Diagnosis of Hypogonadism: Clinical Assessments and Laboratory Tests

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Hypogonadism can be of hypothalamic-pituitary origin or of testicular origin, or a combination of both, which is increasingly common in the aging male population. In the postpubertal male, testosterone replacement therapy can be used to treat the signs and symptoms of low testosterone, which include loss of libido, erectile dysfunction, diminished intellectual capacity, depression, lethargy, osteoporosis, loss of muscle mass and strength, and some regression of secondary sexual characteristics. Before initiation of testosterone replacement therapy, an examination of the prostate and assessment of prostate symptoms should be performed, and both the hematocrit and lipid profile should be measured. Absolute contraindications to testosterone replacement therapy are prostate or breast cancer, a hematocrit of 55% or greater, or sensitivity to the testosterone formulation.
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Hypogonadism is a lack of testosterone in male patients and can be of central (hypothalamic or pituitary) or testicular origin, or a combination of both. Hypogonadism in male patients with testicular failure due to genetic disorders (eg, Klinefelter's syndrome), orchitis, trauma, radiation, chemotherapy, or undescended testes, is known as hypergonadotropic hypogonadism or primary hypogonadism. Hypogonadism in male patients with gonadotropin deficiency or dysfunction as a result of disease or damage to the hypothalamic-pituitary axis

is known as hypogonadotropic hypogonadism, central hypogonadism, or secondary hypogonadism. This might be due to Kallmann's syndrome, tumor, trauma, radiation, sarcoidosis, or tuberculosis. In addition, men older than 50 years might have low testosterone levels with functional abnormalities at multiple levels of the hypothalamic-pituitary-testicular axis.[1,2,3]

The prevalence of hypogonadism has increased in recent years. It has been reported that 12%, 19%, 28%, and 49% of men greater than 50, 60, 70, or 80 years of age, respectively, fit the criteria of hypogonadism.[4]

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During puberty, testosterone is required for the development of male secondary sexual characteristics, stimulation of sexual behavior and function, and initiation of sperm production.[5,6] In adult males, testosterone is involved in maintaining muscle mass and strength, fat distribution, bone mass, red blood cell production, male hair pattern, libido and potency, and spermatogenesis.[1–3,5,6]

In men, the major gonadal steroid hormone is testosterone. Testosterone circulates in 3 major forms: unbound, or free, testosterone; tightly bound testosterone, which is bound to sex hormone-binding globulin (SHBG); and weakly bound testosterone, which is bound to albumin. Only free and weakly bound testosterone is bioavailable or able to bind to the androgen receptor.[2,3]

In males, serum testosterone levels show a circadian variation, with the highest levels in the morning and lowest levels in the late afternoon. In young men, the variation in testosterone levels is approximately 35%. Although the normal range for serum testosterone might vary between different laboratories, the normal range for early morning total testosterone in healthy adult males is approximately 300 ng/dL to 1000 ng/dL.[7,8]

Diagnosis of Hypogonadism

To determine whether a patient is testosterone deficient, a clinician must consider clinical signs and symptoms in conjunction with laboratory values. The initial clinical picture will vary depending on the age of the patient at the onset of the disorder.

Prepubertal

In the normal male, the start of puberty is apparent by enlargement of the testes and the appearance of pubic hair, followed by the appearance of auxiliary and facial hair. At puberty there is also increased penile length and the onset of spermatogenesis. If signs of puberty are not evident in boys by 14 years of age, a workup for delayed puberty is warranted.

In the prepubertal age group, hypogonadism might be either primary hypogonadism or secondary hypogonadism. To differentiate primary from secondary hypogonadism, early morning luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels must be obtained. Because LH and FSH are secreted during the early morning at the beginning of puberty, it is necessary to measure these hormones in the early morning (8:00–10:00 AM). Primary hypogonadism is associated with low levels of testosterone and high-normal to high levels of LH and FSH. Secondary hypogonadism is associated with low levels of testosterone and normal to low levels of LH and FSH.[5,6]

Postpubertal

The signs and symptoms of low testosterone in postpubertal adult males can be more difficult to diagnose and might include loss of libido, erectile dysfunction, diminished intellectual capacity, depression, lethargy, osteoporosis, loss of muscle mass and strength, and some regression of secondary sexual characteristics.[1-3] At the initial visit, the first objective is to distinguish between primary gonadal failure, in which low testosterone is accompanied by increased FSH and increased LH, and hypothalamic-pituitary disorders (secondary hypogonadism), with low testosterone and low to normal FSH and LH levels.

