

Relationship Between Testosterone and Erectile Dysfunction

Jacob Rajfer, MD

University of California, Los Angeles, School of Medicine

Although erectile function is clearly androgen dependent, is it just as clear at what level of testosterone erectile dysfunction (ED) begins? Does the decline in testosterone that occurs with aging always produce ED? Are exogenous androgens the answer to ED? The answers range from clear to complex.
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Of the major causes of erectile dysfunction (ED), disorders of the endocrine system are the rarest. Within this etiologic category, the most common cause of ED is hypogonadism. While logic dictates that treating this underlying endocrinopathy should reverse the ED, there is a lack of clinical evidence to support this expectation; ie, not all patients with ED and a low testosterone level have an improvement in erectile function when treated with exogenous androgen. Similarly, some patients with normal testosterone levels and ED who are given exogenous androgen therapy empirically report improvement in erectile function. This review will cover the relationship between testosterone and ED, highlighting what is known and unknown regarding the effect of testosterone on penile function, what to look for in the evaluation of the ED patient suspected of having a lower-than-normal serum testosterone level, and the methods currently available to treat patients with this hypogonadal condition.

Initial Evaluation of the Impotent Patient

The medical history and physical examination provide important clues to the cause of the patient's complaints and initially guide the physician to order the appropriate laboratory investigations (Table 1). For example, a history of diabetes may suggest a vasculopathy and/or neuropathy, certain dyslipidemic states may infer a vasculopathy, and chronic alcoholism and/or liver disease may induce a hyperestrogenic state, with a resultant low level of circulating free testosterone. A history of previous surgery on the pituitary (hyperprolactinemia) or thyroid gland (hyperthyroidism with increased binding globulin, resulting in a decrease in free testosterone levels), excess endogenous (Cushing syndrome) or exogenous (hypogonadism) steroid exposure, obesity (which causes a decrease in free testosterone levels), and various chronic diseases (AIDS, malnutrition) may also indicate or suggest endocrinopathy. A history of excess blood transfusions for certain hemato-

logic diseases may lead to hemochromatosis, which, in turn, may interfere with testosterone production by the testes. Certain medications (such as antiandrogens, gonadotropin-releasing hormone agonists, cimetidine, ketoconazole, progestins, and cannabis) may alter the hypothalamic-pituitary-testicular axis and affect testosterone production or action. Finally, a history of testicular disorders (trauma, torsion, cryptorchidism, testicular cancer), particularly if these disorders have been bilateral, may affect testosterone production. In addition, many patients with low testosterone levels may complain only of loss of libido.¹

The physical examination may provide important clues to endocrinopathy associated with hypogonadism. Normal pubertal development in the male will lead to axillary and pubic hair and a normal male escutcheon, normal temporal balding, and absence of gynecomastia. Palpation of the neck may reveal a goiter. Goiter may be associated with hyperthyroidism, which affects the binding of testosterone by proteins in the blood. The genitalia should demonstrate a normal phallus, with the meatus at the distal tip of the penis (no hypospadias) as well as bilaterally descended testes of normal size and consistency. The rectal examination should determine the size and consistency of the prostate, the bulbocavernosus reflex, and anal sphincter tone. Additional clues on the physical examination may be obtained by examining the skin for spider angiomas (liver disease) or excessive sweating (hyperthyroidism), by the presence of exophthalmos, or by finding a palpable thyroid (hyperthyroidism).

Role of Testosterone

Androgens have always been assumed to play a major role in male erectile function because:

- There is a decrease in serum testosterone levels with aging^{2,3} and a time period when the preva-

lence of ED increases.

