Considerations for the Diagnosis and Treatment of Testosterone Deficiency in Elderly Men

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Abstract

Increased longevity and population aging will increase the number of men with relative testosterone deficiency, as systemic levels of testosterone decrease by about 1% each year. Androgen deficiency should only be diagnosed in men with definite signs and symptoms, accompanied by low total testosterone levels measured in the morning by a reliable assay. Although clinical trials data are limited, current practice guidelines recommend testosterone replacement therapy for symptomatic men with low testosterone levels to improve bone mineral density, muscle mass and strength, sexual function, and quality of life. Testosterone replacement is not recommended for all older men with low testosterone levels, and should be avoided in patients with prostate or breast cancer, hyperviscosity, erythrocytosis, untreated obstructive sleep apnea, or severe heart failure. The goal of all available testosterone treatment modalities (intramuscular injections, nongenital patch or gel, bioadhesive buccal and oral testosterone, and pellets) is to achieve serum testosterone levels in the mid-normal range during treatment. Cost varies widely among these preparations and may limit their use. Patients receiving testosterone replacement therapy should be re-evaluated 3 months after testosterone initiation and at least annually thereafter. © 2007 Elsevier Inc. All rights reserved.

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Male hypogonadism is defined as failure of the testes to produce normal amounts of testosterone, combined with signs and symptoms of androgen deficiency. Systemic testosterone levels fall by about 1% each year in men. Therefore, with increasing longevity and the aging of the population, the number of older men with testosterone deficiency will increase substantially over the next several decades.1-4 The goal of this article is to provide the primary care physician with guidelines for diagnosing and treating testosterone deficiency in the elderly outpatient population. However, it must be emphasized that treatment of testosterone deficiency in older men is controversial due to the lack of outcomes data from large scale clinical trials. Recommendations in this article are therefore based on recent clinical practice guidelines developed by the Endocrine Society.5

Serum testosterone levels decrease progressively in aging men, but the rate and magnitude of decrease vary considerably. Approximately 1% of healthy young men have total serum testosterone levels below 250 ng/dL; in contrast, approximately 20% of healthy men over age 60 years have serum testosterone levels below this value.6-8 The Baltimore Longitudinal Study on Aging reported an average annual decrease of total serum testosterone of 3.2 ng/dL in men older than 53 years (ie, about 1% per year based on a lower limit of normal of 325 ng/dL).5 According to the Massachusetts Male Aging Study, sex-hormone-binding globulin (SHBG) increases by 1.2% annually. This is important because most circulating testosterone is bound to SHBG or to albumin. Therefore, free and bioavailable testosterone levels decrease with age to a greater degree than is reflected by the total testosterone level. However, free and bioavailable testosterone levels can be calcu-
lated from total testosterone, SHBG, and serum albumin concentrations (http://www.issam.ch/freetesto.htm).9

ETIOLOGY OF MALE HYPOGONADISM

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels decrease with age in healthy men. For this reason, the most common cause of androgen deficiency in elderly men is hypogonadotropic hypogonadism (ie, inappropriately low/normal LH and FSH related to pituitary or hypothalamic insufficiency). In addition, Leydig cell function in the testes decreases with aging and is affected by several medications, including glucocorticoids, spironolactone, opiates, and ketoconazole. Neuroleptic drugs that cause hyperprolactinemia can inhibit the release of gonadotropin-releasing hormone, leading to hypogonadotropic hypogonadism.2,5

Medical conditions associated with a high prevalence of low testosterone levels include type 2 diabetes mellitus, end-stage renal disease, osteoporosis or low-trauma fracture, infertility, diseases of the sellar region, weight loss due to malignancy or human immunodeficiency virus (HIV), and other less common chronic disorders.5

DIAGNOSIS OF MALE HYPOGONADISM

Several questionnaires have been developed to assess symptoms of androgen deficiency (Table 1), but it is essential to distinguish this condition from major depressive disorder, with which there is substantial symptomatic overlap.6,10,11 Other findings suggestive of testosterone deficiency in men include hot flashes and diaphoresis, very small or shrinking testes (adult testes are usually about 4.5 cm × 2.8 cm), reduced need for shaving, breast discomfort and gynecomastia, decreased spontaneous erections, reduced sexual desire and activity, reduced muscle bulk and strength, inability to father children (due to low or zero sperm counts), height loss, low bone mineral density, and low-trauma fractures. Less specific findings include decreased energy, depressed mood, mild anemia, and diminished physical or work performance.5,12

