

GREGORY W. RUTECKI, MD, Section Editor

ALA'A N. FARKOUH

School of Medicine, The University of Jordan,
Amman, Jordan

AYMAN A. ZAYED, MD, MSc, FACE, FACP

Professor of Medicine and Chief, Division of Endocrinology,
Diabetes, and Metabolism, Department of Internal Medicine,
School of Medicine, The University of Jordan,
Jordan University Hospital, Amman, Jordan

An obese 48-year-old man with progressive fatigue and decreased libido

A 48-YEAR-OLD MAN presents to his primary care physician because of progressively decreasing energy and gradual decline in both libido and erectile function for the past 18 months. He has noticed decreased morning erections as well. He rates his libido at 3 to 4 on a scale of 10 for the past 6 months. He also reports poor motivation, depressed mood, impaired concentration, and sleep disturbances. He reports no hair loss, headache, or dizziness, and no decrease in shaving frequency. Review of his systems is otherwise unremarkable.

He has had dyslipidemia for 3 years and is not known to have hypertension or diabetes. His medications include atorvastatin, vitamin E, and multivitamins.

He is married with 3 children and does not wish to have more. He works as a software engineer and leads a sedentary lifestyle. He is a nonsmoker and occasionally drinks alcohol on the weekends.

On physical examination, he is alert and oriented and appears well. His height is 5 feet 10 inches (178 cm), weight 230 lb (104 kg), and body mass index (BMI) 32.8 kg/m². His blood pressure is 115/83 mm Hg and pulse rate is 82 beats per minute and regular. Findings on cardiovascular and pulmonary examination are normal. He has large fatty breasts but without palpable glandular tissue.

Abdominal examination reveals central obesity—waist circumference 48 inches (122 cm)—without tenderness or organomegaly. There are no striae.

Genitourinary examination reveals normal hair distribution, a normal-sized penis, and slightly soft testes with testicular volume of 18–20 mL bilaterally.

doi:10.3949/ccjm.86a.18097

His primary care physician suspects that he has low testosterone and orders some basic laboratory tests; the results are normal except for a low total testosterone level (Table 1).

FURTHER TESTING

1 Which of the following tests should his physician order next?

- Repeat total testosterone measurement
- Free testosterone measurement by commercial assay
- Calculated free testosterone
- Bioavailable testosterone measurement
- Serum inhibin B measurement

This patient presents with several nonspecific symptoms. But collectively they suggest testosterone deficiency (hypogonadism).

Symptoms and signs of low testosterone vary according to age of onset. Prepubertal onset is associated with incomplete or delayed puberty, no development of secondary sexual characteristics, eunuchoid features, and small penis and testes. Postpubertal onset is associated with a wide array of symptoms (Table 2). Most manifestations of low testosterone are nonspecific, such as fatigue, impaired concentration, and sleep disturbance.¹

Together, erectile dysfunction, low libido, and decreased morning erections strongly suggest hypogonadism.² Loss of body hair and decreased shaving frequency are specific symptoms of hypogonadism; however, they require years to develop.³ Gynecomastia can also occur due to loss of the inhibitory action of testosterone on breast growth and a relative increase in estradiol. This occurs more in primary hypogonadism, due to

Men with hypogonadism usually present with nonspecific manifestations

TABLE 1

Results of initial laboratory testing

Test	Value ^a	Reference range
Complete blood cell count		
Hemoglobin	14.5 g/dL	13–17 g/dL
Hematocrit	44%	40%–54%
Mean corpuscular volume	93 fL	80–100 fL
Mean corpuscular hemoglobin	31 pg/cell	26–34 pg/cell
Mean corpuscular hemoglobin concentration	33 g/dL	31–36 g/dL
Red blood cell distribution width	13.5%	11.5%–14.5%
White blood cell count	8.3 × 10 ⁹ /L	4.5–11.0 × 10 ⁹ /L
Neutrophils	63%	40%–75%
Lymphocytes	28%	20%–45%
Monocytes	7%	2%–10%
Eosinophils	2%	1%–6%
Basophils	0%	0%–1%
Platelet count	310 × 10 ⁹ /L	150–400 × 10 ⁹ /L
Metabolic panel		
Serum creatinine	0.8 mg/dL	0.5–1.1 mg/dL
Blood urea nitrogen	14 mg/dL	7–20 mg/dL
Serum sodium	138 mmol/L	135–145 mmol/L
Serum potassium	4.6 mmol/L	3.5–5.3 mmol/L
Serum chloride	97 mmol/L	95–105 mmol/L
Serum bicarbonate	23.6 mmol/L	22–26 mmol/L
Alanine aminotransferase	37 IU/L	7–52 IU/L
Aspartate aminotransferase	32 IU/L	10–40 IU/L
Serum albumin	4.7 g/dL	3.5–5.5 g/dL
Thyroid-stimulating hormone	2.3 mIU/L	0.5–5 mIU/L
Fasting blood glucose	92 mg/dL	< 100 mg/dL
Morning total testosterone	120 ng/dL	270–1,000 ng/dL
Erythrocyte sedimentation rate	13 mm/h	0–22 mm/h

^aAbnormal results are shown in bold.

the increase in luteinizing hormone (LH), which stimulates the remaining Leydig cells to secrete estradiol rather than testosterone.⁴

Screening for hypogonadism in men may be warranted in several conditions, even without clinical manifestations of low testosterone (Table 3).^{5–10}

To diagnose hypogonadism in men and to

start treatment for it, current guidelines recommend that the patient should have clinical features as well as laboratory evidence of low testosterone.^{5,6}

Measuring testosterone: Total, free, bound, and bioavailable

Testosterone, a steroid hormone, circulates in the serum either as free testosterone or bound to several plasma proteins, mainly sex-hormone binding globulin (SHBG) and albumin.