- Castration usually causes a decline in sexual function.^{4,5}
- Sexual function returns to normal in castrated (severely hypogonadal) men who undergo treatment with exogenous androgens.^{6,7}

Erections are clearly androgen-dependent, as evidenced by the observation that men with marked hypogonadism have a marked reduction in the frequency, amplitude, and rigidity of erections.^{8,9} However, the level of hypogonadism required to induce this ED is debatable.¹⁰⁻¹³ It is believed that normal adult testosterone levels are not required for normal erections to occur and that when this threshold of testosterone is reached, additional amounts do not further increase the frequency, amplitude, or rigidity of erections.^{5,10}

It is well accepted that there is a gradual, age-related decline in serum total and free testosterone levels in healthy adult men.^{2,3,14,15} Cross-sectional studies have also demonstrated a significant increase in sex hormone-binding globulin (SHBG) concentrations in the aging male.¹⁵ Thus,

not only does total testosterone decline, but also a higher percentage of the remaining testosterone is bound tightly to SHBG, further reducing the amount of bioavailable (and bioactive) testosterone. Data demonstrate that the free testosterone levels at age 75 are 50% of those found in men at age 25.¹⁵ However, not all aged men have abnormal free testosterone levels, even though the levels may be half those of men much younger. While there is little debate on how to define hypogonadism in the young man, controversy still exists regarding the definition of hypogonadism in the aged individual. Does one compare the total testosterone values found in older men with those found in younger men? Or does one use the free testosterone level to determine hypogonadism, in which case about 50% of aged men will fall into this category?

The cause of the hypogonadism of aging is unclear and may be multifactorial. For example, some experimental evidence suggests that aging induces a Leydig cell dysfunction, while some studies demonstrate the possibility of a hypothalamic-pituitary de-

Table 1
Conditions That May Indicate Endocrinopathy in the Male

AIDS
Chronic alcoholism and/or liver disease
Excess endogenous (Cushing syndrome) or exogenous (hypergonadism) steroid exposure
History of diabetes
History of excess blood transfusions for certain hematologic diseases
History of previous surgery on the pituitary (hyperprolactinemia) or thyroid gland (hyperthyroidism)
History of testicular disorders (trauma, torsion, cryptorchidism, testicular cancer), particularly if disorders bilateral
Loss of libido
Malnutrition
Medications
Antiandrogens
Gonadotropin-releasing hormone agonists
Cimetidine
Ketoconazole
Progestins
Cannabis
Obesity

Main Points

- Although endocrinopathy is a rare cause of erectile dysfunction (ED), within that category, hypogonadism is the most common.
- Normal adult testosterone levels are not necessary for normal erections.
- There is a gradual decline with age of total and free testosterone levels in healthy men.
- ED and hypogonadism are common in the aging male, but they may not be causally related.
- Treatment with exogenous androgens may produce clinical improvement in the signs of hypogonadism but may not improve sexual function.
- Men with hypogonadism are at higher risk for cardiovascular events than are normal men.
- A testosterone replacement agent should mimic diurnal patterns of testosterone production, produce physiologic levels of testosterone and its metabolites, be well tolerated, and be cost-effective to use.

fect.¹⁶⁻¹⁸ Korenman and associates¹⁹ identified an elevated sex steroid-binding globulin protein as the culprit in reducing bioavailable testosterone in elderly men. Measurement of gonadotropins and prolactin may assist in determining the type of hypogonadism (hypo- or hypergonadotropic) in any such individual.

The clinical signs and symptoms of hypogonadism in the aging male may be a decline in libido; a decrease in beard growth, muscle mass, and strength; a lack of energy; osteopenia; a decrease in cognition; irritability; and, occasionally, excessive sweating and hot flushes.³ It is generally accepted, however, that most elderly men seen for ED are clinically not hypogonadal and do not have a low serum testosterone level—even though these aging signs and symptoms are clearly similar to those seen in men with hypogonadism. This is the reason

it is common for physicians to attribute at least part of these clinical indicators to the age-associated decrease in serum testosterone levels.

While hypogonadism is the most common etiology of endocrinopathy causing ED, it is still one of the rarest causes. When free testosterone is measured in impotent patients, some investigators have found that between 20% and 40% of these men have low free testosterone levels^{19,20}; other investigators, however, have failed to corroborate these findings.²¹ It should be reiterated that while ED and hypogonadism are common conditions of the aging male, these 2 conditions may not be causally related.¹⁹

If a low or borderline total testosterone level is obtained during the evaluation of ED patients (Table 2), a second measurement is recommended, because a substantial number of impotent patients with a low serum total

testosterone level at a first determination have a normal level when the test is repeated.²² The reason for the low testosterone level can be ascertained further by measuring the bioavailable fraction of serum testosterone, luteinizing hormone (LH), and prolactin to determine whether the hypogonadism is hypogonadotropic or hypergonadotropic. Measuring gonadotropins is necessary to avoid missing many states of compensated testicular failure in which serum testosterone levels are usually normal.^{23,24} Measuring a single instead of pooled determination of LH samples is preferable and is a cost-effective approach. However, measurement of both gonadotropins, LH and follicle-stimulating hormone (FSH), rather than LH alone can be helpful in certain clinical situations.

