



Clinical Hypogonadism and Androgen Replacement Therapy: An Overview

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Men throughout recorded history have sought to preserve and enhance their virility, and have approached this in several creative ways. In antiquity, the testes were thought to be the seat of both vigor and longevity for men. Greek and Roman men consumed a substance called "satyricon," a combination of goat and wolf testicular extracts. In the 19th and 20th centuries, there was an emergence of therapies derived from organs: consumption of thyroid extract and animal testicular extract were thought to aid in maintaining virility. In the 1930s, technology progressed and it became possible to isolate various androgens (testosterone propionate, androsterone, methyltestosterone) from animal tissue. These substances began to be applied in clinical situations (Freeman, Bloom, & McGuire, 2001).

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Testosterone has a complex variety of roles in male physiology. It is a common belief that testosterone in men declines with age. While this is true, there are several aspects to this decline which make it difficult to diagnose definitively, as other endocrine components can contribute to a patient's symptoms. There are some guidelines to help determine when to begin treatment, based on laboratory assays and symptomatology. Testosterone replacement in men can improve overall quality of life, can reverse some of the effects of hypogonadism, and can be done very safely with available pharmacologic agents.

Present day offers more sophisticated methods for diagnosing and treating men with low testosterone levels. There are a variety of formulations that are commercially available, supplied as tablets, injections, or transdermal gels. The indications for treatment continue to evolve as clinicians work to define terms such as andropause, androgen decline in the aging male (ADAM), and late onset hypogonadism.

In November 2003, the Institute of Medicine (IOM) issued a statement regarding the need for research on testosterone replacement therapies. Methodologic weaknesses identified in previous research included lack of long-term studies of men undergoing replacement therapy. Indeed, it was noted that the longest study to date of patients who received testosterone replacement has been only 36 months in duration. It was recommended that more large-scale clinical trials be conducted on the order of the Women's Health

Initiative (which involved over 160,000 women aged 50 to 79). Additionally, the IOM was critical of the lack of consensus for using testosterone as a treatment vs. using it as a possible preventive measure. The lack of standardized treatment guidelines or clarity regarding specific patient populations that would benefit from treatment also have limitations.

Reservations concerning the use of testosterone arise due to the possibility of significant side effects. Current treatment is further complicated by the fact that it is difficult to compare previously published studies on testosterone therapy. Variations in the definition of hypogonadism as well as differences in replacement doses make such comparisons difficult, which in turn causes difficulty in establishing a goal for treatment.

Physiology of Testosterone

Testosterone is a cholesterol-based steroid hormone (Griffen & Wilson, 2003). This hormone



exerts effects on the male body throughout the life cycle. The initial influence of testosterone is seen during the 7th week of fetal development when it leads to differentiation of the fetal genitourinary tract. The male fetus develops Leydig cells, which begin to produce testosterone. The testosterone then drives the development of the vas deferens, epididymis, and seminal vesicles. Beginning at 8 weeks, the testosterone masculinizes the external genitalia.

At puberty, testosterone begins to exert influence over the development of secondary sexual characteristics and anabolic processes (see Table 1). The pulsatile secretion of gonatropin-releasing hormone (GnRH) from the hypothalamus causes both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) to be released from the anterior pituitary. The release of LH signals the Leydig cells to produce testosterone, resulting in the development of male secondary sex characteristics. The hypothalamic-pituitary axis (HPA) is controlled by a negative feedback loop. As the level of testosterone rises in the blood, GnRH and LH/FSH secretion decline.

The anabolic effects are manifest as overt physical changes in the male. Virilization of the individual becomes evident, as there are changes to body musculature and fat distribution. Bone growth and epiphysial closure are promoted. There is laryngeal enlargement and subsequent vocal cord thickening, as well as testicular growth and the initiation of spermatogenesis.

Once physical maturity has been achieved, testosterone has a more homeostatic function. It sustains spermatogenesis, maintains muscle bulk, maintains secondary sex characteristics, and aids in erectile function.