Initial laboratory testing should include early morning (8:00–10:00 AM) measurement of serum testosterone, prolactin, FSH, and LH levels. For the diagnosis of primary hypogonadism, FSH measurement is particularly important because FSH has a longer half life, is more sensitive, and demonstrates less variability than LH.[2,3]

Serum testosterone levels show a circadian variation, with the highest levels in the morning and lowest levels in the late afternoon.

Aging

The aging male patient can present with signs and symptoms of low testosterone, including loss of libido, erectile dysfunction, diminished intellectual capacity, depression, lethargy, osteoporosis, and loss of muscle mass and strength.[1-3] At the initial visit, laboratory testing should include

early morning (8:00–10:00 AM) measurement of serum testosterone. In elderly men, testosterone levels decrease between 15% and 20% over the course of 24 hours.[8]

Total testosterone levels might be normal with hypogonadism if the SHBG levels are increased.[7-9] Levels of SHBG increase with age, causing a decrease in bioavailable testosterone.[9] If testosterone levels are low-normal but the clinical symptoms and signs indicate hypogonadism, measurement of serum total testosterone levels should be repeated and an SHBG level should be determined. With the total testosterone and SHBG levels, a bioavailable testosterone value can be calculated. A bioavailable testosterone calculator is available at www.issam.ch/freetesto.htm.

Total testosterone values must be interpreted carefully in the aging male because SHBG levels might be elevated.

It is usually not necessary to determine FSH or LH levels in the aging male.

Which Testosterone Value to Measure in Practice?

It is well accepted that testosterone levels should be measured in the early morning, when they are at their peak level. However, in community practice the choice of which testosterone parameter to measure is still debatable.

Total testosterone assay is widely available and inexpensive to perform. Although the ranges and methods vary, physicians can consult their local laboratories for the applicable values in their clinical practice. Total testosterone values, however, must be interpreted carefully in the aging male because SHBG levels might be elevated. If the total testosterone level is normal in the aging male presenting signs of hypogonadism, the clinician can measure free testosterone or measure SHBG and calculate bioavailable testosterone.[9]

Free testosterone can be measured by equilibrium dialysis or ultrafiltration, which are difficult to perform and largely unavailable but reliable. In contrast, the radioimmunoassay for free testosterone is widely available but unreliable. Because total testosterone and SHBG assays are readily available and cheap, calculating bioavailable testosterone might be a good compromise. Whichever method is chosen, if the early morning testosterone level is at or below the lower limit of normal for the individual laboratory, then a repeat measurement of the early morning testosterone level should be performed to confirm the result. Because testosterone is secreted in a pulsatile fashion, it is important to obtain 2 early morning testosterone levels.

In selected patients, FSH, LH, and prolactin can be measured. If the FSH and LH levels are raised, this suggests a primary testicular cause, and if levels are low or normal, a hypothalamic or pituitary cause should be considered. A raised prolactin level suggests that further investigation of the pituitary gland should be undertaken.[1,2]

Clinical Evaluation

The clinical signs and symptoms of hypogonadism will vary depending on whether the patient presents before or after puberty. Depending on the age of the patient, the degree of pubertal development is important for establishing the differential diagnosis.

Prepubertal

Boys aged 14 years or older should be suspected of being hypogonadal if on examination they have underdeveloped testes, lack of penile enlargement, and absence of pubic, auxiliary, and facial hair.

In patients with primary hypogonadism, history might reveal the cause for primary testicular failure, such as familial autoimmune disease, physical trauma to the testes, or trauma to the testes caused by radiation, chemotherapy, or infection.

A karyotype should be obtained to diagnose chromosomal abnormalities, such as Klinefelter's syndrome, and a physical examination will reveal small or absent testes resulting from anorchia, Noonan's syndrome, or other testicular disorders.

Hypothalamic or pituitary deficiency might be transitory or permanent. Transient secondary hypogonadism might be related to malnutrition or stress states and can be diagnosed by physical examination and evaluation of the patient's growth chart. If permanent hypothalamic or pituitary hormone deficiency is suspected, serum levels of pituitary hormones and magnetic resonance imaging of the brain and pituitary should be obtained to screen for hypothalamic or pituitary disease.

