commonly prescribed in clinical practice.[20] The bioavailability of injectable testosterone cypionate is high, which means that combined with the ability to adjust dosing easily, its clinical efficacy in reaching a specific goal serum testosterone level is superior to other formulations. Injections are generally inexpsive when done at home, but for patients who have difficulty with self-injections, repeat clinic visits for dose administration can prove challenging. Pharmacokinetically, testosterone injections result in a high peak-to-trough ratio; testosterone levels peak within 12 to 24 hours after administration and decrease toward the end of the dose interval. This variability can have substantial ramifications on symptomatic outcomes, including mood, sexual performance, and energy levels.[1] Injection-site erythema has been reported in 26% of patients.[21]

For all forms of TRT, monitoring of symptoms and serum testosterone levels is critical to maintaining physiologic testosterone levels and for dose adjustments. Monitoring blood hematocrit levels is also essential because secondary erythrocytosis can occur. Testosterone-induced erythrocytosis leads to an increase in the production of red blood cells that can cause blood hyperviscosity, though it remains unclear to what extent this process plays into thromboembolic events. The Endocrine Society Clinical Practice Guidelines identify blood hematocrit levels greater than 54% as a threshold for therapy discontinuation, with the potential to reinitiate treatment at a lower dose after levels have returned to a normal range.[22] Compared with other formulations of TRT, injectable testosterone cypionate carries the highest risk of secondary erythrocytosis.

Injectable Testosterone Enanthate

Testosterone enanthate, generally administered as an IM injection, has a half-life of 4 to 5 days. Though it is shorter acting than testosterone cypionate, these 2 injectables have the highest potential of all TRT options for erythrocytosis, at almost 40%, and 100 to 200 mg of either testosterone formulation was found to be more likely to cause erythrocytosis than transdermal applications (Testim and AndroGel) or pellet formulations.[23,24] Similar to other injections, testosterone enanthate causes peaks and troughs in testosterone levels so that a patient may have supraphysiologic testosterone levels at the beginning of a dose interval and subphysiologic levels at the end, which can result in fluctuating symptomatic outcomes.[25]

Xyosted (Antares Pharma, Inc) is the first subcutaneous form of testosterone enanthate designed for weekly administration to be approved by the FDA.[26] It comes in 3 doses (50 mg, 75 mg, 100 mg) and is supplied in a 0.5-mL disposable autoinjector, making it an easy self-administration option for patients who have difficulty with standard IM injections.[26] The recommended starting dose is 75 mg, with trough concentrations ranging from 350 to 650 ng/dL, generally providing overall testosterone levels within the normal range for the entire dose interval.[26] Xyosted also carries a lower rate of secondary erythrocytosis than IM testosterone cypionate and can therefore be an option for patients with intractable secondary erythrocytosis, as well.

Injectable Testosterone Undecanoate

With a long half-life compared with other available testosterone esters, testosterone undecanoate (TU) requires less frequent doses while providing more consistent symptomatic relief and more stable serum testosterone levels.[27,28]

Aveed (Endo Pharmaceuticals Inc) is the first TU injectable to be approved by the FDA, and it comes in 750-mg (3-mL) single-use vials. Aveed is an IM injection and does not require dosage titration. It is administered 4 weeks after the initial dose, and then again every 10 weeks. Its efficacy was demonstrated in a multicenter, 24-week clinical trial that established normal serum testosterone levels over a 10-week

dose interval.[29] It carries a low risk of a potentially serious side effect called *pulmonary oil microembolism*, which necessitates patients taking Aveed to wait in the office for 30 minutes after dose administration for monitoring.[29]

Pellets

Crystalline pellets are a form of long-acting testosterone that was approved by the FDA in 1972 under the name Testopel (Endo Pharmaceuticals Inc), though it was not until 2008 that pellets were marketed on a wider scale.[30] When testosterone pellets were introduced, they offered an alternative to IM testosterone injections, which were the only form of TRT available at the time.[30] Pellets are supplied in 75-mg, 1-pellet vials (pellets are 3 × 8 mm and have a surface area of 98 mm^2) and require subcutaneous surgical insertion by the patient's care team, usually within the hip area.[31] Dissolution of pellets occurs gradually so that eugonadal testosterone levels can be maintained for several months (on average, 3-6 months). The implantation of more pellets (between 10 and 12 pellets) has been shown to yield more consistent results and to produce sustained physiologic levels of testosterone.[32] The insertion of at least 8 pellets has been identified as optimal, leading to eugonadal testosterone levels for 4 to 6 months.[32] Compounded pellets, often supplied at higher concentrations (eg, 100 mg), are widely used in community practice to attain higher testosterone levels. Unlike commercial pharmaceutical manufacturing, compounding is not FDA regulated; thus, the dosing, ingredients, and efficacy of compounded pellets can be highly variable.

