Testosterone replacement in elderly men

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Testosterone deficiency, common in aging men, is associated not only with a decrease in libido and sexual functioning but also with the aging process itself and quality of life.

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Abstract

Testosterone deficiency is common in aging men and is associated not only with decreased libido and sexual functioning but also with the aging process and quality of life. This article reviews the findings associated with hypoandrogenism and outlines the treatments that are available for men with documented testosterone deficiency.


Drugs discussed: testosterone replacement therapies

Testosterone deficiency, underdiagnosed and often untreated, is a common disorder in middle-aged and older men. Clinicians tend to overlook it, and the complaints of the androgen-deficient men it affects are merely considered part of aging. Many patients, however, can derive significant benefits from treatment.

Incidence/prevalence

Older men are often compared to menopausal women, both groups experiencing a variety of clinical signs and symptoms of hormone deficiency. Menopause, however, describes an absolute ovarian failure and the effects of abrupt withdrawal of estrogens. Although no such similar event of complete testicular failure occurs in men, it has been well established that testosterone levels drop progressively with age and that the percentage of men with testosterone levels in the abnormal range increases.1 The resulting condition is variously referred to as the syndrome of male hypogonadism, androgen deficiency in the aging male (ADAM), partial androgen deficiency in the aging male (PADAM), male menopause, or andropause.2,3
The decline of serum testosterone levels appears to be a gradual, age-related process resulting in an approximate 1% annual decline after age 30. The prevalence of testosterone deficiency is estimated to be 20% in men aged 60 to 69 and as high as 50% in men older than 80. Of the estimated 2 to 4 million men in the United States suffering from hypogonadism, only 5% are receiving treatment. Based on demographic trends, the number of men with hypogonadism may reasonably be expected to increase.

Pathophysiology

Androgen deficiency most commonly results from decreased production of testosterone in the Leydig cells within the testes. Other causes include a decreased secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, resulting in inadequate production of luteinizing hormone (LH) from the anterior pituitary gland and increased production of sex hormone-binding globulin (SHBG), which binds circulating testosterone, thus leaving fewer hormones available to target tissues.

Medications known to decrease testosterone levels include GnRH agonists and antagonists, estrogens, glucocorticoids, chemotherapy agents, thiazides, opiates, and some psychotropic drugs, such as the selective serotonin reuptake inhibitors. Excess estrogen, for example, increases the circulating levels of SHBG, which leads sequentially to a decline in bioavailable testosterone. Last, a variety of lifestyle factors and clinical situations—such as morbid obesity, tobacco use, alcoholism, HIV infection, diabetes mellitus, hyperthyroidism, and psychological stress—will alter circulating testosterone levels and consequently affect target tissues.

Symptoms

Like any endocrine deficiency, a subnormal level of testosterone causes metabolic changes that produce both short- and long-term consequences in male physiology, growth, and behavior. Testosterone, which has a variety of effects on virtually every organ system, regulates male sexual development and behavior, as well as several domains of sexual function. In addition, testosterone promotes increases in lean body mass, bone mineral density, and erythropoiesis, and it also elevates mood. Testosterone concentrations are also associated with insulin sensitivity, cardiovascular risk, and cognition.

Diagnosis of androgen deficiency can be challenging, mainly because many testosterone-dependent features, including muscle mass, genital development, and facial hair, are maintained after the onset of testicular failure. The International Society for the Study of the Aging Male (ISSAM) suggests 6 major categories of androgen deficiency:

- Decreased sexual desire and erectile quality
- Decreased intellectual capacity (depression, fatigue)
- Decreased lean body mass
- Body hair and skin alterations
- Decreased bone mineral density
- Increased visceral fat.

However, clinical signs of testosterone deficiency can be quite elusive and insidious. The most common clinical manifestations are shown in Table 1 below.
Table 1:

<table>
<thead>
<tr>
<th>Common clinical symptoms of testosterone deficiency</th>
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<tbody>
<tr>
<td>• Loss of libido</td>
</tr>
<tr>
<td>• Erectile dysfunction</td>
</tr>
<tr>
<td>• Decreased lean body mass</td>
</tr>
<tr>
<td>• Body hair and skin alterations</td>
</tr>
<tr>
<td>• Decreased bone mineral density</td>
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<tr>
<td>• Increased visceral fat</td>
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<tr>
<td>• Infertility</td>
</tr>
<tr>
<td>• Depression</td>
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<td>• Reduced cognition</td>
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**Diagnosis**

It is important for physicians caring for older men to ask them about the various signs and symptoms associated with androgen deficiency, and, if these are present, to obtain a total serum testosterone level. Confirmation of hypogonadism requires the clinical diagnosis of a subnormal level of circulating testosterone. Normal values are 300 to 1000 ng/dL. The blood should be drawn and testosterone concentrations measured in the morning, since serum testosterone has a diurnal variation and levels peak between 8 and 10 AM.8

Blood levels below 400 ng/dL are suspect for androgen deficiency, and patients with lower levels (usually 200 ng/dL) should be considered as candidates for testosterone replacement therapy if there are no contraindications.3 Patients with low testosterone levels should have their LH level measured (which will differentiate primary from secondary hypogonadism), as well as their serum prolactin level. Low levels of LH and/or prolactin require an additional workup to rule out tumors of the pituitary gland.10

