According to “Testosterone therapy in adult men with androgen deficiency syndrome: an Endocrine Society clinical practice guideline,” male hypogonadism is defined as a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis.¹
Prevalence of hypogonadism
Several longitudinal and cross-sectional studies have been conducted to determine the prevalence of male hypogonadism, including the Massachusetts Male Aging Study (MMAS), European Male Aging Study, Baltimore Longitudinal Study of Aging (BLSA), Hypogonadism in Males study, and the Boston Area Community Health Survey (BACHS). On the basis of the results from these studies, the prevalence of male hypogonadism has been estimated to be between 5.6% and 39%. This wide range has been attributed to differences between studies in the definitions of hypogonadism, clinical symptoms used to diagnose the condition, inclusion or exclusion of comorbid conditions, and the specific populations studied. As a result, the exact prevalence of male hypogonadism cannot be known with certainty.

The overriding trend noted in these studies is that the prevalence of hypogonadism increased with age, starting at approximately 40 years. In addition, hypogonadism was projected to be much higher in men with comorbidities such as metabolic syndrome, type 2 diabetes, obesity, end-stage renal disease, human immunodeficiency virus (HIV), chronic obstructive pulmonary disease, osteoporosis, sarcopenia, and cardiovascular disease.

Pathophysiology
The hypothalamic-pituitary-gonadal axis is responsible for the pulsatile release of several hormones that determine testosterone production and cessation. Testosterone production is under the control of luteinizing hormone (LH), which acts on the interstitial Leydig cells of the testes (Figure 1). Sperm production is under the control of follicle-stimulating hormone (FSH), which acts on Sertoli cells of the testes to stimulate spermatogenesis. The by-products of stimulation of the testes by both LH and FSH are testosterone from the Leydig cells and inhibin B from Sertoli cells. Inhibin B acts as a negative feedback to control FSH production at the level of the anterior pituitary, whereas testosterone acts as a negative feedback mechanism at the hypothalamic level to decrease gonadotropin-releasing hormone (GnRH) and at the level of the anterior pituitary to decrease LH secretion.

Testosterone circulates in the body in both free and bound forms. Only 1% to 2% of testosterone circulates free. Another 40% to 50% is bound lightly to albumin, whereas 50% to 60% is bound tightly to sex hormone-binding globulin (SHBG). Bioavailable testosterone that contributes to biological action is either in the form of free testosterone or of albumin-bound testosterone. The biological actions of testosterone include promotion of erythropoiesis, spermatogenesis, production of sebum, axillary and body hair growth, maintenance of bone mass and reproductive tissues, and an increase in lean body mass, body weight, and nitrogen retention.

Diagnosis of male hypogonadism
The Endocrine Society recommends that a diagnosis of hypogonadism (androgen deficiency) be made only in men with consistent symptoms and signs and unequivocally low serum testosterone levels. Symptoms include...
reduced libido, reduced muscle mass or strength, low trauma fractures, depressed mood, decreased energy and vitality, osteoporosis, and erectile dysfunction (ED). Other lesser symptoms include lack of initiative or self-confidence, poor concentration, and elevated body mass index.

In terms of defining low serum testosterone, The Endocrine Society pinpoints a TT level of 300 ng/dL as the lower limits of normal. In contrast, the American Association of Clinical Endocrinologists suggests 200 ng/dL, whereas the American Society of Andrology, along with some British and European societies, identifies a TT level of 230 ng/dL as the limit below which a patient will usually benefit from TRT. In my practice, I use The Endocrine Society value of 300 ng/dL to identify patients with low TT levels.

Once a low TT level has been found, The Endocrine Society recommends confirming it with a second TT value checked between 8 am and 10 am. If confirmed, further evaluation proceeds from this point to determine whether the patient’s hypogonadism is primary (testicular origin), secondary (hypothalamic or pituitary origin), or a combination of both. Furthermore, a thorough history and physical examination should be undertaken to determine whether the patient has any family history of genetic abnormalities, history of testicular or brain trauma, radiation, darkened or tanned skin, visual field defects, headaches, chemotherapy, orchitis, undescended testis, cancers, or fertility issues.

The physical examination should include specific attention to digital rectal exam (DRE), distribution of body hair, and testicular size, consistency, mass, and presence bilaterally. The testicular examination is of particular importance because The Endocrine Society recommends that, in men with primary testicular failure of unknown etiology, a karyotype should be obtained to exclude Klinefelter syndrome, especially in those with testicular volume less than 6 mL.

Questionnaires are available to help physicians assess patients for hypogonadism in the office. These include the Androgen Deficiency in Aging Males (ADAM) questionnaire, Aging Male Survey (AMS), MMAS survey, and the Rosen questionnaires. Though these are useful screening tools, they fall short of expectation when it comes to diagnostic utility.