If both physical examination and serum chemistry tests are normal, then by exclusion a diagnosis of constitutional pubertal delay must be considered.

Postpubertal

To establish a diagnosis of hypogonadism, it is important to take a careful history to determine whether there have been major medical problems, toxic exposure, concomitant drug therapy that might cause hypogonadism, or fertility problems.

Low libido, impotence, fatigue, impaired concentration, and sexual dysfunction are important clinical problems that might not be raised by

the patient in the clinic. Therefore, these symptoms need to be asked about specifically if hypogonadism is suspected.[1-3]

Formal assessment of intellectual changes, mood, and cognitive changes can be performed. Changes in lean body mass will be apparent from the medical history and examination, as will changes in hair, skin, and fat distribution. Decreases in bone mineral density might be apparent from a history of recent fractures but can only be confirmed by dual energy x-ray absorptiometry (DEXA).[1]

Physical examination should include testicular examination, including size and consistency. The distribution and amount of body hair should also be noted. Penile size is not affected by postpubertal testosterone deficiency. An assessment of the prostate by digital rectal examination (DRE) should be performed and a prostate-specific antigen (PSA) value obtained.[3]

Aging

To establish a diagnosis of hypogonadism in the aging male, it is important to assess the patient carefully for signs and symptoms. Low libido, impotence, fatigue, impaired concentration, and sexual dysfunction are important clinical problems that might not be raised by the patient in the clinic, especially by an aging patient. Therefore, as with the younger postpubertal patient, these symptoms need to be asked about specifically if hypogonadism is suspected.[1,2] As with the postpubertal patient (see previous section), changes in intellectual functioning; mood; lean body mass; and hair, skin, and fat distribution should all be assessed, and DEXA can be used to confirm decreases in bone mineral density.[1]

In older patients, an important part of the physical examination includes an assessment of the prostate by DRE and PSA assay. In addition, an assessment of prostate-related symptoms should be undertaken. The presence of gynecomastia or carcinoma of the breast are important physical findings.

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Who Should Receive Testosterone Replacement Therapy?

In cases of primary and permanent secondary hypogonadism diagnosed in the prepubertal male, life long testosterone treatment is needed. The usual treatment is initiation of therapy with small doses of testosterone (50–100 mg IM) every 3 to 4 weeks at the appropriate psychosocial stage in development. When a final adult height is thought to have been obtained, the adult dose of testosterone replacement is inaugurated.

In the postpubertal period, once the diagnosis of testosterone deficiency has been made, replacement therapy should be considered in light of the clinical signs and symptoms in conjunction with the laboratory values. The objective of testosterone replacement therapy is to normalize serum testosterone and maintain the level within the eugonadal state. In addition, treatment objectives might include improving sexual dysfunction, intellectual capacity, depression, and lethargy; maintaining bone mineral density and possibly reducing fracture risk; increasing muscle mass and strength; and enhancing the quality of life.[1-3,9]

Although the normal range for serum testosterone might vary between different laboratories, the normal range for early morning testosterone in male adults is approximately 300 ng/dL to 1000 ng/dL.[7] An early morning total serum testosterone level of less than 300 ng/dL clearly indicates hypogonadism, and under most circumstances benefit will be derived from testosterone replacement therapy. A healthy male adult patient with a serum testosterone level greater than 400 ng/dL is unlikely to be testosterone deficient, and therefore clinical judgment should be exercised if he has symptoms suggestive of testosterone deficiency.

There are some absolute contraindications to testosterone replacement therapy. These include prostate cancer, which must be assessed by history and clinical examination. If on DRE the prostate is enlarged or if the PSA level is greater than 4.0 ng/mL, biopsy of the prostate should be undertaken to confirm a diagnosis of prostate cancer or benign prostatic hyperplasia (BPH).[3]

Objectives of testosterone replacement therapy include improving sexual dysfunction, intellectual capacity, depression, and lethargy; increasing muscle mass and strength; and enhancing the quality of life.

An existing or prior history of breast cancer is also an absolute contraindication to testosterone replacement therapy. Testosterone therapy is known to increase the hematocrit, and therefore a pre-existing hematocrit of 55% or greater is an absolute contraindication to replacement therapy.