Oral TRT

The initial form of oral TRT, 17α-methyltestosterone, was found to cause liver toxicity; it provided lessons about drug absorption, efficacy, and safety profile, however, all of which aided in the development of oral TU in the 1970s. Unlike methylated testosterone, oral TU bypasses the liver and is absorbed directly into the lymphatic system through the small intestine. The development of oral testosterone has offered patients an option for easy self-administration, with a potentially lower risk of common side effects compared with other options.[33] Oral testosterone formulations are generally taken twice daily with food. As there is currently limited commercial insurance coverage for oral TRT, some formulations are available as cash-only options. Compared with nearly every other form of TRT, oral TU demonstrates a substantially lower risk of erythrocytosis (<5%) while maintaining excellent symptomatic relief.

Jatenzo (Tolmar, Inc), the first oral TU approved by the FDA (2019), was originally manufactured by Clarus Therapeutics Holdings, Inc. It comes in a soft gel and is available in several doses: 158 mg, 198 mg, 237 mg (recommended starting dose), 316 mg, or 396 mg twice daily. Long-term data for Jatenzo showed the drug to be effective, sustaining eugonadal total serum testosterone levels while improving sexual health and not affecting liver function.[34] To date, however, market challenges in payor coverage have limited overall distribution of this drug. Tolmar, Inc, has acquired Jatenzo and is the current distributor of this drug.

Tlando was approved by the FDA in 2022 (Antares Pharma, Inc) and is supplied in 112.5-mg capsules. The sole available dosage is 225 mg twice daily, so dose titration is not available. An open-label, single-arm, multicenter study that assessed the safety and efficacy of Tlando in men with hypogonadism without dose titration at 225 mg twice daily found that total serum testosterone levels remained stable in 80% of participants throughout the day.[35]

Kyzatrex (Marius Pharmaceuticals LLC), which the FDA approved in 2022, marks the newest oral TU option. It is available in multiple-strength capsules—100 mg, 150 mg, and 200 mg—resulting in dosages of 200 mg, 300 mg, or 400 mg twice daily.[36] Kyzatrex contains a phytosterol ester to aid in absorption, which differentiates it from previous forms of oral TU. The efficacy of Kyzatrex is supported by an open-label, multicenter trial that administered 200 mg twice daily with meals (including dosage adjustments varying from 100 mg each day to 400 mg twice daily

at days 28 and 56).[36] The study found that 88% of patients achieved the primary end point—24-hour average concentration for total serum testosterone—on day 90.[36] Unique to all formulations, Kyzatrex is available solely as a cash-only product, bypassing traditional insurance channels in an effort to improve patient access, which has been an issue with other forms of oral TU.

Conclusions

Testosterone deficiency is becoming increasingly prevalent as comorbidity rates, such as those for obesity and type 2 diabetes, continue to rise. Determination of the optimal therapeutic strategy should incorporate a consideration of the cause of TD, the patient's age, and the patient's plans for future fertility. Exogenous therapy has evolved to offer an array of formulations and administration routes. Injectable testosterone cypionate remains the most common form of TRT but causes peaks and troughs in serum testosterone levels, with substantial rates of secondary erythrocytosis. Xyosted, a subcutaneous autoinjector delivering testosterone enanthate, reduces this risk and maintains once-weekly dosage. Topical testosterone marks a pain-free alternative to injections, but the risks of transference and at times erratic absorption should be taken into account. Testosterone pellets are a long-acting option that may be well suited to patients who desire a hands-off approach. Oral TU is the latest iteration of TRT, and it may offer patients greater convenience with lower rates of erythrocytosis. Testosterone replacement therapy should be chosen through a shared decision-making process involving the clinician and the patient, with several factors to consider, including patient preference, adverse effect profile, risk of testosterone transference, pain tolerance, patient availability (for visits to the clinic if unable to self-administer treatment), and patient financial capabilities, including insurance coverage. With the vast array of options now available, all patients who may benefit from TRT should be able to find an option that suits their individual situation and preferences.

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