Male hypogonadism, also called andropause and androgen deficiency of the aging male, is a clinical condition in which low levels of serum testosterone are found in association with specific signs and symptoms. During the aging process, serum testosterone concentration declines approximately 1.6% per year after the age of 40.¹ Although hypogonadism is a relatively common condition in the aging population, it is one of the most difficult to recognize and treat. This is because the condition closely resembles the physiologic aging process.

Understanding the long-term risks and benefits of testosterone replacement

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Male hypogonadism typically presents as fatigue, weakness, decreased libido and energy, erectile dysfunction, reduced muscle and bone mass, and increased central obesity. These signs and symptoms make it difficult to understand the extent to which the clinical features are due to aging, testosterone deficiency, or both. Detection and treatment are important because testosterone replacement therapy (TRT) can result in clinical benefits. Successful management of TRT requires an understanding of the risks and benefits of treatment (Table 1).

### Treatment risks
The risks of TRT are largely determined by the patient’s age, life circumstances, and other comorbidities. The treating clinician must understand the risks involved, including a risk of prostate cancer, benign prostatic hypertrophy, worsening symptoms of sleep apnea and congestive heart failure (CHF), liver toxicity, polycythemia, and infertility.

### Prostate cancer
It is well established that prostate cancer is an androgen-sensitive disease. Therefore, untreated prostate cancer is often considered an absolute contraindication to TRT. However, current evidence suggests that TRT does not increase the risk of prostate cancer over the general population. It appears that testosterone does not directly cause prostate cancer, but it has been shown to accelerate the growth of prostate cancer, if present. There is some evidence that testosterone replacement can be offered in men with previously treated prostate cancer; however, this decision should be made on a very individualized basis. The risks and benefits must be clearly understood by the patient and informed consent obtained before testosterone replacement.

### Breast cancer
Very little data exist linking testosterone replacement with breast cancer. It is believed that high levels of testosterone may lead to increased aromatization to an active derivative of estrogen, which may then stimulate breast tissue receptors and increase the risk of male breast cancer. Future prospective research will be necessary to determine whether such an association exists between TRT and male breast cancer. Most experts agree that TRT should be avoided in men with a history of breast cancer.

### Benign prostatic hyperplasia
The role of androgen in the development of benign prostatic hyperplasia (BPH) is well documented. Testosterone supplements increase prostate volume, with a mild increase in prostate-specific antigen levels in older men. Although a meta-analysis showed that the total number of prostate events combined was significantly greater in testosterone-treated than in placebo-treated men, the majority of events are due to prostate biopsy. At the same time, many studies have failed to show significant exacerbation of voiding symptoms attributable to BPH during testosterone supplementation. Complications such as urinary retention have not occurred at higher rates than in controls receiving placebo nor has there been any difference in urine flow rates, post-voiding residual urine volumes, and prostate voiding symptoms with patients receiving treatment in these studies. This is explained by the poor correlation between prostate volume and urinary symptoms. Although there are no compelling data to suggest that TRT in men with BPH exacerbates lower urinary tract (LUT) symptoms or promotes acute urinary retention, BPH represents a relative contraindication, which is no longer applicable after successful treatment of LUT obstruction. Monitoring for worsening signs and symptoms of BPH is an important part of TRT.

### Sleep apnea
TRT has been considered to have a negative effect on obstructive sleep apnea (OSA). It is believed to potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases. Though no clear link has been established, men receiving TRT should be informed about the potential risk of OSA when starting testosterone. In addition, physicians should counsel patients already diagnosed with sleep apnea that symptoms may worsen with testosterone replacement. However, in a recent randomized, placebo-controlled trial, testosterone undecanoate was administered intramuscularly (IM) in men with obesity and OSA, and overnight polysomnography was monitored at 0, 7, and 18 weeks.

Testosterone treatment resulted in mild worsening of the sleep apnea at 7 weeks, but then resolved by 18 weeks. At 18 weeks, there were no significant differences in ventilator markers between the 2 groups, suggesting that there may exist a time-dependent relationship between testosterone replacement and sleep apnea. Further research is necessary to explore the safety of TRT in the setting of sleep apnea. Currently, uncontrolled sleep apnea is a relative contraindication to TRT.

### Congestive heart failure
Low levels of testosterone have been associated with increased mortality and morbidity in men with CHF. Despite this observation, severe CHF is currently a relative contraindication of TRT. This recommendation is based largely on animal studies, which have suggested that TRT may induce hypertrophy, fibrosis, and apoptosis in cardiomyocytes. However, there is a growing body of literature to support the use of testosterone in

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_{May 2014 Evaluating and Treating Men with Hypogonadism AOA Health Watch_}
the face of mild-to-moderate CHF in the setting of hypogonadal men. Randomized, placebo-controlled trials have shown improvement of exercise capacity, functional capacity, and ventilator efficiency as well as improved peripheral muscle function. However, despite these improvements, all studies failed to detect any significant changes in central hemodynamics or left ventricular function.