Total testosterone includes both the free and bound fractions, whereas bioavailable testosterone includes both free and the portion bound to albumin, which has low affinity and can dissociate and be used at the tissue level.¹¹

Low levels of total testosterone do not necessarily reflect a hypogonadal state, as a man with altered SHBG levels or binding capabilities can have low total but normal free testosterone levels and no manifestations.¹² Several conditions can alter the levels of SHBG, including obesity, diabetes, aging, thyroid dysfunction, and others.^{5,13}

Because our patient is obese, his total testosterone level is not a reliable indicator of hypogonadism, and repeating its measurement will not add diagnostic value.

Therefore, an alternative measurement should be used to accurately reflect the testosterone levels. From a physiologic point of view, bioavailable testosterone is the active form of testosterone and is the most accurate to be measured in a patient with hypogonadism. Nevertheless, because of technical difficulties in its measurement and lack of evidence correlating bioavailable testosterone with the clinical picture of hypogonadism, it is recommended that the level of free testosterone be used.⁵

The gold standard for direct measurement of serum free testosterone is equilibrium dialysis, but this is expensive and time-consuming.¹⁴ Commercial assays for free testosterone exist but have been deemed unreliable.^{14,15} It is recommended that free testosterone be measured by equilibrium dialysis or calculated using equations based on total testosterone, SHBG, and albumin levels.⁵ These equations are reliable and give results very close to the values obtained by equilibrium dialysis.¹⁵ Therefore, in our patient, it would be suitable to calculate the free testosterone level next.

Serum levels of free testosterone vary according to several factors. Diurnal variation of testosterone has been established: levels are highest in the morning and decline throughout the day.¹⁶ Food decreases testosterone levels.¹⁷ In addition, there is considerable day-to-day variation.¹⁸ Therefore, at least 2 readings of fasting morning testosterone on 2 separate days are recommended for the diagnosis of hypogonadism.⁵

Inhibin B is a hormone produced by Sertoli cells in the testes in response to follicle-stimulating hormone (FSH) stimulation. In turn, it acts as negative feedback, together with testosterone, to inhibit FSH release from the pituitary. Inhibin B has been shown to reflect spermatogenesis in the testes and therefore fertility.¹⁹ Inhibin B levels were found to be low in patients with central hypogonadism, due to less FSH release; however, they did not correlate with testosterone levels.²⁰

■ CASE RESUMED: CHARACTERIZING HIS HYPOGONADISM

The patient's physician orders morning fasting total testosterone, SHBG, and albumin testing and calculates the free testosterone level, which yields a value of 3 ng/dL (reference range 4.5–17). This is confirmed by a repeat measurement, which yields a value of 2.9 ng/dL. Laboratory test results combined with his clinical presentation are consistent with hypogonadism.

2 What is the most appropriate next step?

- Measurement of serum LH and FSH
- Measurement of serum prolactin
- Scrotal ultrasonography
- Gonadotropin-releasing hormone (GnRH) stimulation test
- Semen analysis

After hypogonadism is diagnosed, it is important to distinguish if it is primary or central. This is achieved by measuring serum LH and FSH.⁵ All biotin supplements should be stopped at least 72 hours before measuring LH and FSH, as biotin can interfere with the assays, yielding false values.²¹

TABLE 2

Symptoms and signs of postpubertal male hypogonadism

General and cognitive manifestations

Fatigue, lack of energy
 Poor motivation
 Impaired concentration and memory
 Depressed mood
 Irritability
 Sleep disturbance

Reproductive manifestations

Decreased libido
 Decreased morning erections
 Erectile dysfunction
 Decreased shaving frequency
 Decreased body hair
 Gynecomastia
 Decreased size of testes
 Infertility (decreased sperm production)

Other manifestations

Decreased bone mineral density, osteoporosis, fractures
 Loss of muscle mass and strength
 Increased body fat and body mass index
 Hot flashes (with severe testosterone deficiency)

Both clinical and biochemical evidence should be present to diagnose hypogonadism

Secretion of FSH and LH from the anterior pituitary is under the influence of pulsatile release of GnRH from the hypothalamus. LH acts on Leydig cells in the testes to produce testosterone, whereas FSH acts on Sertoli cells, together with testosterone, to bring about spermatogenesis in the seminiferous tubules. Testosterone acts centrally as negative feedback to decrease the release of LH and FSH.

Primary hypogonadism occurs due to testicular failure, ie, the testes themselves fail to produce testosterone, leading to hypogonadism. The decrease in testosterone levels, together with inhibin B if Sertoli cells are damaged, lead to loss of negative feedback on the hypothalamus and pituitary, and therefore in-