Endogenous testosterone in the circulation can be free (unbound), weakly bound to

Table 1.
Functions of Testosterone

Androgenic	Anabolic
Effects to male reproductive tract and secondary male sex characteristics Ejaculation Erections Libido Prenatal differentiation	Bone formation Erythropoiesis Growth-promoting effects on somatic tissue Muscle bulk Prostate growth

Table 2.
Changes Seen with Lowered Testosterone and Aging

Aspect	Change
Bone mass	Decreases
Cognitive function	Decreases
Erectile function	Decreases
Fat mass	Increases
Hematopoiesis	Decreases
Libido	Decreases
Muscle mass	Decreases
Muscle strength	Decreases
Sense of well-being	Decreases/no change

albumin, or tightly bound to sex hormone binding globulin (SHBG). The free and albumin-bound testosterone is available for use by the body. The largest percentage, however, is bound to SHBG and is unavailable for use in the body. Any condition that increases SHBG will decrease the amount of available testosterone. This includes conditions that elevate estrogens, elevated thyroid hormone, and aging.

Testosterone in circulation can also be converted into other hormones. It can be converted peripherally to dihydrotestosterone (DHT) by 5-alpha reductase. DHT has a role in the growth of prostatic tissue and therefore can influence lower urinary tract symptoms. Testosterone is aromatized to form estradiol (E2) in fatty tissue. In obese men, the increased amount

of fat leads to increased aromatase activity, resulting in increased levels of estradiol. High circulating levels of estradiol down-regulates the hypothalamic-pituitary axis and decreases the amount of circulating testosterone.

As the male body ages, gonadal function slowly declines with a resulting drop in serum testosterone of approximately 1% per year after age 30, a phenomenon that occurs in both males and females (Morales, Heaton, & Carson, 2000). This can lead to multiple clinical manifestations (see Table 2). However, andropause is not analogous to the sudden cessation of reproductive capability seen with women during menopause. Despite a decline in testosterone, men retain their reproductive capacity. It has been suggested that the term *andropause* be



Table 3.
Causes of Hypogonadism

Primary Hypogonadism (increased LH/FSH, Low T)	Secondary Hypogonadism (low T, low-normal FSH/LH)	Combined Hypogonadism
Aging (loss of Leydig cells) Chemotherapy/irradiation Cryptorchidism Chromosome abnormalities (such as Klinefelter syndrome) HIV/AIDS Myotonic dystrophy Orchitis (for example, mumps) Testicular loss from trauma, tumor	Aging COPD Diabetes Hemochromatosis HIV/AIDS Hypogonadotropic hypogonadism Kallman's syndrome Medication-induced (such as anti-estrogens for treatment of prostate cancer) Obesity Pituitary mass lesions Prolactinoma Psychological stress Uremia/Chronic renal failure	Aging Cirrhosis Sickle cell disease

LH = luteinizing hormone

FSH = follicle-stimulating hormone

T = testosterone

reserved for those men who have lost their reproductive capabilities (such as after a bilateral orchiectomy for hormonal control of prostate cancer).

Testosterone Deficiency: Hypogonadism

Testosterone deficiency, *hypogonadism*, may be categorized as primary, secondary, or combined (see Table 3). Some conditions responsible for hypogonadism, such as obesity or the feedback inhibition seen in chronic alcoholism, are reversible. Estimates of the prevalence of hypogonadism in the United States are difficult to compare, as there is disagreement regarding the definition and laboratory values that determine hypogonadism. Estimates from data in the Massachusetts Male Aging Study (MMAS) estimated 2.4 million men aged 40 to 69 had some degree of hypogonadism (Araujo et al., 2004). Other studies estimate the prevalence of age-related hypogonadism due to all causes at 20% to 30% (Allan & McLahan, 2004).

The presentation of clinical hypogonadism will vary, but there is an acknowledged decline in testosterone levels as men age.