**Treatment**

Although testosterone replacement therapies for androgen deficiency do not alleviate all symptoms in all men, many can obtain relief and improve their quality of life through the reduction or elimination of hypogonadal symptoms. The FDA has approved a variety of compounds used to treat hypogonadism, all classified as Schedule III Controlled Substances because of their potential for abuse.11

There are a wide range of therapies, most notably IM long-acting ether injections, transdermal testosterone gels, and transdermal testosterone patches, although oral agents and buccal formulations are also available. IM testosterone injections (200 mg of testosterone propionate or testosterone enanthanate given every 2 weeks) are the least expensive treatments. However, these injections are associated with supraphysiologic peaks (immediately after the injections) and troughs (at the end of the 2-week period), with an accompanied increase in symptoms.3,10 Men receiving testosterone injections achieve a peak testosterone level 48 to 72 hours after injection and reach the nadir 12 to 14 days later. The blood testosterone level should thus be measured just before the next injection.

Transdermal preparations are the most convenient for patients. The testosterone gels and patches applied daily provide the normal physiologic diurnal variation, resulting in blood levels of testosterone that approach physiologic levels. In patients using these methods, the blood testosterone level should be properly measured in the morning, when testosterone levels are highest.
Contraindications

Testosterone is the hormone responsible for the growth of prostate tissue and has the potential side effect of causing an increased growth rate in normal and cancerous prostates. In addition, a possible increased risk of developing prostate cancer may exist. Patients who are known or suspected to have cancer or significant enlargement of the prostate; cancer of the kidney, liver, or breasts; or significant heart, kidney, or liver disease should not be given male hormone treatments. These conditions are all absolute contraindications for testosterone replacement therapy, as are hematocrit levels that are above 55%. Relative contraindications include hematocrit levels at about 52%, untreated obstructive sleep apnea, severe lower urinary tract obstructive symptoms, benign prostatic hyperplasia, and congestive heart failure, because of the risk of fluid retention with testosterone replacement therapy.3

Administration of testosterone in patients with prostate cancer

Although administering testosterone to hypogonadal men rarely results in the development of prostate cancer, and a link between prostate cancer and testosterone is tenuous, a history of prostate cancer has generally been an absolute contraindication for testosterone therapy, as recommended by the World Health Organization from the Third International Consensus Consultation on Prostate Cancer in 2002.13

The ISSAM advised that androgen administration is absolutely contraindicated in men suspected of having carcinoma of the prostate or breast cancer.14 Such recommendations presumably stem from a time when most men with prostate cancer were diagnosed at advanced, usually incurable stages. Recent evidence, however, suggests that selected men with hypogonadism following radical prostatectomy for prostate cancer can safely receive testosterone replacement.15

With earlier detection and improved survival from early-stage prostate cancer, some researchers have suggested that "after a prudent period (this remains an uncharted territory) without recurrence of . . . cancer, the pros and cons of androgen replacement therapy should be carefully considered and the restriction may be lifted."16

A recent report studied a select group of men who had negative surgical margins at the time of their radical prostatectomy, low preoperative prostate-specific antigen (PSA) levels (4.4-6.6 ng/mL), and low Gleason scores (lower than 7) and who were clinically hypogonadal as confirmed by serum testosterone measurements.17 These men received androgen replacement therapy postoperatively; no biochemical or clinical evidence of cancer recurrence was found in any of them after 12 years, and the clinical symptoms of hypogonadism had improved.

One of the authors (NHB) has followed 7 patients with prostate cancer who were treated with radical prostatectomy and were clinically hypogonadal as confirmed by low levels of serum testosterone. They had negligible PSA levels for at least 12 months after their prostate surgery. They agreed to follow-up of their PSA levels every 3 months and were told they would have to discontinue testosterone replacement therapy if the PSA levels increased on 2 successive occasions. None of the patients has had an increase in PSA level, and all experienced relief of symptoms after testosterone replacement therapy.

Follow-up

Because prostate diseases are thought to evolve over 2 or more decades, the actual potential risks of prolonged testosterone replacement therapy will require longer and more extensive studies then those currently available. All men receiving testosterone replacement therapy should have a baseline PSA test and digital rectal exam (DRE) to rule out prostate cancer.3 Patients need to be followed every 4 to 6 months, with monitoring of hemoglobin and hematocrit and checking of the serum testosterone level if there is no obvious improvement in clinical symptoms.
Once the adequate dosage has been determined, follow-up examinations every 6 months and an annual PSA test and DRE are required. If abnormal changes in any of these parameters are noted, testosterone replacement therapy should be stopped.

Men who have elevated total cholesterol and LDL-C levels and who use hormone replacement therapy should have their blood levels of total cholesterol, LDL-C, and HDL-C checked every 4 to 6 months. If there is a significant increase in total cholesterol or LDL-C or a significant decrease in HDL-C, consider adding a cholesterol-lowering medication, decreasing the dosage of testosterone, or both.12

**Conclusion**

The history of androgen deficiency can be easily elicited with a few questions. The diagnosis is confirmed with a blood test, and the treatment is easily accomplished with hormone replacement therapy. Very few men with androgen deficiency should be denied this effective treatment.

**References**