In hypogonadotropic hypogonadism, in which the serum LH and FSH levels are low or are normal with a concomitant low serum testosterone level, the evaluation for identifying a cause of secondary hypogonadism should be mandatory and include a serum iron study, thyroid function tests, and a serum prolactin test (to check for a pituitary adenoma). Routine measurement of prolactin on the initial screening blood tests is usually not recommended; isolated hyperprolactinemia is rare, and most patients with hyperprolactinemia have abnormally low testosterone levels. Patients who present with the symptoms of hyperprolactinemia, such as decreased libido and headache, may have depressed testosterone levels suggestive of a prolactinoma that may be diagnosed by an MRI and/or CT scan.

Role of Thyroid on Testis Function

Thyroxin can affect the male reproductive system. Hyperthyroidism has been associated with an increase in total serum testosterone levels but with normal unbound or bioactive testosterone. This is caused by the increase in the SHBG levels associated

Table 2.
Clinical Evaluation of Serum Testosterone Levels

- Obtain screening serum testosterone measurement.
- If low, repeat serum testosterone measurement.
- If still low, measure luteinizing hormone, testosterone, and prolactin.
- If prolactin level is elevated, obtain MRI of pituitary.

with hyperthyroidism. The increase in SHBG causes a relative decrease in the free testosterone levels, which leads to an elevation of the serum LH (negative feedback), a further increase in serum testosterone and, by peripheral conversion, an increase in serum estradiol. As a result of the increase in circulating estrogens, these men with hyperthyroidism may complain of or present with gynecomastia, spider angiomas, and a decrease in libido.^{25,26} Treatment of the thyrotoxicosis reverses the symptoms and signs of the disorder.

In hypothyroidism, LH and FSH are usually elevated, which is consistent with testicular resistance to gonadotropins. The serum testosterone and SHBG are usually decreased, while the free testosterone has been reported to be increased, decreased, or normal. Some men with hypothyroidism may complain of ED; in this setting, replacement with thyroxin rarely improves potency.

Treatment With Testosterone

The clinical signs of hypogonadism in elderly men with ED can be improved with androgen treatment, although erectile function may not improve. Therefore, in men who have normal or borderline levels of serum testosterone, exogenous androgens may be given for a time to determine the efficacy of the treatment for both ED and non-ED signs and symptoms. In our clinic, we treat such patients for 3 months with exogenous testosterone to determine whether there is an effect on either the ED or the clinical signs of hypogonadism (if present). If the ED is not reversed, which is common,^{27,28} but the other aspects of hypogonadism are improved, it may be prudent to keep these men on exogenous testosterone as long as there are no contraindications to its use (Table 3).²⁹⁻³¹

There is currently little clinical evidence that exogenous androgen treatment will lead to prostate disease,^{3,31,32} such as benign prostatic hyperplasia

or prostate cancer.^{33,34} In spite of this, androgen administration to men above age 50 requires careful monitoring of the prostate. A baseline digital rectal examination (DRE) and measurement of a prostate-specific antigen (PSA) level are recommended prior to starting exogenous androgen therapy. An abnormal DRE and/or an abnormal PSA requires further evaluation of the prostate to rule out prostate cancer before androgen therapy can be initiated.

Epidemiologic studies show that hypogonadal men are at higher risk for cardiovascular events than are normal men. Generally, there is an inverse correlation between testosterone levels and the atherogenic lipid profile, presence of atheromatosis,^{35,36} or degree of coronary artery stenosis³⁷; androgen supplementation within the physiologic range normalizes the lipid profile, probably by increasing insulin sensitivity, and decreases HDL cholesterol with little effect on LDL cholesterol and triglycerides³⁸ (the latter 2 being well-known risk factors for atherosclerosis). Testosterone also has complex effects on both the coagulation and fibrinolytic profiles; supraphysiologic levels of testosterone, nonaromatizable anabolic steroids, or alpha alkylated androgens are clearly atherogenic and often may cause cardiovascular accidents.³⁹⁻⁴¹ As a result, blood hematocrit levels should be determined before starting exogenous androgen therapy. Men with severe coronary disease are

not candidates for androgen therapy.