At age 75, the mean *total* testosterone level is roughly two-thirds of the mean for 20 to 30-year-old men, while the *free* testosterone is only 40% that of the younger men (Vermeulen, 2001). There is an insidious onset and slow progression of the decline of testosterone, with many of the symptoms attributed to existing comorbidities in an individual. There is also significant individual variability as to onset and speed of decline of testosterone levels. Individuals may complain of hypogonadal symptoms at differing ages and to differing degrees. Complaints such as fatigue or loss of muscle mass may be seen as part of normal aging, meaning that the hypogonadism seen with advancing age is likely to be both under-recognized and under-treated.

It is difficult to discuss hypogonadism in the aging male as a singular entity. With age, the responsiveness of the pituitary gland to hormonal signals declines, and there is a gradual desensitization and decline in number of the Leydig cells (testicular failure). LH secretion becomes erratic, further disrupting the signaling system and

leading to a decline in available testosterone. Growth hormone decreases with age, contributing to the decline in lean muscle mass and bone density. Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) also decline with age, and may impact the psychological and well-being aspect of aging.

Clinical Presentation

Establishing the presence of hypogonadism on the basis of clinical symptoms alone is difficult, except in the most profound of cases. There is no consensus as to what laboratory level of testosterone defines a clinically significant deficiency. Significant intra-individual variations in testosterone levels may be attributed to time of day, medications, stress, illness, or recent surgery. An individual may suffer from an overall decline in endocrine function that acts synergistically to produce symptoms of hypogonadism, but it remains unclear what the contribution of testosterone is in the presentation of these symptoms. The loss of muscle mass and bone density, for instance, can be attributed to



Figure 1.
ADAM Questionnaire

Androgen Deficiency in Aging Males (ADAM) Questionnaire

1. Do you have a decrease in 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. Has it been more difficult to maintain your erection throughout sexual intercourse?
9. Are you falling asleep after dinner?
10. Has your work performance deteriorated recently?

Note: A diagnosis of ADAM is suspected if there are “yes” answers to 1 and 7, or any other 3 questions.

Source: Morley et al., 2000.

a decline in physical activity as the incidence of mobility-limiting co-morbidities rises.

There are several accepted elements that compose ADAM. An individual may demonstrate some or all of these components:

- Changes in mood (fatigue, depression, anger).
- Decreased body hair (feminization).
- Decreased bone mineral density and possible resulting osteoporosis.
- Decreased lean body mass and muscle strength.
- Decreased libido and erectile quality.
- Increased visceral fat.
- Oligospermia or azospermia.

The diagnosis of hypogonadism can be facilitated through the use of screening questionnaires such as the ADAM questionnaire (see Figure 1). This survey exhibits a statistical sensitivity of 88%, but a specificity of only 60% (Morley et al., 2000). This means that the ADAM questionnaire will rarely miss diagnosing individuals who actually have hypogonadism, but will also incorrectly identify many non-hypogonadal individuals as having the condition. This is due to the fact that many positive responses in the questionnaire may be indicative of other condi-

tions, such as depression. Its use as a screening tool nonetheless aids in prompting a more detailed discussion of symptoms.

Physical examination in hypogonadism is commonly unremarkable, though there may be evidence of decreased hair distribution, truncal fat distribution, testicles that may be of a softer consistency, or gynecomastia. There is no consensus as to what degree these signs should be present or how severe they must be in order to diagnose ADAM.

There are some conditions in which a male is at increased risk for developing hypogonadism. Diabetic men are at increased risk for the condition, with the prevalence varying between 30% and 55% depending on age (Dhindsa et al., 2004). This is further complicated by obesity, which further increases the risk for both hypogonadism and diabetes due to the aromatization of testosterone to estradiol.

