ABSTRACT

Similar to many other endocrinologic disease states, hypogonadism is a multifactorial disorder with clinical sequelae that reach well beyond those of just androgen deficiency. This syndrome results from failure of the testes to produce physiological levels of testosterone due to disruption of 1 or more levels of the hypothalamic-pituitary-gonadal axis. The condition affects 2 to 4 million men in the United States and becomes increasingly prevalent with age. Modern-day factors, such as increased life expectancy and the rising prevalence of obesity and type 2 diabetes mellitus, are expected to further raise the incidence of male hypogonadism. Although increased clinical awareness of the effects of hypogonadism and the growing interest in hormone replacement therapy for men and women have certainly helped rescue this condition from medical obscurity, fairly recent estimates indicate that only 5% of affected men receive treatment.

DETECTION

The reasons for undertreatment are numerous. Although men are now more forthcoming in reporting health-related complaints to physicians than in the past, many are still embarrassed and may deny symptoms that may be suggestive of hypogonadism. The challenge of detection is another major contributing factor. Although the signs of hypogonadism are readily identifiable in males who have not undergone puberty, the clinical picture of testosterone deficiency in very young and older patients is less clear. Hypogonadism is often unrecognized before the age of puberty, unless it is associated with growth retardation or other anatomic or endocrine abnormalities. The clinical diagnosis of older males with hypogonadism (sometimes referred to as

*Urologist, Men’s Health Boston, Brookline, Massachusetts. Address correspondence to: Abe Morgentaler, MD, Urologist, Men’s Health Boston, One Brookline Place, Suite 624, Brookline, MA 02445. E-mail: amorgent@yahoo.com.
late-onset hypogonadism or partial androgen deficiency of the aging male) might also escape detection because not all signs and symptoms are necessarily present together, they often progress slowly and are subtle in nature, and the nonspecific signs and symptoms might not be discernible from the unavoidable process of aging itself. It's not uncommon for testosterone-dependent physical features, such as muscle mass and beard, to be maintained long after the onset of testicular failure. Furthermore, the symptoms are often modified by comorbid illness, severity and duration of androgen deficiency, variation in androgen sensitivity, and previous testosterone therapy. As a result of these complexities, currently accepted diagnostic criteria rely on laboratory evidence of a subnormal serum testosterone level and the presence of hypogonadal symptoms.

**DIAGNOSIS**

In the Endocrine Society's guidelines, clinicians are instructed to measure serum testosterone levels in patients with clinical manifestations shown in Table 1, and they are also urged to measure levels in patients who experience less specific symptoms (Table 2) in conjunction with those listed in Table 1. In interpreting laboratory studies, it is pertinent to understand the circulatory nature of testosterone, a highly protein-bound hormone of which levels vary significantly throughout the day. Most testosterone is tightly bound to sex hormone-binding globulin (SHBG) and, to a lesser extent, albumin. Therefore, only a small percentage (0.5%–3%) of testosterone is bioavailable, which represents unbound testosterone plus testosterone bound to albumin. The latter portion is still considered bioavailable because testosterone is only loosely bound to albumin. As a result, testosterone concentrations are not only affected by illness and certain medications but also by alterations in SHBG concentrations. Levels are also time-dependant, varying from hour to hour and periodically declining below the normal range in some otherwise normal men. Total testosterone levels are generally used for laboratory diagnosis; however, exclusive reliance on total testosterone may result in an incorrect diagnosis. Confirming low testosterone levels in those with mildly hypogonadal ranges is pertinent because 30% of such patients may have a normal testosterone level on repeat measurement. Also, 15% of healthy young men are known to have testosterone levels below the normal range at some point in a 24-hour period.

### Table 1. Symptoms and Signs Suggestive of Androgen Deficiency in Men

- Incomplete sexual development, eunuchoidism, and aspermia
- Reduced sexual desire (libido) and activity
- Decreased spontaneous erections
- Breast discomfort and gynecomastia
- Loss of body (axillary and pubic) hair and reduced shaving
- Very small or shrinking testes (especially <5 mL)
- Inability to father children and low or zero sperm counts
- Height loss, low-trauma fracture, and low bone mineral density
- Reduced muscle bulk and strength
- Hot flushes and sweats


### Table 2. Other Symptoms and Signs Associated with Androgen Deficiency that Are Less Specific

- Decreased energy, motivation, initiative, aggressiveness, and self-confidence
- Feeling sad or blue, depressed mood, and dysthymia
- Poor concentration and memory
- Sleep disturbance and increased sleepiness
- Mild anemia (normochromic, normocytic, in the female range)
- Increased body fat and body mass index
- Diminished physical or work performance