Measuring serum testosterone levels in the general population to screen for androgen deficiency is not recommended. However, in older men with clinical symptoms and signs consistent with androgen deficiency, the Endocrine Society recommends measuring a mid-morning total serum testosterone level using a reliable assay (Figure). When measuring serum testosterone, several factors need to be considered. Peak testosterone levels occur between 7 and 10 AM. Diet does not significantly affect the serum testosterone level, but a high insulin level (eg, following a high carbohydrate meal) can lower SHBG. Heavy alcohol consumption can decrease serum testosterone. On average, smokers have total and free testosterone levels 5%-15% higher than nonsmokers. SHBG levels are decreased in moderate obesity, hypothyroidism, glucocorticoid use, and nephrotic syndrome, and increased in hyperthyroidism, anticonvulsant use, cirrhosis, and other conditions (Table 2).5

Local laboratories usually cannot reliably or accurately measure free serum testosterone. However, free and bioavailable testosterone can be calculated from total testosterone, SHBG, and albumin (http://www.issam.ch/freetesto.htm).9 Approximately 2% of serum testosterone is unbound or free. Because testosterone can rapidly dissociate from albumin, all non-SHBG-bound testosterone is considered bioavailable. For total testosterone, the lower limit of the normal range is considered to be around 315 ng/dL (11 nmol/L); for free testosterone and bioavailable testosterone, lower limits of normal are around 6.5 ng/dL and 140 ng/dL, respectively.2 The “free testosterone index” is obtained by dividing the total testosterone level (in nanomoles per liter) by the SHBG concentration (in nanomoles per liter), but this is not a valid measure of free testosterone in older men.

If the initial total testosterone level is low (<300 ng/dL or 10.4 nmol/L, or below the lower limit of normal for healthy young men according to the reference range of the local laboratory), the measurement should be repeated, as 30% of men with an initially low level will have a normal level upon repeat testing. Conversely, men with true deficiency states demonstrate persistently low testosterone levels. In addition, LH and FSH levels should be measured, because secondary hypogonadism is a common cause of androgen deficiency in older men (Figure). If total testosterone, LH, and FSH are low, measurement of other anterior pituitary hormones (eg, prolactin) and perhaps a magnetic resonance scan of the pituitary should be considered to exclude intra- and perisellar lesions.

A recent cross-sectional analysis in 2 independent populations of healthy men (Belstress study, consisting of 2322 men aged 35 to 59 years; and Siblos study, consisting of 358 men aged 25 to 45 years) showed androgen receptor polymorphism encoded by a CAG repeat of variable length in exon 1 of the AR gene might play an important role in subject variability in serum (free) testosterone in healthy men because of differences in androgen sensitivity and feedback (LH) setpoint. CAG repeat length

### Table 1 Testosterone Deficiency in Aging Men

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are your erections less strong?</td>
<td>1</td>
</tr>
<tr>
<td>2. Do you have a decrease in libido (sex drive)?</td>
<td>1</td>
</tr>
<tr>
<td>3. Do you have a lack of energy?</td>
<td>1</td>
</tr>
<tr>
<td>4. Are you falling asleep after dinner?</td>
<td>1</td>
</tr>
<tr>
<td>5. Has there been a recent deterioration in your work performance?</td>
<td>1</td>
</tr>
<tr>
<td>6. Have you noticed a decreased enjoyment of life?</td>
<td>1</td>
</tr>
<tr>
<td>7. Do you have decrease in strength and/or endurance?</td>
<td>1</td>
</tr>
<tr>
<td>8. Have you noted a recent deterioration in your ability to play sports?</td>
<td>1</td>
</tr>
<tr>
<td>9. Are you sad and/or grumpy?</td>
<td>1</td>
</tr>
<tr>
<td>10. Have you lost weight?</td>
<td>1</td>
</tr>
</tbody>
</table>

Positive test: if the answer is yes to question 1 or 2, or to any 3 other questions

was positively associated with serum total testosterone in both study populations. Increased CAG repeat length was associated with increased free testosterone levels.13