Patients who present with sexual dysfunction complaints should raise the suspicion of hypogonadism. This is not limited to those men who complain of erectile difficulties or the elderly male. Presentation could include complaints of decreased spontaneous erections, poor quality

erections, and low libido. This may be the only aspect in which some men fit the ADAM criteria, and it is impossible to predict the testosterone required by an individual to maintain sexual function. It is likely that as men age, the hormonal component to sexual function begins to have an increasing role. Hypogonadal patients who have failed a trial of phosphodiesterase-5 (PDE5) inhibitors may respond to these medications if their testosterone levels are returned to normal (Aversa, Isidors, Spera, Lenzi, & Fabbri, 2003), which may enable them to avoid more invasive treatments. However, it is important to remember that men who are hypogonadal can have adequate erectile function. Likewise, restoration of testosterone to normal levels does not alone necessarily restore erectile function in men with concomitant hypogonadism and erectile dysfunction.

Given the widespread influence and maintenance functions that testosterone has, it has been proposed that clinicians begin screening for low or low normal testosterone routinely in their aging patients. There are multiple drawbacks to this approach, with one of the most obvious being the lack of controlled data to indicate what lower limit of the normal range should be used for beginning treatment. Similarly, there is no long-term randomized data that establishes appropriate endpoints or goal for androgen replacement. There is also the question of which laboratory assay(s) would provide the most clinically relevant information.

Laboratory Evaluation

The most practical laboratory test in the diagnosis of hypogonadism is the serum testosterone level. There are controversies concerning which levels are most relevant. The various assays that can be used include total testosterone, bioavailable testosterone, and free testosterone.



Many argue that free testosterone or bioavailable testosterone levels give the best information about a man's androgen status. These tests give an accurate picture of the amount of testosterone available for biological effects, negating problems associated with variations in SHBG. Disadvantages of these tests include the difficulty in achieving accurate results due to differing methods of assays, and the increased cost of obtaining these more complicated tests. Arguments for utilizing total testosterone levels include lower cost, and practitioners in favor of this method argue that there are very few conditions where SHBG levels are abnormal enough to cause a clinically significant change in the level of bioavailable testosterone. The laboratory tests should be drawn between 8:00 am and 11:00 am, due to the circadian rhythm of testosterone secretion. Laboratory standards are defined by morning blood draws.

Additional testing may include gonadotropin levels, and these tests can help in determining whether the individual's hypogonadism is primary (low testosterone, with elevated LH) or secondary (low testosterone with normal or low LH). Men with an inappropriate gonadotropin response to a low testosterone should be evaluated for pituitary pathology, possibly including pituitary gland imaging studies. A serum prolactin level may be obtained to assure hyperprolactinemia is not the etiology of the hypogonadism. If the patient is obese, a baseline estradiol level can be of value. Some authors (Morales et al., 2000) suggest that measurement of the SHBG level can be helpful as part of the initial workup. However, the value of this measurement is less well-defined in planning treatment, as SHBG levels are influenced by both hormonal and nonhormonal factors (Vermeulen,

2001). Bone densitometry may be considered in those men at high risk for osteoporosis.

Testosterone Replacement

Hormone replacement therapy for men should be considered when clinical complaints are accompanied by decreased hormone levels. It would seem intuitive that it should be replaced if the clinical picture is consistent with the accepted description for ADAM. Common goals of treatment are to re-establish sexual functioning, libido, and improve overall mood (Morales et al., 2000). Restoration of normal testosterone levels can also improve muscle mass, prevent osteoporosis, maintain mental acuity, and maintain virilization, especially in elderly males. Prevention of osteoporosis alone can greatly decrease both morbidity and mortality in aged men due to hip fractures (Vermeulen, 2001). It remains unclear as to what target level they should be treated, as even in young men it is not clear if normal testosterone levels are needed for the full anabolic and androgenic benefits of testosterone (Vermeulen, 2001).

The presence of prostate cancer or male breast cancer is an absolute contraindication for testosterone replacement treatment. Severe obstructive uropathy is a relative contraindication.

Types of Testosterone Replacement Therapy

Different preparations of testosterone are used for replacement therapy (see Table 4). While there are advantages and disadvantages to each type of replacement therapy, there are also other important issues.