The ideal testosterone replacement agent should:

- Mimic diurnal patterns of endogenous hormone secretion.
- Produce physiologic levels of not only testosterone but also its metabolites: dihydrotestosterone (DHT) and estradiol (E2).
- Be well tolerated, comfortable and convenient to use, and cost-effective. Medications available in the United States currently include oral, intramuscular, and transdermal agents (Table 4). Implantable testosterone pellets, while used abroad, are not currently available for treatment of patients in the United States.

Oral. Oral agents for testosterone replacement are clearly convenient and comfortable to use. Oral testosterone, however, is absorbed rapidly from the GI tract and circulates through the portal blood.^{42,43} Because of this portal circulation and rapid hepatic metabolism, only a small volume of testosterone is circulated, and only serum testosterone metabolites are raised. Most important, these agents have been reported to produce significant long-term hepatic toxicity.⁴⁴ Oral testosterone does not reproduce the circadian pattern of testosterone production by the testes, nor does it achieve normal physiologic levels of DHT or estradiol.

An example of an active oral preparation is testosterone undecanoate; it

Table 3
Contraindications to Androgen Treatment

<i>Absolute</i>
Breast cancer (past or present)
Polycythemia
Prostate cancer (past or present)
Severe cardiac or coronary insufficiency
<i>Relative</i>
Hyperviscosity states
Lower urinary tract symptoms (prostatism)
Sleep apnea

Table 4
Clinically Available Testosterone Preparations

- Parenteral injections (testosterone enanthate or testosterone cypionate): every 2 - 3 weeks
- Oral, 17 α -alkylated methyltestosterone: 10 - 40 mg daily (not recommended)
- Scrotal patch: 5 mg daily (Testoderm)
- Nonscrotal patch: 5 mg daily (Androderm)
- Skin gel (AndroGel)

is partially absorbed via the lymph, thus escaping first-pass hepatic inactivation. Testosterone undecanoate, unfortunately, is available only outside of the United States.⁴⁵ The usual dose is 120 to 240 mg/d, divided over 2 or 3 doses. Absorption and plasma levels achieved are variable, but the compound restores serum testosterone levels and improves libido in hypogonadal men. Plasma estradiol levels also rise to physiologic levels with oral testosterone undecanoate treatment.

The most effective of oral agents of testosterone are the 17 α alkylated testosterone, such as methyltestosterone. These 17 α alkylated testosterone may be administered either orally or buccally but, because of their high cost, minimal potency, and risk of hepatotoxicity, these types of oral androgens should not be used clinically for androgen replacement.

Parenteral. Intramuscular preparations of testosterone are effective in increasing serum testosterone levels, although they produce significant elevations immediately after administration and a very low nadir before repeat injection. These parenteral androgens do not provide the normal circadian pattern of testosterone, and the injections are uncomfortable at times. Intramuscular testosterone can be administered in its aqueous, unmodified form; however, its rapid absorption and degradation make this form unsatisfactory for testosterone replacement. Similarly, while restoring serum DHT levels, estradiol levels may be excessive in patients with high testosterone levels after injection of aqueous, unmodified testosterone.

The 17 β -hydroxyl esters of testosterone, however, are modifications of aqueous testosterone that are more widely used, can be administered with slow-release injection vehicles, and are more useful for testosterone replacement therapy. These 17 β hydroxyl esters lack inherent androgenic activity and must be hydrolyzed to testosterone before they become active. Parenteral preparations of testosterone are usually administered in an oil-based vehicle, such as cottonseed or sesame oil. In the United States, the 17 β -hydroxyl esters of testosterone include the short-acting testosterone propionate and longer-acting testosterone enanthate and cypionate. Because of the short activity of testosterone propionate, it is impractical to use; it must be injected every second day to maintain serum testosterone levels. In men requiring testosterone replacement, testosterone enanthate and cypionate may be administered every 2 to 3 weeks to maintain normal average testosterone levels.⁴⁶⁻⁴⁸ There are, however, surges in the serum testosterone level about 1 to 2 days after administration, sometimes reaching serum levels as high as 1400 ng/dL, which then decline over 14 to 21 days, reaching a nadir approximately at day 21. Because of these significant peaks and valleys in serum testosterone levels, patients may have mood swings and significant changes in sexual function.

