MSD MANUAL
Professional Version
The trusted provider of medical information since 1899

Male Hypogonadism

*By **Irvin H. Hirsch**, MD, Sidney Kimmel Medical College of Thomas Jefferson University*

Last full review/revision Jul 2019| Content last modified Jul 2019

Hypogonadism is defined as testosterone deficiency with associated symptoms or signs, deficiency of spermatozoa production, or both. It may result from a disorder of the testes (primary hypogonadism) or of the hypothalamic-pituitary axis (secondary hypogonadism). Both may be congenital or acquired as the result of aging, disease, drugs, or other factors. Additionally, a number of congenital enzyme deficiencies cause varying degrees of target organ androgen resistance. Diagnosis is confirmed by hormone levels. Treatment varies with etiology but typically includes gonadotropin-releasing hormone, gonadotropin, or testosterone replacement.

(See also Male Hypogonadism in Children.)

Etiology

Primary hypogonadism involves failure of the testes to respond to follicle-stimulating hormone (FSH) and luteinizing hormone (LH). When primary hypogonadism affects testosterone production, testosterone is insufficient to inhibit production of FSH and LH; hence, FSH and LH levels are elevated. The most common genetic cause of primary hypogonadism is Klinefelter syndrome. It involves seminiferous tubule dysgenesis, failure of spermatogenesis, Leydig cell hyperplasia, and a 47,XXY karyotype.

Secondary hypogonadism is failure of the hypothalamus to produce gonadotropin-releasing hormone (GnRH), as in idiopathic hypogonadotropic hypogonadism, or of the pituitary gland to produce enough FSH and LH. In secondary hypogonadism, testosterone levels are low and levels of FSH and LH are low or borderline normal. Any acute systemic illness can cause temporary secondary hypogonadism. Some syndromes of hypogonadism have both primary and secondary causes (mixed hypogonadism). The table Causes of Hypogonadism lists some common causes of hypogonadism by category.

Some syndromes of hypogonadism (eg, cryptorchidism, some systemic disorders) affect spermatozoon production more than testosterone levels.

Causes of Hypogonadism*

Type	Congenital Causes	Acquired Causes
Primary (testicular)	Klinefelter syndrome Anorchia (bilateral) Cryptorchidism Myotonic dystrophy Enzymatic defects in testosterone synthesis Leydig cell aplasia Noonan syndrome	Chemotherapy or radiation therapy Testicular infection (eg, mumps, echovirus, flavivirus) High doses of antiandrogen drugs (eg, cimetidine, spironolactone, ketoconazole, flutamide, cyproterone)
Secondary (hypothalamic-pituitary)	Idiopathic hypogonadotropic hypogonadism Kallmann syndrome (idiopathic hypogonadotropic hypogonadism with anosmia) Prader-Willi syndrome Dandy-Walker malformation Isolated luteinizing hormone deficiency	Any acute systemic illness Hypopituitarism (tumor, infarction, infiltrative disease, infection, trauma, irradiation or pituitary surgery) Hyperprolactinemia Iron overload (hemochromatosis) Certain drugs (eg, estrogens, psychoactive drugs, metoclopramide, opioids, leuprolide, goserelin, triptorelin, newer androgen biosynthesis inhibitors for prostate cancer) Cushing syndrome Cirrhosis Morbid obesity Idiopathic
Mixed	—	Aging Alcoholism Systemic disease (eg, uremia, liver failure, AIDS, sickle cell disease) Drugs (ethanol, corticosteroids)

* In approximate order of frequency.

Symptoms and Signs

Age at onset of testosterone deficiency dictates the clinical presentation: congenital, childhood-onset, or adult-onset hypogonadism.

Congenital hypogonadism may be of 1st-, 2nd-, or 3rd-trimester onset. Congenital hypogonadism of 1st-trimester onset results in inadequate male sexual differentiation. Complete absence of testosterone's effects results in normal-appearing female external genitals. Partial testosterone deficiency results in abnormalities ranging from ambiguous external genitals to hypospadias. Second- or 3rd-trimester onset of testosterone deficiency results in microphallus and undescended testes. Childhood-onset testosterone deficiency (see Male Hypogonadism in Children) has few consequences and usually is unrecognized until puberty is delayed. Untreated hypogonadism impairs development of secondary sexual characteristics. As adults, affected patients have poor muscle development, a high-pitched voice, a small scrotum, decreased phallic and testicular growth, sparse pubic and axillary hair, and an absence of body hair. They may develop gynecomastia and eunuchoidal body proportions (span > height by 5 cm and pubic to floor length > crown to pubic length by > 5 cm) because of delayed fusion of the epiphyses and continued long bone growth.