Sensitivity to any of the ingredients in the testosterone formulation would also be an absolute contraindication. Relative contraindications include an increased hematocrit, untreated sleep apnea, severe obstructive symptoms of BPH, and advanced congestive cardiac failure.[2,3]

Monitoring Issues and Side Effects of Testosterone Therapy

The goal of replacement therapy is to maintain testosterone in the normal physiological range; therefore, a combination of clinical and biochemical measures should be monitored 6 to 12 weeks after initiating therapy. In most cases, an early morning serum total testosterone level is adequate to determine whether dosage adjustment is necessary. However, patients receiving injections of testosterone enanthate or cypionate every 2 weeks will require an earlier measurement of serum testosterone at 1 to 2 weeks after commencement of therapy.[3]

Examination of the prostate should be performed routinely, although the exact frequency after initiation of testosterone replacement is still debatable. Digital rectal examination of the prostate and PSA assay should be performed before initiation of therapy, along with an assessment of prostate-related symptoms. In elderly men, a DRE and PSA assay should be performed at 3 and 6 months after commencing testosterone therapy and then annually thereafter.[3] A high PSA level should be further evaluated with a highly specific PSA assay, if available. A patient should be referred to a urologist if his PSA level increases over time or if he has a PSA level greater than 4.0 ng/mL.[3]

In elderly men, a DRE and PSA assay should be performed at 3 and 6 months after commencing testosterone therapy and then annually thereafter.

It is known that testosterone stimulates bone marrow production of erythrocytes, which might result in an increased hematocrit in some men, and therefore this should be checked at the same time as the PSA level.[2,3]

Lipid disturbances in testosterone-treated male patients are generally not a problem because the ratio of high-density lipoprotein to total cholesterol usually remains constant. An initial lipid profile should be performed before therapy, and a follow-up profile should be obtained after 6 to 12 months of therapy and annually thereafter.[3]

Conclusion

Hypogonadism can be of hypothalamic-pituitary origin or of testicular origin, or a combination of both, which is increasingly common in the aging male population. It can be easily diagnosed with measurement of the early morning serum total testosterone level, which should be repeated if the value is low. Follicle-stimulating hormone, LH, and prolactin might also need to be measured. If the clinical signs and symptoms suggest hypogonadism but the serum testosterone level is near normal, then assay of serum testosterone should be repeated

Main Points

- Hypogonadism is a lack of testosterone in male patients and can be of central (hypothalamic or pituitary) or testicular origin, or a combination of both.
- Boys ages 14 years or older should be suspected of being hypogonadal if on examination they have underdeveloped testes, a lack of penile enlargement, and an absence of pubic, auxiliary, and facial hair.
- In pre- and postpubertal male patients, primary hypogonadism is associated with low levels of testosterone and high-normal to high levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH); secondary hypogonadism is associated with low levels of testosterone and normal to low levels of LH and FSH.
- In the aging male patient, signs and symptoms of hypogonadism can include loss of libido, erectile dysfunction, diminished intellectual capacity, depression, lethargy, osteoporosis, and loss of muscle mass and strength.
- For aging men, laboratory testing should include early morning (8:00–10:00 AM) measurement of serum testosterone; levels less than 300 ng/dL clearly indicate hypogonadism, and under most circumstances benefit will be derived from testosterone replacement therapy.
- Before initiation of testosterone replacement therapy, an examination of the prostate and assessment of prostate symptoms should be performed, and both the hematocrit and lipid profile should be measured.
- There are few absolute contraindications to testosterone replacement therapy other than prostate or breast cancer, a hematocrit of 55% or greater, or sensitivity to the testosterone formulation.

in conjunction with SHBG because serum testosterone might be normal in the presence of hypogonadism if the SHBG level is raised, which commonly occurs in elderly male patients.

Before initiation of testosterone replacement therapy, an examination of the prostate, including DRE, PSA assay, and assessment of prostate symptoms should be undertaken, and both the hematocrit and lipid profile should be measured. There are few absolute contraindications to testosterone replacement therapy other than prostate or breast cancer, a hematocrit of 55% or greater, or sensitivity to the testosterone formulation. Monitoring of the prostate (assessed with DRE and PSA assay) and hematocrit and lipid profile should be repeated during testosterone replacement therapy.

The benefits of testosterone replacement therapy may include restoring metabolic parameters to the eugonadal state; improving psychosexual function and intellectual capacity, including depression and lethargy; maintaining bone mineral density and reducing bone fractures; improving muscle mass and strength; and enhancing quality of life. ■

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