TABLE 3

Conditions in which screening for hypogonadism may be indicated in men

Condition	Comments
Obesity	Can cause central hypogonadism and is a predictor for testosterone replacement therapy
Type 2 diabetes mellitus	An independent association with male hypogonadism has been reported One-third of men with type 2 diabetes mellitus have low testosterone in cross-sectional studies
Metabolic syndrome	An association with low serum testosterone has been reported
Unexplained anemia	Moderate to severe testosterone deficiency is associated with lower hemoglobin
Low bone mineral density	The relationship between low testosterone and low bone mineral density is not definite, yet guidelines recommend measuring serum testosterone in men with osteoporosis or low-trauma fracture
Chronic obstructive pulmonary disease	22%–69% of men with chronic obstructive pulmonary disease have been reported to have hypogonadism Testosterone replacement may benefit patients in terms of exercise capacity
Human immunodeficiency virus (HIV) infection	Cohort studies showed that 17%–38% of men who are HIV-positive have low testosterone Testosterone replacement in men with HIV-associated weight loss can improve body weight, muscle mass, and mood
Infertility	Pituitary and testicular causes of infertility may also cause hypogonadism
Hypothalamic and pituitary disorders	Can cause central hypogonadism
History of testicular radiation	Direct or scatter radiation may damage Leydig cells leading to primary hypogonadism
History of chemotherapy	Chemotherapy may be a risk factor for low testosterone
Opioid use	Chronic opioid use can lead to testosterone deficiency in up to 50% of men Hypogonadism in a young man should alert physicians to possible opioid abuse
Chronic glucocorticoid use	A risk factor for low testosterone levels
History of androgenic anabolic steroid use	Chronic use can suppress hypothalamic-pituitary-testicular axis, causing hypogonadism upon withdrawal

To confirm low testosterone: ≥ 2 morning measurements while fasting on 2 separate days

creased levels of LH and FSH. This is termed *hypergonadotropic hypogonadism*. Testicular failure may also result in impaired spermatogenesis and infertility due to destruction of testicular structures, in which case fertility cannot be restored.

Central hypogonadism occurs when the pituitary fails to produce LH and FSH (secondary hypogonadism) or when the hypothalamus fails to produce GnRH and subsequently the lack of secretion of LH and FSH from the pituitary (tertiary hypogonadism). The lack

of LH will result in no stimulation of Leydig cells to produce testosterone, and therefore its deficiency. Serum hormone levels in central hypogonadism will reveal low testosterone, with either low or inappropriately normal gonadotropins (LH and FSH). This is termed *hypogonadotropic hypogonadism*. The lack of FSH, together with testosterone deficiency will also result in decreased spermatogenesis and therefore infertility. Testicular structures are preserved, however, and fertility can be restored with appropriate therapy, as discussed below.

Prolactin should be measured only if the patient has central hypogonadism. Its measurement is not warranted at this point in the patient's workup. The implications of prolactin and its relationship to hypogonadism will be discussed later.

Although, this stepwise approach is not convenient for many patients, some physicians follow it because it is cost-effective, especially in those who are not insured. However, other physicians order FSH, LH, and sometimes prolactin with the confirmatory low testosterone measurement. Laboratories can also be instructed to wait to measure the pituitary hormones and to do so only if low testosterone is confirmed.

Varicocele, a possible cause of male infertility, can also impair Leydig cell function and cause low testosterone. In fact, surgical repair of varicocele has been demonstrated to increase serum testosterone.²² Scrotal ultrasonography is used to diagnose varicocele, but this also should be ordered at a later stage in the workup if primary hypogonadism is diagnosed.

The GnRH stimulation test is important for the diagnosis and evaluation of precocious or delayed puberty in children. In boys with delayed puberty, a poorer response to GnRH stimulation indicates central hypogonadism rather than constitutional delay.²³ It has no role in the evaluation of postpubertal or adult-onset hypogonadism.

Semen analysis is important to evaluate fertility if the patient is interested in further procreation.⁵ Low testosterone levels may result in impaired spermatogenesis and therefore infertility. On the other hand, treatment with exogenous testosterone will also result in infertility, by feedback inhibition of LH and FSH and therefore inhibition of spermatogenesis.

If the patient wishes to preserve fertility, treatment options other than testosterone should be considered; examples include clomiphene citrate, human menopausal gonadotropin, and human chorionic gonadotropin.^{23,24}

Our patient has no desire to expand his family; therefore, a semen analysis and attempts to preserve spermatogenesis are not indicated.

**■ CASE RESUMED:
SEARCHING FOR CAUSES**

His physician orders testing of serum LH and FSH, yielding the following values:

- LH 1.6 mIU/mL (reference range 1.8–12)
- FSH 1.9 mIU/mL (reference range 1.5–12.5).

The diagnosis of central hypogonadism is established.

3 Which investigation is the least appropriate in the further evaluation of this patient?

- Serum free thyroxine (T₄) and morning cortisol measurement
- Serum prolactin measurement
- Serum ferritin measurement
- Pituitary magnetic resonance imaging (MRI)
- Chromosomal karyotyping

Low total testosterone does not necessarily reflect hypogonadism

The diagnosis of central hypogonadism warrants evaluation for possible causes. These are summarized in **Table 4**.

Serum free thyroxine and morning cortisol

Since this patient's LH and FSH values are abnormal, it is important to evaluate the status of other anterior pituitary hormones. In patients with pituitary abnormalities, serum free T₄ is a more reliable test for assessing thyroid function than thyroid-stimulating hormone (TSH), because of loss of the negative feedback of thyroid hormones on the diseased pituitary. In contrast, serum TSH is considered the best single thyroid test to assess primary thyroid dysfunction.

Other measurements include prolactin and morning cortisol (reflecting adrenocorticotrophic hormone status).

TABLE 4

Causes of central hypogonadism

Local (pituitary and hypothalamus)

- Congenital
 - Kallmann syndrome
 - Prader-Willi syndrome
 - Idiopathic panhypopituitarism
 - Mutations in luteinizing hormone or follicle-stimulating hormone subunits
- Acquired
 - Pituitary masses and tumors
 - Pituitary destruction (surgery, radiation)
 - Pituitary apoplexy
 - Head trauma
 - Meningitis (especially tuberculosis)
 - Infiltrative diseases (eg, hemochromatosis)
 - Idiopathic

Systemic

- Metabolic
 - Hyperprolactinemia
 - Obesity
 - Malnutrition
 - Eating disorders (eg, anorexia nervosa)
 - Excessive exercise
- Drug- or substance-related
 - Glucocorticoids, opioids, estrogens, and progestins
 - Androgen withdrawal
 - Alcohol and marijuana abuse
- Others
 - Acute critical illness (eg, myocardial infarction, surgery)
 - Chronic systemic disease (eg, cirrhosis, organ failure, acquired immunodeficiency syndrome)

Prolactin measurement

Prolactin measurement is important to evaluate for hyperprolactinemia, as this will lead to hypogonadism by inhibition of GnRH secretion.²⁵ Different pathologic, pharmacologic,

and physiologic conditions can result in hyperprolactinemia, including prolactinomas, other pituitary and hypothalamic lesions, primary hypothyroidism, and medications such as antipsychotics.²⁵ Dopamine agonists are the mainstay treatment for hyperprolactinemia.

Ferritin measurement

Ferritin measurement is indicated to diagnose iron overload conditions such as hemochromatosis, which can result in primary hypogonadism via testicular damage or in secondary hypogonadism via pituitary damage.²⁶

Pituitary MRI with contrast

Pituitary MRI with contrast is used to diagnose structural lesions of the pituitary or hypothalamus. This diagnostic modality is indicated for patients with pituitary dysfunction, including central hypogonadism, manifestations of a mass effect (headache, visual field defects), persistent hyperprolactinemia, and panhypopituitarism, among others. To improve the diagnostic yield of pituitary MRI, the Endocrine Society guidelines recommend it for men with serum total testosterone levels below 150 ng/dL.⁵ However, some clinicians have a lower threshold for ordering pituitary MRI for patients with central hypogonadism. Physician judgment and expertise should be exercised and the decision made on an individual basis.

Chromosomal karyotyping

Chromosomal karyotyping is not indicated in our patient. It is reserved for those with primary hypogonadism to diagnose Klinefelter syndrome, which has a karyotype of 47,XXY.

■ CASE RESUMED: MOSH SYNDROME

Our patient’s prolactin, free T₄, morning cortisol, and ferritin levels are measured, yielding normal values. No abnormalities are seen on pituitary MRI. A clinical reevaluation is conducted, revealing no history of head trauma or head and neck radiation. The lack of an obvious cause in our patient’s clinical presentation and workup, together with his obesity (BMI 32.8 kg/m²) supports the diagnosis of obesity as the cause of his hypogonadism.

Obesity can be a cause of secondary hypogonadism, which has led to the term “MOSH”

Measure LH and FSH to distinguish whether hypogonadism is primary or central

(male obesity-associated secondary hypogonadism) syndrome. In fact, a cross-sectional study has demonstrated that 40% of nondiabetic obese (BMI ≥ 30 kg/m²) men over age 45 have low serum free testosterone levels, compared with 26% for lean (BMI < 25 kg/m²) men.²⁷ Moreover, obesity has been found to be a strong predictor of testosterone replacement therapy.²⁸ Other studies have also found an inverse relationship between BMI and testosterone levels.²⁹

Several mechanisms interact in the pathogenesis of MOSH syndrome. Adipose tissue possesses aromatase activity, which converts androgens into estrogens.³⁰ Peripheral estrogen production can in turn exert feedback inhibition on pituitary gonadotropin secretion.³¹ In obese men, increased adipose tissue leads to increased aromatase activity and more estrogen, so more feedback inhibition on the pituitary and subsequently secondary hypogonadism.

Leptin, a hormone produced by adipocytes, is also increased in obesity, and was found to be inversely correlated with serum testosterone.³² Studies have demonstrated that leptin has an inhibitory effect on the enzymatic pathway that synthesizes testosterone in Leydig cells.³³

Proinflammatory cytokines have also been implicated, as central obesity is associated with an increase in these cytokines, which in turn act negatively on the hypothalamus and impair GnRH release leading to lower testosterone.^{34,35}

Treating obesity-related hypogonadism

In a pilot study,³⁶ lifestyle attempts to reduce obesity were shown to improve hormonal levels. Bariatric surgery has also been demonstrated to be successful.³⁷

Clomiphene citrate, a selective estrogen receptor modulator, increases endogenous testosterone secretion by inhibiting the negative feedback of estrogen on the hypothalamus and pituitary and thus increasing LH and FSH. It also preserves endogenous testosterone production, since it does not suppress the hypothalamic-pituitary-testicular axis.³⁸ This made clomiphene citrate a potential treatment for men with central hypogonadism including those with MOSH.³⁹

Nevertheless, there are no randomized

trials to prove its safety and efficacy in the management of central hypogonadism.⁵ Regarding its use in men wishing to preserve fertility, most studies did not show improvement. However, a meta-analysis demonstrated statistically significant increased pregnancy rates in partners of men with idiopathic infertility if the men used 50 mg of clomiphene citrate daily.⁴⁰

Testosterone deficiency can be a marker of metabolic syndrome, which needs to be managed more urgently than hypogonadism. A cross-sectional study found not only an association between metabolic syndrome and low serum testosterone, but also with each individual component of metabolic syndrome on its own, all of which need to be addressed.¹⁰

■ CASE CONTINUED: BEGINNING TREATMENT

The physician counsels the patient regarding the implications, potential adverse outcomes, and available treatments for his obesity, including lifestyle modification and bariatric surgery. The patient declines surgery and wishes to adopt a weight-reducing diet and exercise program, for which he is referred to a dietitian.

In addition, in view of the patient's clinically and biochemically proven hypogonadism, his physician offers testosterone replacement therapy. He orders a serum prostate-specific antigen (PSA) level, which is 1.3 ng/dL (reference range < 4 ng/dL). The patient is prescribed 5 g of 1% testosterone gel daily.

■ TESTOSTERONE REPLACEMENT THERAPY

4 Which is the most common adverse effect of testosterone replacement therapy?

- Cardiovascular events
- Erythrocytosis
- Prostate cancer
- Infertility
- Obstructive sleep apnea

Testosterone is indicated for men with an established diagnosis of hypogonadism. The benefits of testosterone replacement are summarized in **Table 5**.^{5,6}

In central hypogonadism, testosterone is low, LH and FSH are low or inappropriately normal

TABLE 5

Benefits of testosterone therapy

Proven

- Virilization and maintenance of secondary sexual characteristics
- Improved sexual function: increased libido, better erectile function
- Increased muscles mass and strength
- Decreased fat mass
- Increased bone mineral density

Not proven (conflicting or no evidence)

- Improved energy
- Improved cognitive function
- Improved mood
- Improved depressive symptoms

TABLE 6

Prostate monitoring for patients on testosterone replacement therapy, according to age

Age

(years) Endocrine Society Guidelines⁵

< 40	No need for prostate monitoring
40–54	Baseline prostate-specific antigen and digital rectal examination if high risk, ^a repeat at 3 to 12 months after starting testosterone replacement therapy, then continue according to screening guidelines
55–69	Baseline prostate-specific antigen and digital rectal examination, repeat at 3 to 12 months after starting testosterone replacement therapy, then continue according to screening guidelines
≥ 70	No need for prostate monitoring

^a High-risk patients include African Americans and patients with a first-degree relative with confirmed prostate cancer.

Clinicians should be very cautious in initiating testosterone replacement therapy in any patient with an unstable medical condition.

There are several formulations of testosterone replacement therapy, including intramuscular injections, transdermal gels or patches, buccal tablets, an intranasal gel, and oral tablets. Of note, there are 2 different forms of oral testosterone preparations: testosterone

undecanoate and 17-alpha alkylated testosterone. The former is unavailable in the United States and the latter is not recommended for use due to its proven hepatic toxicity.⁴¹

Testosterone and erythrocytosis

Meta-analyses have concluded that the most frequent adverse event of testosterone replacement therapy is a significant rise in hematocrit.⁴² This rise was found to be dose-dependent and was more marked in older men.⁴³ Although all preparations can cause erythrocytosis, parenteral forms have been observed to raise it the most, particularly short-term injectables.^{44,45}

The mechanism behind this increase is attributed to increased erythropoietin levels and improved usage of iron for red blood cell synthesis.⁴⁶ In fact, testosterone replacement therapy has been shown to improve hemoglobin levels in patients with anemia.⁴⁷ On the other hand, increasing hematocrit levels may lead to thrombotic and vasoocclusive events.⁴⁴

It is strongly recommended that baseline hematocrit levels be measured before initiating testosterone replacement therapy.^{5,6} The hematocrit level should also be monitored 3 to 6 months into treatment and yearly thereafter while on testosterone.⁵ **Figure 1** summarizes the appropriate steps to undertake regarding hematocrit levels, according to the American Urological Association.⁶

Testosterone and prostate cancer

The relationship between testosterone treatment and prostate cancer has long been studied. Historically, testosterone replacement therapy was believed to increase the risk of prostate cancer; however, recent studies and meta-analyses have shown that this is not the case.^{42,48} Nevertheless, clinical guidelines still recommend prostate monitoring for men on testosterone replacement therapy.^{5,6}

Furthermore, the clinician should make sure the patient does not have prostate cancer before initiating testosterone replacement therapy. Since there is a significant incidence of prostate cancer in men with serum PSA of 2.5–4.0 ng/mL, a patient with hypogonadism and a serum PSA in that range or higher should have appropriate evaluation before initiating testosterone replacement therapy.⁴⁹

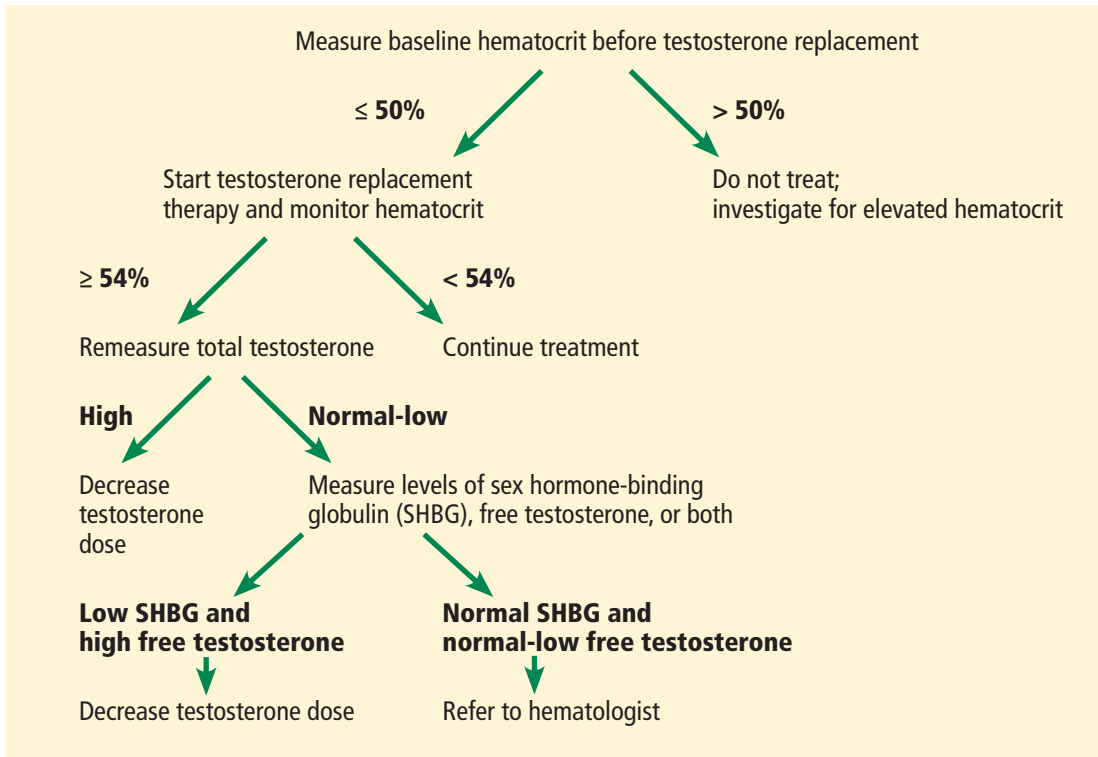


FIGURE 1. Hematocrit monitoring for patients on testosterone replacement therapy.

The Endocrine Society recommendations for prostate monitoring are summarized in **Table 6**.⁵

Testosterone and cardiovascular risk

The evidence regarding this issue has been contradictory and inconsistent. Meta-analyses have demonstrated that low testosterone is associated with higher risk of major adverse cardiovascular events.⁵⁰ These studies argue for the use of testosterone replacement therapy in hypogonadal men to decrease the risk. However, other studies and meta-analyses have found that testosterone replacement therapy is associated with increased cardiovascular risk and have concluded that major adverse cardiac events are in fact a risk of testosterone replacement therapy.⁵¹

Current recommendations advocate against the use of testosterone replacement therapy in men with uncontrolled heart failure or with cardiovascular events in the past 3 to 6 months.^{5,6} Cardiovascular risk factors should be addressed and corrected, and patients should be educated on cardiovascular symptoms and the need to report them if they occur.

Testosterone and infertility

As described earlier, testosterone replacement therapy increases negative feedback on the pituitary and decreases LH and FSH production, leading to less spermatogenesis. Other treatment options should be sought for hypogonadal men wishing to preserve fertility.

Other adverse effects

Other adverse effects of testosterone replacement therapy include acne, oily skin, obstructive sleep apnea, gynecomastia, and balding.

Given all the adverse events that can be associated with testosterone replacement therapy, the risks and benefits of treating hypogonadism in each patient should be taken into consideration, and an individualized approach is required.

■ CASE RESUMED: FOLLOW-UP

The patient presents 3 months later for follow-up. He reports significant improvement in his presenting symptoms including energy, libido, and erectile function. He also reports some improvement in his mood and concentration. He has lost 12 lb (5.4 kg) and is still trying to

In central hypogonadism, obtain pituitary MRI and free T₄, prolactin, morning cortisol, and ferritin

improve his diet and exercise program. He is compliant with his testosterone gel therapy.

His serum calculated free testosterone level is 7.8 ng/dL (4.5–17), and his hematocrit is 46%. The patient is instructed to continue his treatment and to return after 9 months for further follow-up.

■ TAKE-HOME POINTS

- Men with hypogonadism usually present with nonspecific manifestations, so clinicians should keep a high index of suspicion.

- Both clinical and biochemical evidence of hypogonadism should be present to diagnose and start treatment for it.
- Low levels of serum total testosterone do not necessarily reflect hypogonadism.
- The hormonal profile of central hypogonadism reveals low serum testosterone with low or inappropriately normal serum LH and FSH levels.
- Obesity can cause central hypogonadism and should be suspected after pituitary and other systemic causes are excluded. ■

■ REFERENCES

1. Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab* 2007; 92(11):4241–4247. doi:10.1210/jc.2007-1245
2. Wu FCW, Tajar A, Beynon JM, et al; EMAS Group. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med* 2010; 363(2):123–135. doi:10.1056/NEJMoa0911101
3. Arver S, Lehtihet M. Current guidelines for the diagnosis of testosterone deficiency. *Front Horm Res* 2009; 37:5–20. doi:10.1159/000175839
4. Narula HS, Carlson HE. Gynaecomastia—pathophysiology, diagnosis and treatment. *Nat Rev Endocrinol* 2014; 10(11):684–698. doi:10.1038/nrendo.2014.139
5. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2018; 103(5):1715–1744. doi:10.1210/jc.2018-00229
6. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and management of testosterone deficiency: AUA guideline. *J Urol* 2018; 200(2):423–432. doi:10.1016/j.juro.2018.03.115
7. Balasubramanian V, Naing S. Hypogonadism in chronic obstructive pulmonary disease: incidence and effects. *Curr Opin Pulm Med* 2012; 18(2):112–117. doi:10.1097/MCP.0b013e32834feb37
8. Atlantis E, Fahey P, Cochrane B, Wittert G, Smith S. Endogenous testosterone level and testosterone supplementation therapy in chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. *BMJ Open* 2013; 3(8):pii:e003127. doi:10.1136/bmjopen-2013-003127
9. Bawor M, Bami H, Dennis BB, et al. Testosterone suppression in opioid users: a systematic review and meta-analysis. *Drug Alcohol Depend* 2015; 149:1–9. doi:10.1016/j.drugalcdep.2015.01.038
10. Tan WS, Ng CJ, Khoo EM, Low WY, Tan HM. The triad of erectile dysfunction, testosterone deficiency syndrome and metabolic syndrome: findings from a multi-ethnic Asian men study (The Subang Men’s Health Study). *Aging Male* 2011; 14(4):231–236. doi:10.3109/13685538.2011.597463
11. Goldman AL, Bhasin S, Wu FCW, Krishna M, Matsumoto AM, Jasuja R. A reappraisal of testosterone’s binding in circulation: physiological and clinical implications. *Endocr Rev* 2017; 38(4):302–324. doi:10.1210/er.2017-00025
12. Antonio L, Wu FC, O’Neill TW, et al; European Male Ageing Study Group. Low free testosterone is associated with hypogonadal signs and symptoms in men with normal total testosterone. *J Clin Endocrinol Metab* 2016; 101(7):2647–2657. doi:10.1210/jc.2015-4106
13. Liu F, Shen X, Wang R, et al. Association of central obesity with sex hormone binding globulin: a cross-sectional study of 1166 Chinese men. *Open Med (Wars)* 2018; 13:196–202. doi:10.1515/med-2018-0030
14. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab* 1999; 84(10):3666–3672. doi:10.1210/jcem.84.10.6079
15. Halmenschlager G, Rhoden EL, Riedner CE. Calculated free testosterone and radioimmunoassay free testosterone as a predictor of subnormal levels of total testosterone. *Int Urol Nephrol* 2012; 44(3):673–681. doi:10.1007/s11255-011-0066-z
16. Brambilla DJ, Matsumoto AM, Araujo AB, McKinlay JB. The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men. *J Clin Endocrinol Metab* 2009; 94(3):907–913. doi:10.1210/jc.2008-1902
17. Lehtihet M, Arver S, Bartuseviciene I, Pousette Å. S-testosterone decrease after a mixed meal in healthy men independent of SHBG and gonadotrophin levels. *Andrologia* 2012; 44(6):405–410. doi:10.1111/j.1439-0272.2012.01296.x
18. Brambilla DJ, O’Donnell AB, Matsumoto AM, McKinlay JB. Intraindividual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. *Clin Endocrinol (Oxf)* 2007; 67(6):853–862. doi:10.1111/j.1365-2265.2007.02976.x
19. Manzoor SM, Sattar A, Hashim R, et al. Serum inhibin B as a diagnostic marker of male infertility. *J Ayub Med Coll Abbottabad* 2012; 24(3–4):113–116. pmid:24669628
20. Kolb BA, Stanczyk FZ, Sokol RZ. Serum inhibin B levels in males with gonadal dysfunction. *Fertil Steril* 2000; 74(2):234–238. pmid:10927037
21. Trambas CM, Sikaris KA, Lu ZX. More on biotin treatment mimicking Graves’ disease. *N Engl J Med* 2016; 375(17):1698. doi:10.1056/NEJMc1611875
22. Li F, Yue H, Yamaguchi K, et al. Effect of surgical repair on testosterone production in infertile men with varicocele: a meta-analysis. *Int J Urol* 2012; 19(2):149–154. doi:10.1111/j.1442-2042.2011.02890.x
23. Crosnoe-Shipley LE, Elkelay OO, Rahnama CD, Kim ED. Treatment of hypogonadotropic male hypogonadism: case-based scenarios. *World J Nephrol* 2015; 4(2):245–253. doi:10.5527/wjn.v4.i2.245
24. Majzoub A, Sabanegh E Jr. Testosterone replacement in the infertile man. *Transl Androl Urol* 2016; 5(6):859–865. doi:10.21037/tau.2016.08.03
25. Majumdar A, Mangal NS. Hyperprolactinemia. *J Hum Reprod Sci* 2013; 6(3):168–175. doi:10.4103/0974-1208.121400
26. El Osta R, Grandpre N, Monnin N, Hubert J, Koscinski I. Hypogonadotropic hypogonadism in men with hereditary hemochromatosis. *Basic Clin Androl* 2017; 27:13. doi:10.1186/s12610-017-0057-8
27. Dhindsa S, Miller MG, McWhirter CL, et al. Testosterone concentrations in diabetic and nondiabetic obese men. *Diabetes Care* 2010; 33(6):1186–1192. doi:10.2337/dc09-1649
28. Jasuja GK, Bhasin S, Reisman JI, et al. Who gets testosterone? Patient characteristics associated with testosterone prescribing in the Veteran Affairs system: a cross-sectional study. *J Gen Intern Med* 2017; 32(3):304–311. doi:10.1007/s11606-016-3940-7
29. Kaplan SA, Lee JY, O’Neill EA, Meehan AG, Kusek JW. Prevalence of low testosterone and its relationship to body mass index in older men with lower urinary tract symptoms associated with benign prostatic hyperplasia. *Aging Male* 2013; 16(4):169–172. doi:10.3109/13685538.2013.844786

30. Lee HK, Lee JK, Cho B. The role of androgen in the adipose tissue of males. *World J Mens Health* 2013; 31(2):136–140. doi:10.5534/wjmh.2013.31.2.136
31. Raven G, De Jong FH, Kaufman JM, De Ronde W. In men, peripheral estradiol levels directly reflect the action of estrogens at the hypothalamo-pituitary level to inhibit gonadotropin secretion. *J Clin Endocrinol Metab* 2006; 91(9):3324–3328. doi:10.1210/jc.2006-0462
32. Hofny ER, Ali ME, Abdel-Hafez HZ, et al. Semen parameters and hormonal profile in obese fertile and infertile males. *Fertil Steril* 2010; 94(2):581–584. doi:10.1016/j.fertnstert.2009.03.085
33. Isidori AM, Caprio M, Strollo F, et al. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. *J Clin Endocrinol Metab* 1999; 84(10):3673–3680. doi:10.1210/jcem.84.10.6082
34. El-Wakkad A, Hassan NM, Sibaii H, El-Zayat SR. Proinflammatory, anti-inflammatory cytokines and adiponkines in students with central obesity. *Cytokine* 2013; 61(2):682–687. doi:10.1016/j.cyto.2012.11.010
35. Maggio M, Basaria S, Ceda GP, et al. The relationship between testosterone and molecular markers of inflammation in older men. *J Endocrinol Invest* 2005; 28(suppl proceedings 11):116–119. PMID:16760639
36. de Lorenzo A, Noce A, Moriconi E, et al. MOSH syndrome (male obesity secondary hypogonadism): clinical assessment and possible therapeutic approaches. *Nutrients* 2018; 10(4):pii:E474. doi:10.3390/nu10040474
37. Escobar-Morreale HF, Santacruz E, Luque-Ramírez M, Botella Carretero JI. Prevalence of ‘obesity-associated gonadal dysfunction’ in severely obese men and women and its resolution after bariatric surgery: a systematic review and meta-analysis. *Hum Reprod Update* 2017; 23(4):390–408. doi:10.1093/humupd/dmx012
38. Lo EM, Rodriguez KM, Pastuszak AW, Khera M. Alternatives to testosterone therapy: a review. *Sex Med Rev* 2018; 6(1):106–113. doi:10.1016/j.sxmr.2017.09.004
39. Soares AH, Horie NC, Chiang LAP, et al. Effects of clomiphene citrate on male obesity-associated hypogonadism: a randomized, double-blind, placebo-controlled study. *Int J Obes (Lond)* 2018; 42(5):953–963. doi:10.1038/s41366-018-0105-2
40. Chua ME, Escusa KG, Luna S, Tapia LC, Dofitas B, Morales M. Revisiting oestrogen antagonists (clomiphene or tamoxifen) as medical empiric therapy for idiopathic male infertility: a meta-analysis. *Andrology* 2013; 1(5):749–757. doi:10.1111/j.2047-2927.2013.00107.x
41. Westaby D, Ogle SJ, Paradinas FJ, Randell JB, Murray-Lyon IM. Liver damage from long-term methyltestosterone. *Lancet* 1977; 2(8032):262–263. PMID:69876
42. Fernández-Balsells MM, Murad MH, Lane M, et al. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2010; 95(6):2560–2575. doi:10.1210/jc.2009-2575
43. Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB, Bhasin S. Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. *J Clin Endocrinol Metab* 2008; 93(3):914–919. doi:10.1210/jc.2007-1692
44. Ohlander SJ, Varghese B, Pastuszak AW. Erythrocytosis following testosterone therapy. *Sex Med Rev* 2018; 6(1):77–85. doi:10.1016/j.sxmr.2017.04.001
45. Jones SD Jr, Dukovac T, Sangkum P, Yafi FA, Hellstrom WJ. Erythrocytosis and polycythemia secondary to testosterone replacement therapy in the aging male. *Sex Med Rev* 2015; 3(2):101–112. doi:10.1002/smrj.43
46. Bachman E, Travison TG, Basaria S, et al. Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point. *J Gerontol A Biol Sci Med Sci* 2014; 69(6):725–735. doi:10.1093/gerona/glt154
47. Roy CN, Snyder PJ, Stephens-Shields AJ, et al. Association of testosterone levels with anemia in older men: a controlled clinical trial. *JAMA Intern Med* 2017; 177(4):480–490. doi:10.1001/jamainternmed.2016.9540
48. Klap J, Schmid M, Loughlin KR. The relationship between total testosterone levels and prostate cancer: a review of the continuing controversy. *J Urol* 2015; 193(2):403–413. doi:10.1016/j.juro.2014.07.123
49. Gilbert SM, Cavallo CB, Kahane H, Lowe FC. Evidence suggesting PSA cutpoint of 2.5 ng/mL for prompting prostate biopsy: review of 36,316 biopsies. *Urology* 2005; 65(3):549–553. doi:10.1016/j.urology.2004.10.064
50. Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Clinical review: Endogenous testosterone and mortality in men: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011; 96(10):3007–3019. doi:10.1210/jc.2011-1137
51. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med* 2013; 11:108. doi:10.1186/1741-7015-11-108

ADDRESS: Ayman A. Zayed, MD, MSc, FACE, FACP, Department of Internal Medicine, Jordan University Hospital, The University of Jordan, Queen Rania Street, Amman, Jordan, 11942; baraaayman@gmail.com