THERAPY

In older men, the testosterone level below which testosterone replacement therapy is recommended is controversial; some experts favor treating symptomatic men with testosterone levels below 300 ng/dL, whereas others favor a threshold of 200 ng/dL.5 In either case, for men with classical androgen deficiency signs and symptoms accompanied by persistently low testosterone levels, testosterone replacement therapy is recommended to improve sexual function, bone mineral density, and sense of well-being, and to induce and maintain secondary sex characteristics.5,12,14,15 Testosterone also is suggested for men with low testosterone levels and erectile dysfunction (ED) after other causes of ED have been excluded.12 Short-term adjunctive therapy with testosterone may be considered in HIV-infected men with low testosterone levels and weight loss to improve muscle strength and promote weight gain. Testosterone also should be considered in men with low testosterone levels who are receiving high dose glucocorticoid therapy in order to help preserve bone mineral density.

Improved sexual activity scores and increased duration and frequency of nocturnal erections result from effective testosterone therapy in young hypogonadal men,5 but data are limited in older men, among whom the association between androgens and sexual function is more controversial.5,16 Dose-dependent increases in hemoglobin concentration and in bone mineral density are typically seen with testosterone therapy.17,18 The cardiovascular effects of tes-
Testosterone replacement appear to be neutral or mildly beneficial in young men; in older men, there is no convincing evidence that testosterone therapy is either beneficial or harmful to the cardiovascular system. Testosterone has minimal effect on serum lipids, whereas the effect on insulin sensitivity is controversial.

Hormone-dependent malignancies, such as prostate and breast cancer, may grow faster during testosterone therapy. Therefore, testosterone replacement is not recommended in such patients. It also is not recommended in patients with a palpable prostate nodule, a prostate-specific antigen (PSA) >3 ng/mL (pending further urological evaluation), hyperviscosity, erythrocytosis (hematocrit >50%), untreated obstructive sleep apnea, severe benign prostatic hyperplasia, or decompensated heart failure. Additional factors that may influence the decision to initiate testosterone therapy in older men include functional status and the presence of cognitive dysfunction. For example, a man who is bedridden is unlikely to benefit from testosterone administered to improve muscle strength. Importantly, the uncertainties about the benefits and risks of testosterone should be discussed with older men on an individualized basis before embarking on a course of testosterone therapy.

The goal of testosterone therapy is to achieve a serum testosterone level in the mid-normal range during treatment. Several formulations and therapeutic regimens are available, and selection should be based on patient preference, pharmacokinetics, and cost (Table 3). Testosterone enanthate or cypionate is administered intramuscularly, weekly at a dose of 100 mg, or biweekly at 200 mg. Alternatively, a 5- or 10-mg nongenital testosterone patch can be applied to the skin (away from pressure areas) each night. Newer preparations include testosterone gel applied daily to non-genital skin (away from pressure areas) each night. Patients on testosterone gel may have levels checked anytime after at least 1 week of therapy. Testosterone doses are generally lower in older than in younger men because testosterone is metabolized more slowly in the elderly.

After therapy is initiated, the patient should be re-evaluated at 3 months and at least annually thereafter. Special attention should be directed to symptoms before and after treatment to determine whether there has been a satisfactory response and to assess for adverse effects. A mid-morning total serum testosterone level should be obtained, with a target range of 350-700 ng/mL (12.3-24.5 nmol/L); for older men, a range of 400-500 ng/dL (14.0-17.5 nmol/L) is suggested. For injectable testosterone, the serum level should be measured between injections. For men treated with a transdermal testosterone patch, the serum level should be measured 3 to 12 hours after patch application. In patients receiving buccal testosterone tablets, the serum level should be measured immediately before application of a fresh system. Patients on testosterone gel may have levels checked anytime after at least 1 week of therapy.

The hematocrit should be measured at baseline, at 3 months, and annually thereafter. If the hematocrit exceeds 54%, testosterone therapy should be discontinued. Digital rectal examination and PSA measurement should be performed before starting testosterone therapy. If the PSA increases above 4 ng/mL, or by more than 1.4 ng/mL within 12 months of treatment, urological consultation should be obtained.

Patients on testosterone replacement should be evaluated for adverse drug effects specific to each preparation. These include excessive erythrocytosis and fluctuations in mood or libido (injectable testosterone); skin reactions (patch); and alterations in taste and gum irritation (buccal testosterone).