First, oral agents really have no place in hormone therapy in men. There is a first pass effect after absorption into the portal system that allows the liver to metabolize the drug, leading to a very small amount of hormone entering the circulation. The

resultant down-regulation of GnRH and LH will result in very little change in circulating levels of testosterone in all men except those with a profound decline in testosterone. The first pass absorption of oral agents through the liver causes the highest degree of toxicity of all the replacement therapy options. These include lowering of HDL cholesterol (Bagatell & Bremner, 1995) and liver toxicity (Yoshida, Erb, Scudamore, & Owen, 1994). An exception to this discussion of oral agents is testosterone undecanoate, which is absorbed via lymphatics and must be taken four times per day. It is available outside of the United States, and there are no plans to pursue FDA approval.

Injectable agents are more often used for replacement therapy. The testosterone esters in these compounds are put in depot injections that leach hormone out over a period of weeks. The average dosage is 100 mg per week. Injections are formulated such that a person may receive 200 mg every 2 weeks or 300 mg every 3 weeks, etc. There is an initial peak in testosterone level right after an injection. If this level rises above the normal range, increased adverse events such as those described in the following section may be seen. There may also be a drop of the testosterone level below the normal range shortly before the next injection, leading to increased symptoms. This cyclical nature of highs and lows can be minimized by shortening the interval between injections, and lowering the dose. A target of 200 mg every 2 weeks is usually a good compromise between toxicity and beneficial effects.

Topical or transdermal delivery for testosterone replacement is also available. Since these agents are administered daily in low dose, the risk of supraphysiological or subtherapeutic levels is minimized. The use of topical



Table 4.
Forms of Testosterone Replacement

Name	Route	Dose	Frequency	Comments
Buccal testosterone (Striant®)	To the gum region	30 mg	BID	
Testosterone cypionate (Depo-Testosterone®) Testosterone enanthate (Delatestryl®)	IM	200 mg-400 mg	200 mg every 2 weeks 300 mg every 3 weeks 400 mg every 4 weeks	Long-acting Does not mimic physiologic levels, creates peaks and troughs
Transdermal hydroalcoholic gel (Androderm®, Testim®)	Topical	5 gram, delivering 50-mg dose		Mimics physiologic dosing Transfer risk if gel not completely dry
Transdermal testosterone patch (Androderm®, Testoderm TTS®)	Topical	5 mg	Daily Daily at bedtime	Mimics physiologic dosing Contact dermatitis

Note: Oral forms are rarely seen prescribed in the United States due to the high incidence of liver toxicity.

agents is thought to minimize adverse events. Indeed, in most series examining the toxicity of topical agents, adverse events are nearly nonexistent (Steidle et al., 2003). The main disadvantage of the topical agents are their high cost (\$100 to \$150 per month), substantially higher than self-administered injection therapy (\$30 per month). Specific disadvantages of individual agents are listed in Table 4.

Side Effects of Testosterone Replacement

Coronary artery disease risk. Because men have a higher incidence of cardiovascular risk, it is proposed that they are at higher risk for heart disease. In reality this relationship is poorly defined. Published studies of testosterone replacement have not shown an increase of adverse cardiac events (Rhoden & Morgentaler, 2004) but patients with established risk factors must be carefully assessed.

Fluid retention. This side effect may be most pronounced in the frail or ill elderly male,

and generally resolves after the first few months of treatment.

Alteration of serum lipid profile. While many of the existing studies are inconsistent in their reporting of the effects of testosterone replacement therapy on serum lipid levels (Rhoden & Morgentaler, 2004), evidence suggests that testosterone replacement does not affect the lipid profile. Nonetheless, some data seems to indicate that supraphysiologic doses of testosterone will raise low-density lipoproteins, lower high-density lipoprotein, and raise triglycerides (Morales et al., 2000). However, as the goal of testosterone treatment is restoration to the normal range, the risk seems to be modest.