Adult-onset testosterone deficiency has varied manifestations depending on the degree and duration of the deficiency. Decreased libido; erectile dysfunction; decline in cognitive skills, such as visual-spatial interpretation; sleep disturbances; vasomotor instability (in acute, severe male hypogonadism); and mood changes, such as depression and anger, are common. Decreased lean body mass, increased visceral fat, testicular atrophy, osteopenia, gynecomastia, and sparse body hair typically take months to years to develop. Testosterone deficiency may increase the risk of coronary artery disease and prostate cancer.

Diagnosis

Testing, beginning with FSH, LH, and testosterone levels

Congenital and childhood-onset hypogonadism are often suspected because of developmental abnormalities or delayed puberty. Adult-onset hypogonadism should be suspected on the basis of symptoms or signs but is easily missed because these clinical markers are insensitive and nonspecific. Klinefelter syndrome should be considered in adolescent males in whom puberty is delayed, young men with hypogonadism, and all adult men with very small testes. Hypogonadism requires confirmatory testing (see figure Laboratory Evaluation of Male Hypogonadism).

Diagnosis of primary and secondary hypogonadism

Increases in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are more sensitive for primary hypogonadism than are decreases in testosterone levels. Levels of FSH and LH also help determine whether hypogonadism is primary or secondary. High gonadotropin levels, even with low-normal testosterone levels, indicate primary hypogonadism, whereas gonadotropin levels that are low or lower than expected for the level of testosterone indicate secondary hypogonadism. Alternatively, in boys of short stature with delayed puberty, low testosterone plus low gonadotropin levels might result from constitutional delay of puberty. Elevation of serum FSH with normal levels of serum testosterone and LH often occurs when spermatogenesis is impaired but testosterone production is normal. The cause of hypogonadism is often evident clinically. Primary hypogonadism requires no further testing, although some clinicians do a karyotype to definitively diagnose Klinefelter syndrome.

Total (and, when possible, free) serum testosterone, serum FSH, and serum LH levels are measured simultaneously. The normal range for total testosterone is 300 to 1000 ng/dL (10.5 to 35 nmol/L). The testosterone level should be drawn in the morning (before 10:00 AM) to confirm hypogonadism. Because of the increase in sex hormone–binding globulin (SHBG) with aging, total testosterone level is a less sensitive indicator of hypogonadism after age 50. Although serum free testosterone more accurately reflects functional testosterone levels, its measurement requires equilibrium dialysis, which is technically difficult and not widely available.

