

Spotlight on Health

Low Testosterone (Hypogonadism)

June is Men's Health Month, and one health concern of many aging men is low testosterone, or "low T." Also known as testosterone deficiency or hypogonadism, low T causes symptoms in 2% to 6% of all men.¹ Older age, obesity, and diabetes are common risk factors.^{1,2} Low T is easily treatable, but testosterone therapy may cause adverse effects such as erythrocytosis, reduced fertility, and possibly prostate cancer.³ So guidelines recommend only treating men with low T who are symptomatic. In this newsletter, we will discuss how to diagnose the syndrome, determine etiology, and monitor treatment.

Diagnosis of Low T

Both clinical and biochemical criteria should be used to diagnose low T, according to the Endocrine Society³ and other groups.² Clinical criteria are signs and symptoms that are consistent with the syndrome. The more prominent signs and symptoms are related to the reproductive system: reduced sex drive and erectile dysfunction. However, some are more general or affect other systems: fatigue, depression, lethargy, sleep disturbance, irritability, increased body fat, and decreased muscle mass and bone mineral density.¹⁻³

Guidelines on biochemical criteria are more detailed:

- **Morning measurements:** Samples for testosterone measurements should be taken in the morning (7-11 AM),² when levels peak.³ This should be followed even for older men, who have less variation in levels throughout the day.³
- **Testosterone fractions:** Total testosterone should be used as the initial measurement for diagnosis. It includes all 3 circulating forms of the hormone: unbound, weakly bound (bound to albumin), and tightly bound (bound to sex hormone binding globulin [SHBG]). If the initial measurement is near the lower limit of normal, bioavailable T (unbound + weakly bound) and free T measurements (unbound) can be used.³
- **Cutoff levels:** The normal range that is established in the testing laboratory should be used. The cutoff for low T varies by laboratory and assay.^{2,3}
- **Result confirmation:** In patients with an initial low measurement, a second measurement should be done.³ If possible, the second measurement should be done using an LC-MS/MS assay, which is accurate below and near the lower limit of normal. Immunoassays are reliable for measuring T in the normal range and are sufficient for an initial measurement. But they are less accurate below or near the lower limit of normal.^{4,5}



Causes of Hypogonadism

Primary hypogonadism is caused by defects at the level of the testes. Secondary hypogonadism is caused by defects at the level of the hypothalamus or the pituitary gland. Mixed hypogonadism involves more than 1 cause.

Primary Hypogonadism¹

Age (mixed hypogonadism)
Cryptorchidism
Drugs
Hemochromatosis
Irradiation to testes
Klinefelter syndrome
Mumps orchitis
Noonan syndrome
Surgery
Trauma to testes

Secondary Hypogonadism¹

Age (mixed hypogonadism)
Diabetes
Drugs
Hyperprolactinemia
Hypogonadotropic hypogonadism
Irradiation to hypothalamus or pituitary gland
Kallmann syndrome
Obesity
Prader-Willi syndrome
Surgery
Tumors in the central nervous system

Determining the Cause of Low T

If low T is confirmed, the next step is to figure out why hormone production is failing (ie, distinguish primary vs secondary hypogonadism [sidebar, page 1]).³ Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) can provide clues about cause and indicate follow-up tests.³

If testosterone levels are low:

- *High LH and FSH levels* suggest primary hypogonadism. If the cause is unknown, karyotyping may help identify Klinefelter syndrome.
- *Low or normal LH and FSH levels* suggest secondary hypogonadism. The cause may be identified by testing prolactin, iron saturation, or pituitary hormones; an MRI may help in some cases.

Testosterone Replacement Therapy

If low T is properly diagnosed (ie, symptoms are present and morning serum levels have been confirmed), the syndrome is treatable with testosterone replacement therapy (TRT). However, TRT is contraindicated in some patients. In others, a co-morbid condition may need to be resolved or further evaluation may be needed before beginning TRT.^{2,3} It is also important to confirm that morning serum levels are low.

- *Do not start TRT* in patients who have prostate cancer, breast cancer, or erythrocytosis (hematocrit >52%).
- *Resolve untreated obstructive sleep apnea or untreated severe heart failure* before starting TRT.
- *Conduct further urological examination* before starting TRT if a patient has a palpable prostate nodule or induration or PSA levels >4 ng/mL (>3 ng/mL in patients at high risk of prostate cancer).

Target testosterone levels for TRT should be in the mid-normal range of healthy, young men. Testosterone levels and clinical response should be monitored at 3 to 6 months after starting therapy and then annually.^{2,3} Hematocrit, PSA, and bone mineral density should also be monitored in men on TRT.³

How the Laboratory Can Help

Quest Diagnostics offers tests that can help with diagnosis and management of low T:

- **Diagnose low T:** immunoassays and LC-MS/MS assays to measure free, bioavailable, and/or total testosterone
- **Differentiate primary and secondary hypogonadism:** LH and FSH assays
- **Determine the cause:** karyotyping, prolactin, iron saturation, and pituitary hormone assays
- **Identify TRT candidate and monitor:** hematocrit, PSA, bone mineral density assays

References

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2. Wang C, Nieschlag E, Swerdloff R, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. *Eur J Endocrinol.* 2008;159:507-514.
3. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2010;95:2536-2559.
4. Paduch DA, Brannigan RE, Fuchs EF, et al. The laboratory diagnosis of testosterone deficiency. *Urology.* 2014;83:980-988.
5. Rosner W, Auchus RJ, Azziz R, et al. Position statement: Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. *J Clin Endocrinol Metab.* 2007;92:405-413.