Liver toxicity. All prescribing information for available forms of exogenous testosterone includes some mention of risk for liver toxicity. The risk for liver toxicity is highest with oral preparations, modest with injections, and exceedingly low with the topical preparations. No incidence of liver toxicity has been reported in any clinical trial, but

this continues to influence how caregivers follow patients on testosterone replacement.

Polycythemia. Some men exhibit a marked increase in red blood cell production that requires testosterone therapy be stopped, be significantly titrated, or can even require phlebotomy (Vermeulen, 2001). The risk appears to be higher with IM preparations (Rhoden & Morgentaler, 2004) and may be due to the supraphysiologic levels that are seen. This risk is also higher in men who have co-morbidities known to increase hematocrit levels, such as chronic obstructive lung disease.

Prostate disease. This is the most troublesome potential side effect. Tumors of the prostate are androgen sensitive, and the growth of the prostate itself is influenced by the presence of testosterone and its metabolite DHT. Rhoden and Morgentaler (2004) reported that several studies failed to show an acceleration of voiding symptoms after androgen replacement therapy. These authors also reported that there has been a low frequency of



prostate cancer in men treated for hypogonadism, although the available data extends only 36 months. They concluded that there are no data to support the claim that treatment with exogenous testosterone increases the risk for prostate cancer.

Sleep apnea. Androgen replacement appears to have some poorly understood influence centrally on the control of breathing (Rhoden & Morgentaler 2004) and may worsen sleep apnea in patients who have been previously diagnosed. This correlation has not been conclusively established.

Impairment of spermatogenesis. Administration of exogenous testosterone interrupts the normal signaling of the HPA, and will result in oligospermia or azoospermia that may not be reversible. While this may be of little concern to the patient with ADAM, it can significantly alter the management of hypogonadism in men who wish to preserve their fertility.

Recommendations For Followup

Prior to beginning androgen replacement, the patient should have a baseline voiding history, blood pressure, rectal examination, and be specifically asked about a history of sleep apnea. Baseline laboratory work should include PSA, fasting cholesterol profile, complete blood count, and liver function tests. After a method for replacement has been agreed upon (see Table 4), the patient should have morning testosterone levels within 2 to 3 weeks of starting the testosterone if it is gel, patch, or buccal, and in approximately 8 weeks if an injectable form is used. When treating with injectable preparations, levels should be checked at the halfway time point between injections. This is to confirm that the proper dose has been prescribed. The managing clinician may decide to schedule an interval appointment

to monitor the patient's progress. There is no upper age limit to starting testosterone therapy; it is limited only by a patient's co-morbidities and tolerance of side effects.

After 3 months, the patient should return for an efficacy assessment. This includes a voiding history, blood pressure, rectal examination, repeat blood tests, and morning total testosterone level for patch users. He should specifically be asked if he has noticed improvements in the symptoms that led to the diagnosis of hypogonadism, be it sexual function, energy level, or muscle mass. If the patient exhibits no changes in repeat blood tests, and has noticed improvements to his overall symptomatology, he can be followed every 6 months.

Every 6 months thereafter, the patient should receive an efficacy assessment, voiding history, blood pressure, rectal examination, PSA, and testosterone level. Other laboratory values can be followed yearly. It is important to keep in mind that monitoring must be tailored to the individual. There is no target level for replacement, and the patient's reports of the effectiveness of the therapy are generally a reliable indicator of success. Once testosterone replacement therapy is initiated, the treatment is likely to be lifelong.

Conclusions

Testosterone replacement offers men the opportunity to regain some of the vigor of their youth. Done while closely monitored, it is a relatively low-risk proposition that has many benefits, including boosting cognition, muscle mass, and bone density while decreasing abdominal fat. Restoration of a eugonadal state can restore well-being and increase compliance with other aspects of health care. While there is a need for large-scale clinical trials, data from such studies would not be available to guide treatment for several years. Until

that time, patients can continue to be treated safely with the current recommendations and formulations that are available. □

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