Liver dysfunction
Benign and malignant hepatic tumors, intrahepatic cholestasis, hepatotoxicity, and liver failure have been reported with TRT. Prolonged use of high doses of orally active 17-α-alkyl androgens (methyltestosterone) has been associated with serious hepatic adverse effects. For this reason, the oral forms of testosterone, with the exception of testosterone undecanoate, are discouraged. These unfavorable hepatic effects do not appear to be associated with transdermal or IM injections. However, current standards recommend periodic liver function testing when receiving TRT.

Polycythemia
There is a correlation between high testosterone levels and high hemoglobin, most likely because testosterone stimulates erythropoiesis. Erythrocytosis can develop during TRT, especially in older men. Hypogonadism causes a decline in hemoglobin that can be restored with TRT. But, the elevation in hemoglobin above a certain level may increase morbidity, particularly in the elderly. The elevated hemoglobin concentration levels lead to an increase in blood viscosity, which could exacerbate vascular disease in the coronary, cerebrovascular, or peripheral vascular circulation. This is especially true in patients with other diseases that cause secondary polycythemia, such as chronic obstructive pulmonary disease.

Testosterone injections are more likely to cause polycythemia than topical preparations. Approximately 5% of transdermal users developed polycythemia, and the majority of changes took place over the first 3 months of treatment. It has been demonstrated that testosterone dosage correlates with the incidence of erythrocytosis. Periodic hematological assessment is indicated before treatment, then at 3 to 6 months and 12 months in the first year of treatment, and then annually thereafter. If hematocrit becomes elevated, therapy should be discontinued until hematocrit decreases to an acceptable level. The clinician can consider restarting the therapy, but this may require a dose adjustment, a change in formulation or delivery method, and/or periodic phlebotomy to keep hematocrit below 52% to 55%.

Infertility
All forms of exogenous testosterone replacement have a suppressive effect on the hypothalamic-pituitary-gonadal axis through feedback inhibition of pituitary follicle-stimulating hormone. This suppression results in decreased endogenous production of testosterone and spermatogenesis. This negative impact is usually transient and disappears some months after discontinuation of TRT. However, testosterone replacement is associated with a decreased likelihood of achieving conception. Hypogonadal patients considering TRT should be informed about infertility risks, and if fertility is desired, alternative treatments with gonadotrophins or antiestrogens may be useful.

Treatment benefits
As the prevalence of hypogonadism continues to rise, understanding the benefits of TRT is increasingly important. The treating clinician must analyze the risk-to-benefit ratio on an
However, the effect of TRT appears to be beneficial in improving muscle strength in the face of hypogonadism. However, many of these studies failed to show significant changes in functional ability. Meta-analyses of randomized trials in both middle-aged and older men with hypogonadism have shown that TRT is associated with increased lean muscle mass, decreased fat deposition, and increased strength when compared to placebo. Some studies have failed to show these benefits. The long-term benefits of testosterone on functional improvements require further investigation.

**Bone mineral density**

The pivotal role of testosterone in bone mass acquisition, bone turnover, and fracture risk is well documented. Thus, it is reasonable to consider that hypogonadism contributes to bone loss. There is a strong association between low bone density, bone loss, osteoporosis, and low testosterone in aging men. A meta-analysis of 14 randomized, placebo-controlled trials revealed an increase in BMD in the testosterone replacement groups. However, many of these studies were small in nature. TRT has never been shown to prevent the occurrence of fractures. Further investigation will be necessary to confirm the long-term benefits of testosterone therapy for improving bone strength, preventing osteoporosis, and associated fractures.

**Muscle mass**

Declining testosterone levels have been associated with decreased strength and muscle mass in aging men. The New Mexico Aging Process Study revealed correlations between testosterone levels and muscle strength. Several studies found TRT to be beneficial in improving muscle strength in the face of hypogonadism. However, many of these studies failed to show significant changes in functional ability. Meta-analyses of randomized trials in both middle-aged and older men with hypogonadism have shown that TRT is associated with increased lean muscle mass, decreased fat deposition, and increased strength when compared to placebo. Some studies have failed to show these benefits. The long-term benefits of testosterone on functional improvements require further investigation.

**Metabolic syndrome**

Metabolic syndrome (MetS) is characterized by central obesity, insulin resistance, dyslipidemia, and hypertension. Low testosterone is associated with each of these MetS characteristics. The relationship of testosterone to these conditions is complex. An inverse relationship exists between serum testosterone levels and degree of obesity in men, particularly visceral obesity. TRT has been shown to decrease body fat mass and waist circumference, a marker for central adiposity (Table 2).