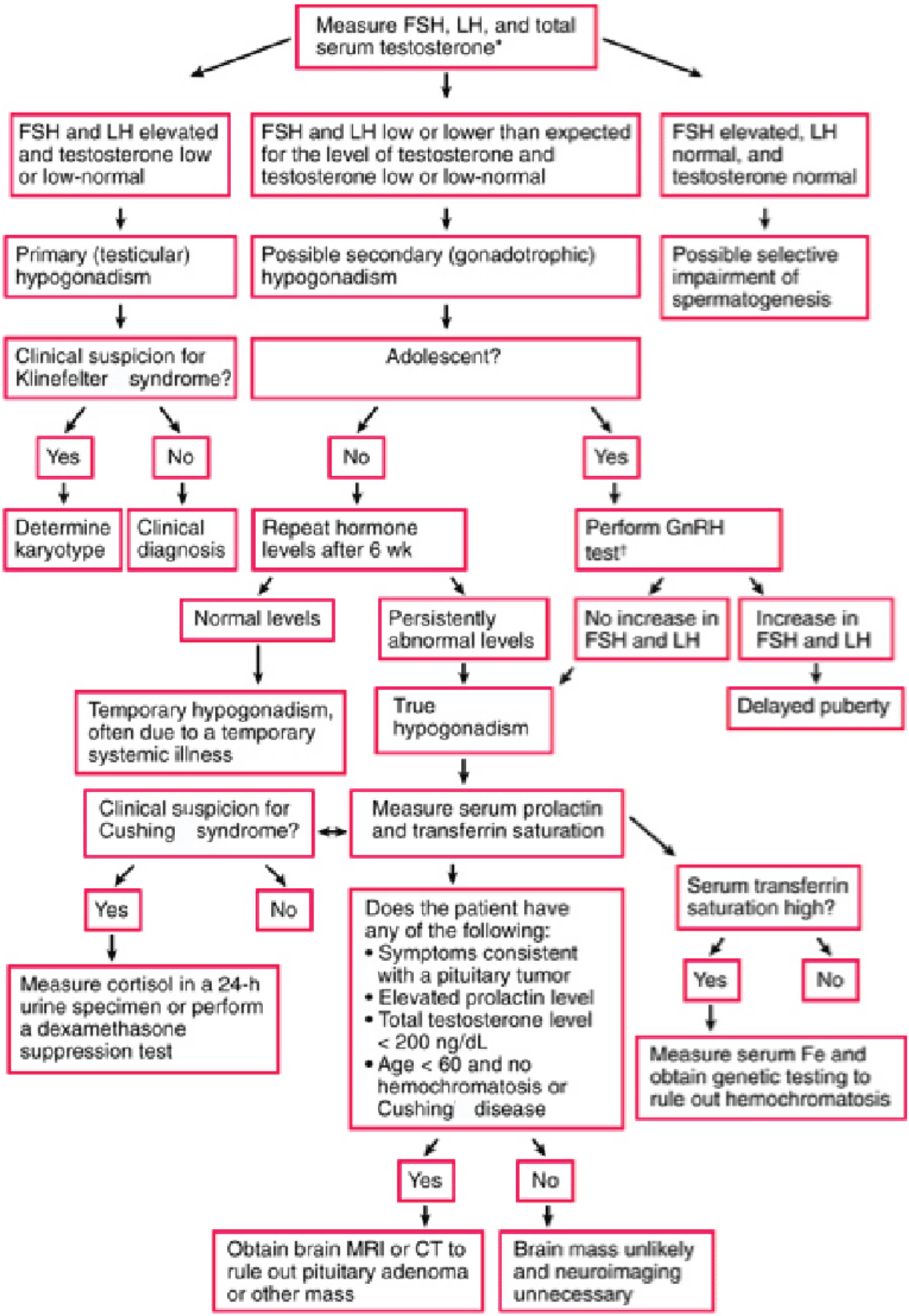
Some commercially available kits, including the analog free testosterone assay, attempt to measure serum free testosterone levels, but the results are often inaccurate, particularly in conditions (such as type 2 diabetes, obesity, and hypothyroidism) that alter SHBG levels. Free testosterone levels can be calculated based on SHBG, albumin, and testosterone values; there are calculators available online. See the Free and Bioavailable Testosterone Calculator.

Because of the pulsatile secretion of FSH and LH, these hormones are sometimes measured as a pooled sample of 3 venipunctures taken at 20-minute intervals, but these pooled samples seldom add clinically important information compared with a single blood sample. Serum FSH and LH levels are usually ≤ 5 mIU/mL (5 IU/L) before puberty and between 5 and 15 mIU/mL in adulthood.

Semen analysis should be done in all men who are seeking fertility treatment. In adolescents or adults, a semen sample collected by masturbation after 2 days of abstinence from ejaculation provides an excellent index of seminiferous tubular function. A normal semen sample (World Health Organization [WHO] standards) has a volume of > 1.5 mL with > 15 million sperm/mL, of which 50% are of normal morphology and are motile (see also Sperm Disorders).

Laboratory evaluation of male hypogonadism

* Total testosterone has lower sensitivity for hypogonadism in men aged > 50 years. If the test for free and weakly bound testosterone is available, levels are measured. If not, levels are calculated.
† Recommended by some physicians.
Fe = iron; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone.


Measure FSH, LH, and total serum testosterone*
FSH and LH elevated and testosterone low or low-normal
FSH and LH low or lower than expected for the level of testosterone and testosterone low or low-normal
FSH elevated, LH normal, and testosterone normal
Primary (testicular) hypogonadism
Possible secondary (gonadotrophic) hypogonadism
Possible selective impairment of spermatogenesis
Clinical suspicion for Klinefelter syndrome?
Adolescent?
Yes
No
No
Yes
Determine karyotype
Clinical diagnosis
Repeat hormone levels after 6 wk
Perform GnRH test†
Normal levels
Persistently abnormal levels
No increase in FSH and LH
Increase in FSH and LH
Temporary hypogonadism, often due to a temporary systemic illness
True hypogonadism
Delayed puberty
Clinical suspicion for Cushing syndrome?
Measure serum prolactin and transferrin saturation
Yes
No
Does the patient have any of the following:
• Symptoms consistent with a pituitary tumor
• Elevated prolactin level
• Total testosterone level < 200 ng/dL
• Age < 60 and no hemochromatosis or Cushing disease
Serum transferrin saturation high?
Measure cortisol in a 24-h urine specimen or perform a dexamethasone suppression test
Yes
No
Measure serum Fe and obtain genetic testing to rule out hemochromatosis
Yes
No
Obtain brain MRI or CT to rule out pituitary adenoma or other mass
Brain mass unlikely and neuroimaging unnecessary