Testosterones enanthate or cypionate may be administered in doses of 200, 300, or 400 mg every 2 to 4 weeks.⁴⁸ The 200-mg injections maintain normal testosterone levels for ap-

proximately 2 weeks, while 300-mg levels will maintain serum testosterone levels in the eugonadal range for approximately 3 weeks. The 400-mg doses, while obtaining higher peak values, will not maintain eugonadal levels beyond the 3-week limit. In hypogonadal men, these agents will produce an improvement in libido, sexual function, potency, energy level, and mood if these abnormalities are due to the androgen depletion.⁴² Increased sexual aggressiveness and overall aggressive behavior during peak levels of injectable testosterone have been reported,⁴⁶ and careful counseling about these mood and behavioral changes in patients undergoing injectable testosterone therapy is essential. These adverse effects are rare, however, and testosterone enanthate has become the most widely used agent for exogenous testosterone replacement in the United States. It is safe, cost-effective, and convenient.

Besides aggression, there are other side effects from androgen therapy, such as the development of an atherogenic lipid profile, insulin resistance, polycythemia, sleep apnea, fluid retention, acne, and hypertension.⁴⁹ Supraphysiologic levels of testosterone in the blood lead to increased peripheral aromatization of testosterone to estradiol, and this may produce gynecomastia.^{5,50,51}

Patches. Because of concern that supraphysiologic levels of testosterone play a major role in the development of side effects from testosterone treatment, transdermal testosterone patches, notwithstanding their high cost, avoid supraphysiologic levels of testosterone and restore the normal diurnal testosterone pattern.⁵² Another advantage of the patch over the injection is that if and when any disturbing side effects from testosterone occur, the patches can be removed immediately.

Transdermal testosterone is currently available as a scrotal or nonscrotal patch.⁵³ Transdermal vehicles use unmodified testosterone and are an alter-

native to intramuscular or oral medications. When applied prior to bedtime, these transdermal patch systems provide normal testosterone levels with diurnal variations in a physiologic fashion. Peak testosterone levels are achieved in the early morning, with a nadir prior to bedtime. While the scrotal patch (Testoderm) requires scrotal shaving weekly and increases DHT levels somewhat beyond the normal range, normal physiologic serum testosterone levels can be obtained. The nonscrotal transdermal patch (Androderm) also maintains a diurnal serum concentration curve with normal testosterone, estradiol, and DHT levels. Because testosterone levels do not increase beyond normal, the mood swings and aggressiveness that sometimes occur with intramuscular testosterone should not be seen with the transdermal preparations. While long-term studies are still unavailable on these issues, a smoother, more natural serum testosterone level can be obtained with the patches. Transdermal systems, however, are much more expensive than the parenteral preparations.

Clinical studies of these transdermal preparations demonstrate improved sexual function, libido, and nocturnal penile tumescence response, with normal hematocrit, lipid, and PSA levels. The side effect of dermatitis makes the transdermal agents inappropriate for some men.

Summary

Hypogonadism is the most common cause for endocrinopathy leading to ED, although the endocrine disorders themselves are some of the rarest of all causes of ED. Most men experience a lowering of their serum testosterone levels with age, but these levels usually are not low enough to induce ED. When hypogonadism is suspected of causing ED, treatment with exogenous androgens is recommended if there are no contraindications to its use in this setting. If the ED does not resolve af-

ter a finite time of treatment with the exogenous testosterone, other causes (vascular and/or neurologic) must be suspected. Even men with normal serum testosterone levels may require or request exogenous testosterone therapy because of other constitutional symptoms.⁵³ Patients on long-term androgen therapy require follow-up of their PSA, hematocrit, and liver enzymes about every 6 to 12 months. ■

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