In diagnosing hypogonadism in older men, it is important to understand that age-related declines in free testosterone are more rapid than decreases in total testosterone, which appears to be related to increasing SHBG levels. Therefore, it is essential to measure total and free testosterone levels. Although free testosterone is only a small percentage of the actual bioavailable testosterone, it serves as a reasonable surrogate for bioavailable testosterone, which is not always available as an assay. Measuring SHBG levels is optional. Because hypogonadism that is associated with advancing age involves defects in both testicular and hypothalamic-pituitary function, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels are typically mildly increased. The circadian variation in serum testosterone levels may also be lost with aging.
Currently, there is no universal consensus as to what level of serum testosterone represents clear-cut hypogonadism. Part of the difficulty is that different individuals may have different vulnerabilities to hypogonadal symptoms for a given testosterone level. Another confounding factor is that total testosterone is most commonly used for assessment, but may not accurately reflect bioavailable testosterone, for reasons explained earlier in this article. Furthermore, the testosterone concentration below which testosterone administration improves outcomes is unknown and may vary among individuals and among target organs. However, in providing some guidance, a number of clinicians believe that total testosterone levels above 12 nmol/L (346 ng/dL) or free testosterone levels above 250 pmol/L (72 pg/mL) do not require replacement therapy. Other clinicians depend on clinical judgment in the absence of hard evidence. There is general consensus that serum total testosterone levels below 8 nmol/L (231 ng/dL) or free testosterone levels below 180 pmol/L (52 pg/mL) do require replacement therapy. Other clinicians depend on clinical judgment in the absence of hard evidence. There is general consensus that serum total testosterone levels below 8 nmol/L (231 ng/dL) or free testosterone levels below 180 pmol/L (52 pg/mL) do require treatment. However, it should be noted that reference ranges vary widely from laboratory to laboratory. Therefore, most clinicians consider clinical symptoms to be more important than test results, which are mainly used for confirmation of a diagnosis. Thus, in a male patient who exhibits characteristic signs and symptoms, but has low-normal testosterone levels, a trial of testosterone therapy may be reasonable.

Besides measuring testosterone levels, the diagnostic process also involves evaluating serum LH and FSH to determine whether the hypogonadism is related to a primary testicular disorder (hypergonadotropic hypogonadism) or to a secondary pituitary-hypothalamic disease (hypogonadotropic hypogonadism). Patients with primary hypogonadism may have increased FSH levels, increased LH levels, low testosterone levels, and impaired production of sperm. Those patients with secondary disease have deficient release of gonadotropin-releasing hormone and typically have low-normal or low levels of FSH, LH, and testosterone. In men who are suspected of having secondary hypogonadism, additional diagnostic evaluation may be needed to exclude other complicating conditions, such as pituitary neoplasia, hyperprolactinemia, hemochromatosis, obstructive sleep apnea, and genetic disorders associated with gonadotropin deficiency.

The list of possible causes of hypogonadism is quite long and is highly dependent on whether the patient suffers from primary or secondary hypogonadism. Basically, disorders that affect the testicles lead directly to primary hypogonadism, whereas offenders of the hypothalamic-pituitary regulation lead to secondary hypogonadism. Some causes of primary hypogonadism include testicular trauma, varicoceles, irradiation, chemotherapy, mumps orchitis, leprosy, and chromosomal genetic disorders such as Klinefelter’s syndrome, XYY syndrome, XX masculinization, XY/XO mixed gonadal dysgenesis, and 5α-reductase deficiency. Secondary hypogonadism is often caused by acquired gonadotropin deficiencies, prolactin-secreting tumors, severe systemic illness, and uremia. Combined primary and secondary etiology results from aging, hepatic cirrhosis, and sickle cell disease.

**Physiological Aspects**

Hypogonadism may manifest itself with testosterone deficiency, infertility, or both conditions. Assessment of men for androgen deficiency should, first and foremost, include a detailed patient history, and then a thorough physical examination. In patients with postpubertal onset of secondary hypogonadism, it’s important to consider other endocrine deficiencies, such as central hypothyroidism or secondary adrenal insufficiency. Visual field disturbances, headaches, or seizures may indicate the presence of pituitary tumors. Use of certain medications (eg, antifungals, opioids, LH-releasing hormone agonists, estrogens, chemotherapy, high-dose glucocorticoids, and recreational drugs), including herbal preparations or home remedies, should also be documented because they can affect testosterone production or metabolism. This is further addressed in Dr Duggal’s review article. Pharmacists can play an integral role in contributing to patient history by reviewing medication profiles for offending drugs and investigating any herbal preparations that patients are using. Although little is known about herbal products compared to US Food and Drug Administration-regulated pharmaceuticals, many major drug databases now contain relatively detailed herbal monographs that include side effects and drug interactions.

The primary symptoms (Table 1) of hypogonadism in adult men include diminished libido, erectile dysfunction (ED), loss of energy and motivation, and depressed mood. Signs of hypogonadism may include anemia, reduced muscle mass and bone mineral densi-
ty (resulting in osteopenia or osteoporosis), increased visceral fat mass, and decreased lean body mass and muscle. There may be gynecomastia and reduced testicular size or firmness. Occasionally, men may notice the need to shave less frequently, or reduced body hair. Balding and voice changes are not associated with hypogonadism, nor with its treatment.