Once the presence of low TT has been confirmed, an LH and FSH value should be obtained to determine the etiology as primary or secondary hypogonadism, as well as to direct further evaluation. A diagnosis of hypogonadism should never be made in a patient during an acute illness. A borderline low testosterone finding in a patient during an acute illness will be noted in patients with primary hypogonadism, as well as to direct further evaluation. A diagnosis of hypogonadism should never be made in a patient during an acute illness. A borderline low testosterone finding in a patient during an acute illness is of particular importance because The Endocrine Society recommends that, in men with primary testicular failure of unknown etiology, a karyotype should be obtained to exclude Klinefelter syndrome, especially in those with testicular volume less than 6 mL.

Table 1. Conditions with high and low SHBG levels

<table>
<thead>
<tr>
<th>Increased SHBG concentrations</th>
<th>Decreased SHBG concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Hepatic cirrhosis</td>
<td>Obesity; metabolic syndrome</td>
</tr>
<tr>
<td>Use of anticonvulsants</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Use of estrogens</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Use of glucocorticoids,</td>
</tr>
<tr>
<td>HIV infection</td>
<td>progestins, and anabolic</td>
</tr>
<tr>
<td>Catabolic conditions</td>
<td>steroids</td>
</tr>
<tr>
<td>(malnutrition; malabsorption)</td>
<td></td>
</tr>
</tbody>
</table>

SHBG, sex hormone-binding globulin; HIV, human immunodeficiency virus


Primary hypogonadism (hypergonadotropic)

Elevated LH and FSH will be noted in patients with primary hypogonadism, suggesting a testicular etiology. Causes of primary hypogonadism include karyotype abnormalities, with Klinefelter syndrome (47, XXY syndrome) being the most common genetic abnormality, toxin exposure or chemotherapy, congenital defects, such as anorchia or cryptorchidism, orchitis from mumps or autoimmune disease, testicular trauma or infarction, medications that inhibit androgen synthesis, such as ketoconazole, and increased temperature of the testicular environment due to varicocele or large pannus. The Endocrine Society recommends that, in men with primary testicular failure of unknown etiology, a karyotype be obtained to exclude Klinefelter syndrome, especially in those with testicular volume less than 6 mL.

Secondary hypogonadism (hypogonadotropic; normogonadotropic)

Low to normal levels of LH and FSH point to a pituitary-hypothalamic process as the etiology for secondary hypogonadism. Hypogonadotropic hypogonadism can be divided into acquired and congenital causes. Patients with congenital causes usually present in their late teenage years when they fail to undergo usual pubertal changes with secondary virilization. Congenital causes of secondary hypogonadism include Kallmann syndrome (GnRH deficiency), congenital adrenal hypoplasia, genetic mutations associated with pituitary hormone deficiency (PROP-1 mutation, HERS1 mutation), Prader Willi syndrome, congenital spherocytosis, Moebius syndrome, cerebellar ataxia, and retinitis pigmentosa.

Acquired causes of hypogonadotropic hypogonadism include central nervous system-derived abnormalities, such as head trauma or pituitary tumors, autoimmune disease, Crohn disease, ß-thalassemia/hemoglobinopathies, hereditary hemochromatosis, and disorders of lipid metabolism.
Other acquired conditions that can contribute to secondary hypogonadism include aging, obesity, type 2 diabetes, sleep apnea, estrogen excess, severe obstructive sleep apnea, cirrhosis, hypothyroidism, alcohol abuse, pubertal delay, renal failure, rheumatoid arthritis, acute illness, anorexia nervosa, HIV, anabolic steroid abuse, and medications such as opiates or corticosteroids. Further laboratory evaluation for secondary hypogonadism should be undertaken to include serum prolactin levels, thyroid-stimulating hormone, free thyroxine (T4), ferritin level, and total iron-binding capacity. In patients with a TT level at <150 ng/dL in conjunction with panhypopituitarism, persistent hyperprolactinemia, or symptoms of tumor mass effect, such as headache, visual impairment, or visual field defects, The Endocrine Society recommends that pituitary magnetic resonance imaging be performed to evaluate for hypothalamic or pituitary masses. If a pituitary mass is found, the patient should be referred to a neurosurgeon.

When is treatment not recommended?

There are several scenarios in which low TT levels do not warrant treatment. The Endocrine Society Guidelines recommend against TRT in patients who desire fertility. In addition, male patients with prostate or breast cancer, severe lower urinary tract symptoms (International Prostate Symptom Score [I-PSS] score, >19), severe untreated sleep apnea, untreated congestive heart failure, a hematocrit level of >50%, abnormal results of DRE, or a prostate-specific antigen (PSA) level of >4 ng/dL should avoid TRT.

Patients aged 40 years or older with a baseline PSA level of more than 0.6 ng/dL should have a DRE and PSA assessment before initiation of therapy. Last, high-risk patients, such as an African American or an individual with a first-degree relative with prostate cancer and a PSA level of >3 ng/dL, should not be treated. Urological consultation should be obtained before consideration of treatment for any of the above-described prostate-related symptoms or PSA values. Other specialty referrals may be necessary, depending on the comfort level of the primary care physician or mid-level practitioner working up this disease state.

Who should be treated with testosterone replacement therapy?