Several epidemiology studies have shown a close association between low serum testosterone levels and type 2 diabetes mellitus (DM) in men. There is a positive correlation between serum testosterone levels and insulin sensitivity in men across the full spectrum of glucose tolerance, and an improvement in insulin sensitivity was noted after testosterone replacement. However, the effect of TRT on glycemic control of men with DM is still uncertain. Testosterone plays a role in lipid metabolism as well. TRT decreases low-density lipoprotein (LDL) and total cholesterol. However, HDL has also been shown to decrease, which may temper any cardiovascular benefit in lowering LDL.

TRT appears to have no significant effect on triglyceride (TG) levels. The decrease in cholesterol is believed to be related to the decrease in the visceral abdominal fat under the influence of androgens, which inhibit lipoprotein lipase activity and increase lipolysis with improvement of insulin sensitivity and mobilization of TGs. Although TRT appears to be a new strategy for the treatment of MetS, concerns about its effect on adipocytokines, such as adiponectin, have prevented widespread usage for the management of MetS. Currently, TRT is viewed as an adjuvant therapy in MetS in the hypogonadal male.

**Sexual function**

Hypogonadism may be responsible for sexual dysfunction. When low testosterone levels are found, many aging men experience symptoms of low libido, changes in erectile function, and sexual satisfaction. It is thought that low serum testosterone level is rarely the major cause of erectile dysfunction in the aging male, although it may play a subsidiary role in many cases of erectile dysfunction. TRT has been shown to be the most beneficial to sexual function in men with a testosterone level below 346 ng/dL. A meta-analysis of testosterone replacement effects on sexual dysfunction has shown that the largest improvement occurs in the individual’s libido, whereas only

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**Table 1. Potential risks and benefits associated with TRT**

<table>
<thead>
<tr>
<th>Risks</th>
<th>Benefits</th>
</tr>
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<tbody>
<tr>
<td>Prostate cancer</td>
<td>Increased muscle mass</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Increased bone mineral density (BMD)</td>
</tr>
<tr>
<td>Worsening of benign prostatic hyperplasia</td>
<td>Improved lipid metabolism</td>
</tr>
<tr>
<td>Worsening of sleep apnea</td>
<td>Improved sexual function</td>
</tr>
<tr>
<td>Worsening of congestive heart failure (CHF)</td>
<td>Improved mood</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>Improved cognitive function</td>
</tr>
<tr>
<td>Infertility</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2. Positive impact of TRT on characteristics of metabolic syndrome**

<table>
<thead>
<tr>
<th>Decreases</th>
<th>Increases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body fat mass</td>
<td>Insulin sensitivity</td>
</tr>
<tr>
<td>Waist circumference</td>
<td></td>
</tr>
<tr>
<td>Low-density lipoproteins (LDLs)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
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</table>
small, nonsignificant, and inconsistent improvements in erectile function and sexual satisfaction were observed.\textsuperscript{12}

**Mood**

Depression is more commonly found in the aging hypogonadal man. TRT has been associated with improved mood and overall sense of well-being. A meta-analysis showed some beneficial effects of TRT on depression scores.\textsuperscript{13} However, this has not been consistently shown across all trials. The usage of testosterone replacement as an antidepressant for the general population is not recommended. Concomitant usage of testosterone replacement and serotonin reuptake inhibitors has been shown to be beneficial in hypogonadal men.\textsuperscript{14} Additional studies will be required to assess the role of TRT in the depressed hypogonadal male.

**Cognitive function**

As men age, many changes occur in their cognitive abilities. Declining cognitive ability occurs due to a number of comorbidities, such as vascular disease and neurological pathology. Hypogonadism appears to be one of the causes. Lower levels of testosterone appear to have an effect on abilities, such as spatial abilities, verbal abilities, and cognitive function.\textsuperscript{15} Many of the studies that have shown a benefit to cognitive function with testosterone replacement have been smaller in sample size and short in duration. This makes the long-term effects difficult to predict. Studies of longer duration and larger sample sizes are needed to confirm the benefits of TRT on cognitive performance.

**Final notes**

The incidence of male hypogonadism is rapidly increasing, and more treatment options are available than ever before. These rapid changes have increased awareness of the condition, and revealed the complex nuances of the management, of hypogonadism. Before initiating treatment, the risks and benefits of testosterone therapy must be clearly discussed with the patient while assessing for other comorbidities in which TRT may be dangerous.

Men with significant erythrocytosis, severe untreated sleep apnea, prostate cancer, or high risk of cardiovascular event should avoid TRT. In many scenarios, the benefits of TRT on muscle mass, strength, BMD, sexual function, mood, and overall well-being may outweigh the risks, but careful consideration must be taken with each patient. Response to testosterone replacement should be assessed, and if there is no improvement of symptoms, TRT should be discontinued and further investigation into other causes conducted.

Many questions regarding the treatment of hypogonadism remain to be answered. The long-term benefits and risks of testosterone replacement will become clearer as the effects of testosterone replacement on all health-related outcomes are studied over an extended period of time.\textsuperscript{\textsuperscript{16}}

### References


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