SUMMARY

Aging in healthy men is associated with a decrease in serum testosterone levels. Clinically significant androgen deficiency in older men is most often related to pituitary or hypothalamic abnormalities rather than to primary testicular failure. The challenge in diagnosing androgen deficiency in the elderly is to link signs and symptoms to serum testosterone levels. Questionnaires for assessing symptoms of testosterone deficiency in the aging male have been developed, and these instruments also may be helpful in evaluating for depression. Measuring serum testosterone levels accurately and reliably is problematic, and measurement issues must be taken into consideration when making a diagnosis of testosterone deficiency in an elderly man. Total serum testosterone should be measured in the morning in a man with signs and symptoms consistent with androgen deficiency. If low, the measurement should be repeated to confirm the diagnosis, because there is a 30% “false positive” rate with initial screening. LH and FSH should also be measured to distinguish primary from secondary hypogonadism.

Although data from large scale clinical trials in elderly men are lacking, testosterone replacement therapy is recommended in men with definite symptoms and signs of androgen deficiency in conjunction with a persistently low serum testosterone level. Several testosterone preparations are available, and selection of a therapeutic modality should be based on considerations of personal preference, side effect profile, pharmacokinetics, and cost. In addition, factors such as functional status and cognitive impairment may influence the decision to treat and the choice of therapy in older men. Following initiation of treatment, re-evaluation for efficacy and side effects should be performed after 3 months of therapy and at least annually thereafter. Finally, given the anticipated increase in the number of older men with androgen deficiency, there is a compelling need for additional research, including large scale clinical trials, to determine the short- and long-term benefits and risks of testosterone replacement therapy.
<table>
<thead>
<tr>
<th>Formulation</th>
<th>Replacement Dosage</th>
<th>Approximate Cost</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Testosterone (T) esters</strong></td>
<td>T enanthate or cypionate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 mg/wk IM or 200 mg q 2 wk IM</td>
<td>$70/month</td>
<td>Extensive clinical experience</td>
<td>IM injection, uncomfortable fluctuations in T levels and in libido, energy, mood</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(200 mg per 2 weeks)</td>
<td>Inexpensive</td>
<td></td>
</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Injectable long-acting T</td>
<td>T undecanoate in oil</td>
<td></td>
<td>Corrects symptoms of androgen deficiency</td>
<td>IM injection of a large volume (4 mL), more uncomfortable</td>
</tr>
<tr>
<td></td>
<td>1000 mg IM, then 1000 mg at 6 wk, and 1000 mg every 12 wk</td>
<td>Not available in the US</td>
<td>Requires less frequent administration</td>
<td></td>
</tr>
<tr>
<td>Nongenital transdermal T</td>
<td>5 mg, 1-2 patches every night, applied to nonpressure</td>
<td>$192/month (5 mg/d)</td>
<td>Physiological circadian T levels, no injection,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T patch</td>
<td></td>
<td>Good adhesion, normal DHT levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scrotal T patch</td>
<td>$131 for 30 patches</td>
<td>Symptoms of androgen deficiency are corrected</td>
<td>Scrotal skin needs to be shaved. High DHT levels</td>
</tr>
<tr>
<td></td>
<td>6 mg over 24 h applied daily</td>
<td></td>
<td>Physiological T levels, Little skin irritation</td>
<td>Potential transfer of T to women and children by contact (prevented by washing after 4-6 hr). Costly. High DHT levels</td>
</tr>
<tr>
<td>T gels</td>
<td>5-10 gm every AM</td>
<td>$205-248/month (5 g/d)</td>
<td>Dose flexibility, Musk odor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buccal T tablets</td>
<td>bioadhesive T pellets implanted</td>
<td>$190/month</td>
<td>Steady-state T levels, No hand washing</td>
<td>Twice daily, gum irritation, Taste alteration, high DHT levels</td>
</tr>
<tr>
<td></td>
<td>4-6 200 mg pellets implanted SC</td>
<td>$150 per 10 pellets</td>
<td>Symptoms of androgen deficiency are corrected</td>
<td>Surgical incision needed and pellets may extrude</td>
</tr>
</tbody>
</table>

RESOURCES
http://www.hormone.org/public/factsheets.cfm
http://www.endo-society.org/quickcontent/clinicalpractice/
clinical-guidelines/CG_Androgen.cfm
cfm
http://www.aace.com/pub/guidelines/
http://www.issam.ch/freetesto.htm


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References