Hypogonadism was perhaps at one point considered to be a normal part of aging. However, like many other age-related conditions such as poor eyesight, hearing, cognition, arthritis, and atherosclerosis, hypogonadism is no longer dismissed as just part of getting old. Because many age-related conditions are now treated in order to improve quality of life, or even to prolong life, it seems reasonable to treat hypogonadism in a similar manner. Therefore, it is necessary to be thoroughly acquainted with all the potential physiologic signs of hypogonadism. Symptoms, such as diminished libido and ED, are easily recognized, but because hypogonadism adversely affects the function of multiple organ systems, patients may also experience other, more indirect symptoms, such as changes in mood with concomitant decreases in intellectual activity, cognitive functions, and spatial orientation ability. They may also suffer from fatigue, depression, irritability, and sleep disturbances. These symptoms may appear to be nonspecific, especially to a pharmacist who often has no more than a few minutes to counsel a patient. However, taking a minute to simply observe a patient who is willing to talk about specific complaints, such as sexual dysfunction, may help piece together a clearer diagnostic picture.

**SCREENING STRATEGIES**

Although routine screening of the general population for androgen deficiency is not yet recommended, clinicians are encouraged to measure total testosterone levels in men with certain clinical disorders that are associated with a high prevalence of low testosterone levels, such as HIV-associated weight loss, end-stage renal disease, moderate to severe chronic obstructive lung disease, infertility, osteoporosis, type 2 diabetes mellitus, and chronic therapy with glucocorticoids or opioids. Screening for hypogonadism in men with ED may also be useful.

Although there are conflicting data, some investigators have reported that men with ED frequently are found to have hypogonadism. These men frequently respond to testosterone therapy with improvement in erectile function. Others may still experience significant ED; however, the response to phosphodiesterase-5 (PDE-5) inhibitors appears to be improved in many of these men. Therefore, screening for hypogonadism in men with ED is necessary to identify those with severe hypogonadism and patients with mild to moderate hypogonadism who may benefit from testosterone treatment. Consequently, it is also important to screen for hypogonadism in men who fail PDE-5 inhibitors. In evaluating ED, use of a screening tool, such as the International Index of Erectile Function, provides a useful, reliable, and self-administered measure of erectile function that is cross-culturally valid and has sensitivity and specificity for detecting treatment-related changes in patients with ED.

Screening tools are also useful in catching the sometimes elusive diagnosis of hypogonadism. Because clinicians don’t always consider the possibility of this disorder when performing system assessments, a screening tool may minimize the chances of missing a diagnosis by capturing more vague hypogonadal symptoms (eg, fatigue, loss of stamina, and depression). One instrument used commonly is the Androgen Deficiency in Aging Males (ADAM) questionnaire, a 10-question survey developed and validated by a group of Canadian physicians (Figure). The questionnaire was initially used by researchers trying

---

**Figure. The Androgen Deficiency in Aging Males Questionnaire**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have a decrease in libido (sex drive)?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2. Do you have a lack of energy?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3. Do you have a decrease in strength and/or endurance?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4. Have you lost height?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5. Have you noticed a decreased “enjoyment of life”?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6. Are you sad and/or grumpy?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>7. Are your erections less strong?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>8. Have you noticed a recent deterioration in your ability to play sports?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9. Are you falling asleep after dinner?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>10. Has there been a recent deterioration in your work performance?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*If you answer “yes” to questions 1 or 7 or any 3 other questions, you may have low testosterone. A simple blood test can determine your testosterone level. Talk with your doctor.

to determine whether certain symptoms were more commonly present in males with low bioavailable testosterone levels. They used the ADAM questionnaire to screen for low bioavailable testosterone in 316 Canadian physicians aged 40 to 62 years. Low levels were present in 25% of this population. In a second study of 34 ADAM-positive patients, 37% of those with clearly normal levels demonstrated some evidence of dysphoria. Finally, in 21 patients who were treated with testosterone, improvements on the ADAM questionnaire were demonstrated in 18 of the patients. The results not only validated the ADAM screening tool, but they also supported the association between a symptom complex and low bioavailable testosterone levels in aging males. The questionnaire has a sensitivity of 88% for detecting low free testosterone levels in aging males but a specificity of only 60%. Therefore, the screening tool may detect cases of clinical depression or even hypothyroidism—instead of hypogonadism.

CONCLUSIONS

The overt signs and symptoms of hypogonadism are easily recognized, but as with many other diseases, the presentation doesn’t always follow a textbook. Clinicians must be familiar with not only the obvious physical manifestations of hypogonadism, but also with subtle, nonspecific symptoms. Untreated hypogonadism will not only affect a patient’s quality of life, but it may also be associated with very real adverse health outcomes, such as osteoporosis and cardiovascular disease. This is an area where various healthcare providers can really contribute by helping to identify at-risk male patients.

Historically, pharmacists have been the healthcare providers that patients turn to before or after the diagnosis has been established. In the past, a pharmacist’s contribution to the actual diagnosis was limited at best. However, times have changed, especially when it comes to healthcare. The medical team no longer consists of one player—the physician. Other healthcare providers, especially pharmacists, have become essential members of the medical team. They no longer just see patients behind a counter. They now see them at the bedside in hospitals and at ambulatory clinics. They no longer are only responsible for medications but for the entire patient care. Pharmacists can speak to patients about much more than just their medications—and if they listen, perhaps they can hear, even in passing, about a critical symptom.

REFERENCES