Evaluation of secondary hypogonadism

Because any systemic illness can temporarily decrease levels of testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), secondary hypogonadism should be confirmed by measuring these levels again at least 4 weeks after resolution of the systemic illness. To confirm secondary hypogonadism in adolescents, the gonadotropin-releasing hormone (GnRH) stimulation test may be considered. If levels of FSH and LH increase in response to IV GnRH, puberty is simply delayed. If levels do not increase, true hypogonadism is likely.
To help determine the cause of confirmed secondary hypogonadism, testing should include serum prolactin level (to screen for pituitary adenoma) and transferrin saturation (to screen for hemochromatosis). Sella imaging with MRI or CT is done to exclude a pituitary macroadenoma or other mass in men with any of the following:

- Age < 60 years with no other identified cause for hypogonadism
- Very low total testosterone levels (< 200 ng/dL [6.94 nmol/L])
- Elevated prolactin levels
- Symptoms consistent with a pituitary tumor (eg, headache, visual symptoms)

Also, if there are symptoms or signs of Cushing syndrome, 24-hour urine collection for free cortisol or a dexamethasone suppression test is done. If no abnormalities are identified, the diagnosis is acquired idiopathic secondary hypogonadism.

Treatment

- Testosterone replacement therapy
- Gonadotropin replacement therapy for restoration of fertility due to secondary hypogonadism

Treatment is directed toward providing adequate androgen replacement conveniently and safely. Although patients with primary hypogonadism may not become fertile with any endocrine therapy, patients with secondary hypogonadism often become fertile with gonadotropin therapy. Testosterone formulations discussed here are those available in the US. Other formulations may be available in other countries.

Testosterone replacement therapy (TRT)

Because exogenous testosterone impairs spermatogenesis, TRT should be avoided, when possible, in secondary hypogonadism or when subsequent fertility is a concern (unless there is irreversible primary testicular failure). Treatment of secondary hypogonadism in boys with gonadotropin replacement therapy (see Treatment of infertility due to hypogonadism) usually stimulates androgen production as well as spermatogenesis.
TRT can be used for males who

- Have no signs of puberty
- Are near age 15
- Have had secondary hypogonadism excluded

They may be given long-acting testosterone enanthate 50 mg IM once/month for 4 to 8 months. These low doses cause some virilization without restricting adult height. Older adolescents with testosterone deficiency receive long-acting testosterone enanthate or testosterone cypionate at a dose that is increased gradually over 18 to 24 months from 50 to 100 to 200 mg IM every 1 to 2 weeks. Transcutaneous gel may also be used, although it is more expensive, could possibly be transferred to others during intimate contact, and is more difficult to accurately dose. It is reasonable to convert older adolescents to testosterone gel preparations at adult dosages when their IM dosage has reached the equivalent of 100 to 200 mg every 2 weeks.
Adults with established testosterone deficiency may benefit from replacement therapy. Treatment slows the course of osteopenia, muscle loss, vasomotor instability, loss of libido, depression, and occasionally erectile dysfunction. The effects of testosterone on coronary artery disease are not well understood. TRT may improve coronary artery blood flow and may decrease the risk of coronary artery disease. Concerns that TRT increases risk of cardiovascular events have been raised in a few recent studies. However, a large body of expert opinion has refuted these concerns. Advantages of testosterone treatment must be weighed against possible increased cardiovascular risk for each individual patient.
Options for replacement therapy include

- Testosterone gel 1% or 1.62% (5 to 10 g of gel daily to deliver 5 to 10 mg of testosterone daily)
- Transdermal axillary solution (60 mg once a day)
- A buccal mucosal lozenge (30 mg twice a day)

Transdermal testosterone patch (4 mg once day)

A nasal formulation (one spray of 5.5 mg in each nostril 3 times a day)

Subcutaneous testosterone implants (75 mg/pellet) given as 4 to 6 units placed every 3 to 6 months

IM testosterone enanthate or cypionate (100 mg every 7 days or 200 mg every 10 to 14 days); available for self-injection

Testosterone gel maintains physiologic blood levels more consistently than other treatments, but IM or patch systems are sometimes preferred because of their lower cost. Oral formulations are unpredictably absorbed.