The Endocrine Society recommends therapy for patients whose hypogonadism has been confirmed by 2 morning TT levels and those who are symptomatic. The goal of therapy is to induce and maintain secondary sexual characteristics, as well as to improve sexual function, sense of well-being, and bone mineral density (BMD).

The risk of developing hypogonadism increases with comorbid conditions, such as metabolic syndrome, obesity, end-stage renal disease, and osteoporosis.

When prescribing testosterone therapy, the goal is to raise serum testosterone levels to the mid-normal ranges (between 400 and 700 ng/dL). The goal is not to treat for supratherapeutic TT levels, because this may increase the risk for cardiovascular-related events. The Endocrine Society recommends treatment for men with low libido plus low testosterone as well as men with ED plus low testosterone (once other causes of ED have been ruled out). Furthermore, if a patient has a borderline confirmed low TT, an SHBG level should be checked, because certain conditions and medications may increase or decrease these levels, affecting the amount of bioavailable testosterone (Table 1).

Treatment options

There are several different formulations of testosterone for the treatment of male hypogonadism. Treatment options include 1% to 2% transdermal gels, subcutaneous (SC) implantable pellets, intramuscular injections, buccal formulations, transdermal patches, and oral testosterone. Because these options have various advantages and disadvantages, the prescribing decision should be based on physician considerations and patient preference.

Testosterone injections are usually the cheapest choice of treatment and can be administered at the office or at home by the patient or a designate. Disadvantages of this type of therapy include the potential for supraphysiologic TT levels, greater risk of elevated hematocrit levels, short dosing intervals (every 2 weeks or less), and possible injection-site pain. Long-acting formulations, which would decrease the dosing interval to 4 times per year, have been developed. The US Food and Drug Administration recently approved a long-acting injection that became available in March 2014. It will be dosed at initiation, at 4 weeks, and then once every 10 weeks thereafter.

Transdermal patches are applied once-nightly and approximate the normal circadian plasma testosterone levels. These patches are applied to the back, abdomen, upper arms, or thighs. Disadvantages of these patches are skin irritation that results in treatment discontinuation, the need for more than 1 patch to be applied at a time to sustain therapeuetic testosterone levels, and daily administration.

Transdermal gels and solutions are applied daily and provide flexibility of dosing, less incidence of skin irritation, as compared with patches, and
invisibility of application. These gels and solutions are typically available in 1% to 2% concentrations. Disadvantages include the risk of transference to the patient’s partner or children. This risk can be minimized by washing hands after application, covering the site of application with clothing after the gel has dried, and washing the application site when skin-to-skin contact is anticipated. 3

Subcutaneous (SC) pellets are implanted in the SC tissues of the buttocks or lower abdomen. This is the only long-acting formulation of TRT that is approved in the United States. Redosing occurs at 4- to 6-month intervals. Drawbacks to this type of treatment are the potential for pellet extrusion, the necessity of surgical implantation, and the risk of surgical-site infections. 3 This treatment option may be best suited to patients who have already established a tolerance to TRT. 3

Buccal tablets are adhesive tablets that are applied to the gums just above the incisor teeth. 4 Disadvantages include the need to apply 2 tablets per 24-hour period, a 16% chance of gum and buccal irritation, and alteration in taste. 3,5

Oral testosterone tablets are not approved for use in the United States. Such treatment is not recommended because of its hepatotoxic side effects and association with the development of liver tumors. 3

Monitoring treatment
The Endocrine Society presents clear guidelines for patient monitoring in “Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline.” In particular, patients should be evaluated at 3 and 6 months after initiation of therapy and once per year thereafter. Their testosterone level and hematocrit should be checked within 3 to 6 months of initiating TRT and then annually for hematocrit. In addition, BMD should be assessed within 1-2 years in patients with osteoporosis or low trauma fracture.

PSA should be screened according to the recommendations of the family physician’s preferred guidelines. Guidelines are provided by a number of societies, including the National Comprehensive Cancer Network, the American Cancer Society, and the American Urological Association. A DRE should always be performed when checking a PSA level, especially when monitoring annually.

Final notes
Due to a surge in media attention, awareness of TRT is increasing. As a result, more patients are asking about treatment options in the family practice setting. Annual prescriptions for testosterone increased more than 5-fold from 2000 to 2011, reaching a total of 5.3 million prescriptions, with market sales of $1.6 billion in 2011. 14 Furthermore, $3.47 billion were spent on advertising to the consumer in 2012. 15

It is important to keep in mind that treatment is not necessary for every individual, either because of comorbidities or lack of symptoms. Additional clinical trials must be conducted to further assess the risks and benefits of TRT. I hope that this article and the review of guidelines help clarify the issues affecting the decision of whether to treat or to refer patients to a urologist, an endocrinologist, or even a neurosurgeon.

References

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Resources
AUA/IPSS score: http://www.urospec.com/uro/Forms/ipss.pdf
AMS questionnaire: http://www.biomedcentral.com/content/supplementary/1477-7525-1-15-s2.pdf