Adult-onset hypogonadism: evaluation and role of testosterone replacement therapy

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Testosterone deficiency (TD) has become a growing concern in the field of men's sexual health, with an increasing number of men presenting for evaluation of this condition. Given the increasing demand for testosterone replacement therapy (TRT), a panel of experts met in August of 2015 to discuss the treatment of men who present for evaluation in the setting of low or normal gonadotropin levels and the associated signs and symptoms of hypogonadism. This constellation of factors can be associated with elements of both primary and secondary hypogonadism. Because this syndrome commonly occurs in men who are middle-aged and older, it was termed adult-onset hypogonadism (AOH). AOH can be defined by the following elements: low levels of testosterone, associated signs and symptoms of hypogonadism, and low or normal gonadotropin levels. Although there are significant benefits of TRT for patients with AOH, candidates also need to understand the potential risks. Patients undergoing TRT will need to be monitored regularly because there are potential complications that can develop with long-term use. This review is aimed at providing a deeper understanding of AOH, discussing the benefits and risks of TRT, and outlining each modality of TRT in use for AOH.

Keywords: Hypogonadism; testosterone deficiency (TD); testosterone replacement

Brief overview/definition/prevalence

The Sexual Medicine Society of North America defines adult-onset hypogonadism (AOH) as a clinical and biochemical syndrome characterized by a deficiency of testosterone with associated signs and symptoms and a failure of the body to produce an adequate compensatory response (1). AOH can be caused by testicular and/or hypothalamic-pituitary dysfunction, making it clinically distinct from primary and secondary hypogonadism. The previously quoted dichotomous distinction of primary and secondary hypogonadism was seen to be falsely applicable to a large majority of the population of men being treated for AOH. In these men, low testosterone levels are often accompanied by normal or low levels of

gonadotropins, indicating physiologic failure at both the testicular and hypothalamic-pituitary levels. When defining the prevalence of AOH, the Sexual Medicine Society of North America examined data from large epidemiologic studies, such as the European Male Ageing Study (2). In this study of 3,369 men between 40 and 79 years of age from eight different European cities, the gonadal status was defined based on normal cut-off values of 300 ng/dL for total testosterone (TT) and 9.4 U/L for luteinizing hormone (LH). Using these aforementioned thresholds, the study identified an overall prevalence of hypogonadism of 13.8%; however, 85.5% of these men were diagnosed with secondary hypogonadism with low testosterone and low or normal LH, a similar presentation seen with AOH.

It is important to note that this classification of secondary hypogonadism does not accurately establish the extent to which low testosterone is due to inadequate gonadotropins because many of these men may have a testicular failure component as well. In a study by Corona and Maggi, nearly 90% of men with secondary hypogonadism had no identifiable medical condition that could account for their hypogonadism other than a concomitant metabolic disease (i.e., diabetes mellitus, obesity, or metabolic syndrome), which was seen in over 70% of these men (3). Although the gonadal status is a key component to the clinical entity of AOH, it should be noted that the actual prevalence of symptomatic hypogonadism defined as low testosterone (<300 ng/dL) with at least three signs of symptoms of hypogonadism ranges from 2% to 6%, as identified in the European Male Ageing Study and Boston Area Community Health Survey studies (4).

Clinical presentation/evaluation

AOH is an overlooked and underdiagnosed condition because signs and symptoms can be variable and nonspecific and can present slowly over time (5). As a result, many men ignore their symptoms, and many clinicians fail to diagnose AOH without a high clinical index of suspicion. The most common presenting symptoms are centered on sexual dysfunction, given testosterone's critical role in sexual response. These symptoms may include reduced sexual desire, reduced nocturnal and morning erections, reduced sex-induced erections, delayed ejaculation, and reduced semen volume (6). The most prevalent clinical symptoms in both older and younger men with hypogonadism are decreased spontaneous erections, low libido, and difficulty maintaining an erection (7). The most prevalent nonsexual symptoms are fatigue, muscle weakness, depressed mood, and increased body fat. Other reported symptoms include excessive irritability, memory difficulties, poor concentration, sleep disturbances, and diminished work performance (2,6,7).

Once a history is taken, a physical exam should be performed to identify any physical signs to help supplement and support a diagnosis of hypogonadism based on a clinical history. Although the clinical examination is usually normal in men with testosterone deficiency (TD), a number of genital abnormalities may suggest the presence of TD, including cryptorchidism, small or soft testes, and varicocele (8). The following parameters should be documented: assessment of general body habitus, any signs of breast development, muscle development, hair growth, inspection of the penis to assess postpubertal development, and palpation of scrotal contents. When evaluating the testes, it is important to note maldescent, evidence of varicocele, size and consistency of the testes and epididymis, and any evidence of scarring from previous inflammation or infection. A digital rectal exam should be discussed for any man over the age of 40 as part of screening for prostate adenocarcinoma before any treatment for TD is recommended.

Laboratory testing

When clinical suspicion indicates the need to evaluate the patient for hypogonadism, biochemical testing should be pursued. Patients presenting with acute or subacute symptoms may have a low testosterone level and should have their evaluation deferred. When testing for testosterone levels, morning blood testing is recommended due to diurnal variation; although, this may not be necessary in men over the age of 40 due to the minimal observed diurnal changes in that population (9). There is no universally accepted serum testosterone concentration indicative of low testosterone. In most clinical trials, a cut-off value of 300 ng/dL is used to define hypogonadism. However, multiple academic societies, including the International Society of Andrology, the International Society for Study of the Aging Male, the European Association of Urology, the European Association of Andrology, and the American Society of Andrology do not recommend therapy for TT levels >350 ng/dL but recommend testosterone replacement therapy (TRT) for TT levels below 230 ng/dL when associated symptoms are noted. For levels between 230–350 ng/dL, a repeat TT with sex hormone binding globulin (SHBG) is recommend for the calculation of free or bioavailable testosterone.

Since the interpretation of TT concentrations can be confounded by SHBG concentrations, it is often useful to obtain free testosterone levels in conjunction with TT. Free testosterone can be measured directly by radioimmunoassay (RIA) or calculated from TT and SHBG concentrations. Reference ranges for free testosterone provided by laboratory reports should be used cautiously, with the knowledge that they vary widely from laboratory to laboratory and are not clinically based. A number of authorities have suggested the use of calculated free testosterone values less than 80–100 pg/mL (10,11).

If initial testing is indicative of hypogonadism, free and TT should be repeated and testing of LH, thyroid-

Table 1 Summary of purported beneficial effects of testosterone supplementation in hypogonadal males

Symptom	Level of evidence*
Body composition, physical activity, strength	
Increased lean body mass	1A
Decreased fat mass	1A
Improved bone mineral density	1A
Sexual function and libido	
Improved libido	1A
Improved morning erections	1A
Improved erectile function	1A
May improve response to PDE5s in those previously refractory to PDE5s	1B–
Medical comorbidities	
DM-improved fasting glucose, HbA1c, insulin sensitivity	1A
Lipids-improved TG, total cholesterol; variable results on HDL and LDL	1A–
Psychological/cognition	
Inconsistent and contradictory results with mood, cognition, behavior	1B–
Potential benefit in improving depression in hypogonadal or HIV positive males	1A–

*, level of evidences is assigned by the authors based on Oxford criteria and utilizing the data provided in the current review. Reprinted: AUA Core Curriculum Sexual medicine: Hypogonadism medical treatment (https://www.auanet.org/university/core_topic.cfm?coreid=102). This table is open to all AUA members.

stimulating hormone, and prolactin can be ordered to help delineate causes of hypogonadism before commencement of TRT. Hemoglobin/hematocrit (Hct) and prostate-specific antigen (PSA) levels in men over 40 years of age should also be considered to provide baseline measurements for future long-term monitoring.

Treatment types

Once AOH is accurately diagnosed, the physician must discuss all treatment options for TRT, including the option of no treatment. When considering TRT, the goals of therapy should include restoration of testosterone levels to the mid-normal range, approximation of endogenous production, avoidance or reduction of significant adverse effects, and alleviation of the associated the signs and symptoms of AOH. Overall, there is evidence suggesting improvement in physical condition, sexual libido, glucose control, lipid metabolism, mood, and cognition (*Table 1*). These benefits may differ in older men as exemplified in a recent trial by Snyder *et al.* (12). The effects of restoring

testosterone levels in hypogonadal men aged 65 years and older over the course of 1 year were evaluated, and benefits were noted in sexual function, mood, and depressive symptoms; although, no change was noted in vitality or walking distance. These are the benefits often sought by men seeking treatment for hypogonadism and should be thoroughly discussed prior to the initiation of therapy in an effort to help manage long-term expectations of TRT.

When considering TRT, there are multiple options between various testosterone preparations that differ in their ease of use, route of delivery, and cost. The physician should educate the patient on the differences of each of the preparations in order for the patient to best understand the route of therapy most beneficial for their specific circumstance. The first question to answer when initially counseling a patient on TRT should discuss their desire for future fertility. Exogenous testosterone supplementation results in decreased gonadotropic secretion at 3–4 months by feedback inhibition at the level of the hypothalamus and pituitary gland. This feedback inhibition leads to a suppression of follicle stimulating hormone (FSH) and,

ultimately, a decrease in spermatogenesis (13). Patients with low testosterone who desire fertility may be treated with agents that avoid the feedback suppression of FSH, such as human chorionic gonadotropin, aromatase inhibitors, or selective estrogen receptor modulators (SERMS). Human chorionic gonadotropin is a gonadotropin analog that can stimulate the release of LH and FSH from the pituitary gland, ultimately increasing testosterone levels, while avoiding concomitant suppression of spermatogenesis. Aromatase inhibitors have also been used as an alternative to TRT for AOH. They work by reducing peripheral conversion of testosterone to estradiol 2 (E2) via enzymatic inhibition of aromatase (14). This medication increases testosterone and reduces E2, altering the testosterone:E2 ratio. For patients with hypogonadism, several trials have demonstrated significant improvements in testosterone over placebo (14-16). Given its effect on E2, concern developed regarding bone health and bone mineral density, and data remains conflicted over the long-term effect on bone strength (16,17). The last medication category, the one used most commonly, is SERMs. This category of medications is commonly used off-label for the treatment of symptomatic hypogonadism and subfertility or infertility. As partial estrogen-blocking agents, these medications decrease negative feedback on the pituitary gland and increase secretion of FSH and LH with resultant increased testosterone production. One recently conducted trial suggests equivalency of SERMs with topical testosterone gel in achieving physiologic testosterone levels, with improved or maintained sperm counts (18).

If fertility is not a concern, testosterone can be directly administered for supplementation and treatment of AOH. There are a variety of formulations currently used (*Table 2*) (19). The most widely used testosterone preparations in the United States are transdermal and injectable preparations because of their ease of use (transdermal) and relatively low cost (injectable). We will review testosterone supplementation according to the form by which it is administered.

Oral

Oral testosterone undecanoate undergoes first-pass metabolism and is inactivated in the liver. An oral preparation was created to bypass first-pass metabolism with the methylation at the 17α. Significant hepatotoxic adverse effects have been noted long-term with this modality, and

as such, its use is not recommended (20). Oral testosterone undecanoate is not currently available in the United States. Another preparation, oral testosterone undecanoate in castor oil, has been developed and is available in Europe and Canada. This preparation avoids first-pass metabolism because it is preferentially absorbed into the lymphatic system, and as a result, there are fewer hepatic adverse effects. This formulation needs to be taken 2 to 4 times daily with a normal meal, but without adequate dietary fat content, absorption may be incomplete and testosterone levels may not equilibrate.

Buccal

The testosterone buccal system (Striant) is the only available oral testosterone therapy in the United States. Buccal systems are applied every 12 hours to the upper gum, overlying the incisor tooth, with patches alternating between the left and right sides (21). Administration provides a steady delivery of testosterone, which is maintained in physiologic ranges. Two noninferiority trials comparing Striant to either a testosterone transdermal system (Androderm) or testosterone gel (Androgel) demonstrated equivalent physiologic testosterone levels (22-24). Safety and tolerability data from two open-label phase III trials demonstrated a 12% rate of discontinuation over a 2-year period due to adverse events, most commonly altered taste and gum irritation.

Transdermal

Multiple transdermal systems of testosterone delivery are currently available with similar pharmacokinetic and adverse event profiles. Although the sites of delivery vary between formulations, all therapies achieve normal physiologic concentrations of testosterone in over 75% of patients, with slight differences in the rates and peak levels of testosterone achieved (25-29). Dose adjustment is important because transdermal absorption varies between men, and may vary in an individual over time, depending on long-term skin changes at administration sites (20). Skin irritation with blisters is more common with patches compared to gels. Patients undergoing transdermal testosterone supplementation should be cautioned to the potential for direct transference to others, particularly to women and children. As direct skin-to-skin contact is required for transference, this may be avoided by placement of clothing over the administered site and thorough hand washing following topical application.

Table 2 Testosterone replacement therapy (TRT) options

Formulation	Preparation (US tradename)	Dosage forms	Usual dosing	Site of application	Advantages	Disadvantages and risks
Intramuscular						
Long-acting	Testosterone cypionate (Depo-Testosterone)	100 or 200 mg/mL	100–200 mg every 2 w or 50–100 mg every 1 w	Thigh or buttock	Home IM injection, infrequent treatment, low cost, high efficacy	Peak effects or fluctuating testosterone levels, pain or irritation at injection site
	Testosterone enanthate (Delatestryl)	200 mg/mL				
Extra-long-acting	Testosterone undecanoate (Aveed)	250 mg/mL	750 mg initially, then 750 mg at 4 w, then 750 mg every 10 w ongoing	Buttock	Long-acting	Administered in office or hospital by REMS-certified provider, risk of pulmonary oil microembolism and anaphylaxis
Transdermal						
Gels	Androgel (1% gel)	25 mg in 2.5 g packet or 50 mg in 5 g packet	50–100 mg daily	Dry intact skin or back, abdomen, upper thighs or arm	Steady serum testosterone concentration	Risk of transfer, requires daily application, may not achieve normal testosterone levels in all men, occasional skin irritation
	Testim (1% gel)	50 mg in 5 g packet				
	Androgel (1.62% gel)	20.25 mg in 1.25 g packet, 40.5 mg in 2.5 g packet, 20.25 mg per actuation, metered-dose pump	20.25–81 mg daily			
	Fortesta (2% gel)	10 mg per actuation, metered-dose pump	10–70 mg daily	Dry intact skin of front and inner thighs	Ease of application	
	Axiron (2% solution)	30 mg per actuation, metered-dose pump	30–120 mg daily	Dry, intact skin of axilla	Ease of application, reduced risk for transfer	
Patch	Androderm	2 mg/24 h patch, 4 mg/24 h patch	2–6 mg daily	Dry intact skin of arm or torso	Limited risk of transfer, no injection	Skin irritation or rash (about 1/3 of men), daily application
Other						
Implanted subcutaneous pellet	Testopel	75 mg pellets	150–450 mg every 3–6 mo	Implanted into subcutaneous fat of buttock, lower abdominal wall or thigh	No risk of transfer, no daily treatment	Extrusion, infection, fibrosis at pellet sites / Placed in clinic or hospital by trained provider under sterile conditions
Nasal	Natesto	5.5 mg per actuation, metered-dose pump applicator	11 mg (2 pumps, 1 in each nostril) 3 times daily	Intranasal	Minimal risk of transfer	Frequent administration, rhinorrhea, epistaxis, sinusitis, nasal scab
Buccal	Striant SR	30 mg buccal system	30 mg twice daily	Adhere to depression in the gingiva superior to upper incisors	No injection	Frequent administration, gingival irritation
Oral	Not recommended					

Adapted from reference (19) with permission.

Injections

Injection therapies with testosterone provide an alternative method for testosterone supplementation. Deep intramuscular injections are performed in a home or office setting every 1 to 4 weeks in the gluteal or quadricep areas. A characteristic of injectable testosterone is the rapid rise to supraphysiologic levels of testosterone within 1 to 2 days of administration, with a gradual decline into the hypogonadal range at the end of the dosing interval (20). Testosterone enanthate 200 mg administered intramuscularly every 2 weeks achieves normal physiologic testosterone levels for 72% of the treatment interval compared to 82% with the testosterone transdermal system (30). Although costs vary by region and insurance plan, in general, intramuscular therapies are currently the least expensive alternative for testosterone supplementation. Adverse events with injectable testosterone include local pain and higher levels of polycythemia secondary to the supraphysiologic surge of testosterone associated with the injections (20).

Pellets

A long-lasting option for testosterone supplementation is subcutaneous testosterone pellets inserted into the lateral buttock or lower abdomen every 3 to 4 months. Different pellet presentations are available around the world. The procedure involves local anesthetic, with the pellets inserted into subcutaneous fat with a small trocar (20). Subcutaneous testosterone pellet insertion achieves peak testosterone levels approximately 12 hours following insertion, with a half-life of approximately 71 days. The total and duration of physiologic testosterone levels vary based on the number of pellets inserted and the patient's body mass index. Patients with elevated body mass indices achieve lower peak concentrations and may require a larger number of pellets compared to men in the low or normal body mass index range (31-34). Common adverse events associated with testosterone pellet administration include, local pain, erythema, pellet extrusion, and ecchymosis (34).

Monitoring

Monitoring for treatment efficacy and possible adverse events should be based on the Endocrine Society's guidelines for monitoring patients on TRT (35). Once a decision is made to proceed with TRT, follow-up should be set up for 3 to 6 months, at which time symptoms can be assessed, testosterone levels can be rechecked, and monitoring can be continued for weight, Hct, and PSA. Should TT remain <400 ng/dL, consideration to increase dosing may be pursued. If Hct >54%, TRT should be stopped until it returns to a normal level, and TRT may be reinitiated at a lower dose. In men older than 40 years with a baseline PSA >0.6 ng/mL, one should perform a PSA and digital rectal exam before TRT and at intervals of 3 and 6 months once TRT is initiated. If PSA remains stable, follow-up can continue annually thereafter. If the patient has tolerated TRT well with no laboratory abnormalities, follow-up can continue annually. After 1 to 2 years of TRT in men with osteoporosis or history of low trauma fracture, a bone mineral density test should be pursued. If no improvement is noted after 3 to 6 months of TRT, one should consider other causes of the initial presenting symptoms.

Risks of TRT

Cardiovascular

Hypogonadism and low testosterone levels have been associated with an increased risk of cardiovascular disease (CVD) (36). In this meta-analysis, lower testosterone was correlated with increased risk of CVD and cardiovascular mortality. However, this research did not definitively determine whether low testosterone is simply associated with cardiovascular risk or whether it is an actual causative and potentially modifiable factor. Several analyses have raised concern regarding TRT and increased CVD risk (37-40). Given this concern, the Food and Drug Administration recently required manufacturers of testosterone products to modify the labeling of their product to include a warning regarding potentially increased risks of cardiovascular events (CVE) in the setting of TRT. The debate over the use of TRT and the associated cardiovascular risks remains undecided because no adequately designed, randomized controlled trials have been performed with cardiovascular endpoints. In the largest meta-analysis on the subject of CVE and TRT in 2014, Corona *et al.* (41) reviewed 75 articles with a combined 5,464 patients over a mean duration of 34 weeks. In this study, no evidence for a causal relationship between TRT and CVE was established. Even at-risk groups, such as elderly men, those with prior CVE, and frail men, did not experience higher rates of CVE, and those with metabolic diseases who received TRT experienced lower rates of CVE compared to placebo. Calof

et al. (42) examined 19 placebo-controlled TRT trials and reported no increased risk of CVE in the TRT population compared to control patients. In addition, a large meta-analysis of 51 studies, ranging in methodologic quality from low to medium, found no increased risk of CVE or all-cause mortality associated with TRT (43). Given these conflicting findings, the need for an unambiguous conclusion regarding TRT and CVE remains of paramount importance for the community of providers seeking to best manage and counsel patients with AOH.

Prostate cancer

No adequately designed or appropriately powered study has been conducted to date to assess prostate cancer related risks of TRT. The detrimental effect of testosterone in locally advanced or metastatic prostate cancer has been well established, with early studies demonstrating significant progression of disease following exogenous testosterone administration (44,45). Hsing (46) noted no difference in the incidence of prostate cancer in patients undergoing TRT compared to the general population. Two meta-analyses of placebo-controlled TRT studies revealed no increased risk of the development of prostate cancer for patients undergoing TRT (42,43). As such, the available evidence suggests it is safe to administer testosterone in the setting of AOH without increasing an individual's long-term risk of prostate cancer.

Several retrospective studies have studied TRT in patients who have undergone definitive therapy for their prostate cancer and have demonstrated no increased risk of prostate cancer recurrence (47-50). These studies have significant limitations given their retrospective nature, and larger randomized controlled trials are needed to evaluate TRT in patients diagnosed with prostate cancer. Current evidence recommends against TRT in the setting of untreated prostate cancer but permits administration at a prudent interval following successful definitive local therapy with no evidence of recurrence.

Lower urinary tract symptoms (LUTS)

Although androgens are thought to play a large role in prostate development, no difference in prostatic androgens has been noted in men with and without benign prostatic hyperplasia (BPH) (51). Many physicians may be concerned about TRT in the setting of BPH; however, multiples studies have demonstrated either no change or improved parameters

of voiding and LUTS in patients with BPH undergoing TRT, and thus, BPH should not be a contraindication to TRT in the setting of AOH (42,43,52-57).

Polycythemia

Polycythemia (erythrocytosis) is a common adverse event associated with TRT, that is both dose and serum-level dependent (42,43,58). The overall effect noted varies by dose and patient age, but the risk of an increase in Hct >50% has been noted to be 3 to 4 times higher in patients receiving TRT compared to controls (42,43). The initial rise in hemoglobin and Hct is seen in the first 5 to 6 months, with a decline noted 3 to 12 months after TRT discontinuation (59-62). Although it has been hypothesized that enhance blood viscosity may be a risk for CVE, a causal relationship for TRT and its related erythrocytosis with CVE and mortality have not been well-defined through current studies, as described noted. As such, the Endocrine Society's Clinical Practice Guidelines are used to guide clinical management of TRT-related polycythemia and state that Hct values >54% warrant discontinuation of TRT until further assessment (35). In cases of extremely elevated or persistent polycythemia, therapeutic phlebotomy has been described as a management option (63).

Acknowledgements

Footnote

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