Potential adverse effects of testosterone and its analogs include

Erythrocytosis (particularly in men over age 50 receiving IM testosterone)

Venous thromboembolism unrelated to erythrocytosis

Acne

Gynecomastia

Low sperm count

Very rarely prostatic enlargement may occur. This is thought to be a physiologic rate of growth due to the normalization of serum testosterone. Prostatic obstructive symptoms are rare. Currently, replacing testosterone to physiologic levels is not thought to cause new prostate cancer or accelerate growth or spread of localized prostate cancer. TRT is thought to have a minimal effect on serum prostate-specific antigen (PSA) levels in men with benign prostatic hyperplasia and in men with treated prostate cancer. However, product inserts do state that TRT is contraindicated in men with prostate cancer, and men who have or are at high risk of prostate cancer should be counseled and carefully followed with digital rectal examinations and PSA measurements while taking TRT. A prostate biopsy may be needed if PSA elevation persists after TRT is stopped. Hypogonadal men with effectively treated prostate cancer or suspected of having prostate cancer should seek consultation with an expert. Oral formulations of testosterone carry risks of hepatocellular dysfunction and hepatic adenoma.

Men taking supplemental testosterone should be monitored periodically. Hematocrit (Hct), PSA, and testosterone levels should be measured quarterly during the first year of TRT and semiannually thereafter. Digital rectal examination should be offered at the same times. If Hct is ≥ 54%, the testosterone dose should be reduced. Significant increases in PSA level should prompt consideration of prostate biopsy in men who would otherwise be candidates for prostate cancer diagnosis and treatment.

Treatment of infertility due to hypogonadism

Infertility has many possible causes other than hypogonadism. Infertility due to primary hypogonadism (elevated FSH) does not respond to hormonal therapy. Men with primary hypogonadism occasionally have a few intratesticular sperm that can be harvested with various microsurgical techniques and used to fertilize an egg by assisted reproductive technique (eg, intracytoplasmic sperm injection).

Infertility due to secondary hypogonadism usually responds to gonadotropin replacement therapy. Other symptoms of secondary hypogonadism respond well to testosterone replacement therapy alone. If secondary hypogonadism results from pituitary disease, gonadotropin replacement therapy usually is successful. Therapy begins with replacement of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Luteinizing hormone replacement is initiated using human chorionic gonadotropin (hCG) at doses of 1500 IU subcutaneous 3 times a week. Follicle-stimulating hormone replacement, which is expensive, uses human menotropic gonadotropin or human recombinant FSH, at doses of 150 IU 3 times a week. Doses may be adjusted based on the results of periodic testing with semen analysis and levels of serum FSH, LH, and testosterone. Once an adequate sperm count is achieved, FSH can be stopped and hCG monotherapy continued.

Most men who have secondary hypogonadism due to a hypothalamic defect (eg, idiopathic hypogonadotropic hypogonadism, Kallmann syndrome) become fertile with treatment despite sperm counts that are low (eg, < 5 million/mL). When LH and FSH treatment is ineffective, pulsatile gonadotropin-releasing hormone replacement therapy (every 2 hours subcutaneous by a programmable minipump), although less readily available, might be more effective. Most (80 to 90%) of men respond successfully to these regimens.

Key Points

Levels of FSH and LH help differentiate between primary hypogonadism (high levels) and secondary hypogonadism (low or borderline normal levels).

Age-related symptoms of male hypogonadism include inadequate sexual differentiation (congenital), delayed puberty (childhood onset), and various nonspecific symptoms such as decreased libido, erectile dysfunction, cognitive decline, decrease in percentage of lean body mass, sleep disturbances, and mood changes (adult onset).

Free testosterone levels, which can be calculated and sometimes measured, better reflect gonadal sufficiency than do total testosterone levels.

Diagnosis can be approached systematically, using an algorithm.

Testosterone replacement therapy can relieve symptoms of hypogonadism but does not restore fertility.

Gonadotropin replacement therapy can usually restore fertility in men with secondary hypogonadism.

MSD

© 2020 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA)