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. Older age, obesity, and diabetes are common risk factors. Low T is easily treatable, but testosterone therapy may cause adverse effects such as erythrocytosis, reduced fertility, and possibly prostate cancer. 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 Society and other groups. 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.

Guidelines on biochemical criteria are more detailed:

- **Morning measurements:** Samples for testosterone measurements should be taken in the morning (7-11 am), when levels peak. This should be followed even for older men, who have less variation in levels throughout the day.
- **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.
- **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.
- **Result confirmation:** In patients with an initial low measurement, a second measurement should be done. 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.

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 Hypogonadism**

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

**Secondary Hypogonadism**

- Age (mixed hypogonadism)
- Diabetes
- Drugs
- Hyperprolactinemia
- Hypogonadotropic hypogonadism
- Irradiation to hypothalamus or pituitary gland
- Kallmann syndrome
- 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]). Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) can provide clues about cause and indicate follow-up tests.

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. 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. Hematocrit, PSA, and bone mineral density should also be monitored in men on TRT.

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

Low Testosterone (Hypogonadism)

June is Men’s Health Month, so we are looking at a health issue that affects men. Two to 6% of men have symptoms caused by low testosterone (low T).\(^1\) (Low T is also called testosterone deficiency or hypogonadism.) In this newsletter, we discuss how a doctor can identify and treat low T.

**What is Low T?**

As you can tell from its name, low T is a condition marked by low levels of testosterone. Testosterone is a male sex hormone. It is important for sex drive, but it also affects muscle mass, bone density, and mood. That’s why low T can cause many symptoms that aren’t linked to sex (sidebar).

Not all men with low T have symptoms. And many symptoms of low T could be caused by other conditions. Plus, treatment comes with some risks. So for low T to be diagnosed, 2 criteria must be met.\(^2,3\)

- Symptoms of low T must be present (sidebar).
- Laboratory tests must show low T. If levels are in the low normal range, a doctor should order a second test to confirm.\(^2\) Samples for all tests should be taken in the morning, when testosterone levels are highest.

**What Causes Low T?**

Low T has many causes, such as drugs, surgery, and disease. Treatment can be different for different causes. That’s why doctors often do more tests to find the cause.

The causes of low T are linked to a problem either in the testicles or in other glands. Since testosterone is made in the testicles, a problem there could cause low T. This would be called primary hypogonadism.

Other glands make hormones that trigger the testicles to make testosterone. A problem in these glands could result in a low amount of these hormones in the blood. That, in turn, would cause low T. Low T that is caused by problems in glands other than the testicles is called secondary hypogonadism.

Knowing if low T is caused by primary or secondary hypogonadism helps the doctor know how best to treat the patient.

**Symptoms of Low T**

Low T can cause symptoms that affect many parts of the body.\(^1-3\) But these symptoms can also be caused by other health issues. Thus, lab tests are also needed to diagnose low T.

- Reduced sex drive
- Erectile dysfunction
- Decreased muscle mass
- Decreased bone mineral density
- Depression
- Fatigue
- Increased body fat
- Irritability
- Lethargy
- Poor sleep
Can Low T be Treated?
The good news is that low T can be treated. A doctor can prescribe testosterone. This is called testosterone replacement therapy (TRT). But not everybody can be treated safely. So even if a patient has low T, a doctor needs to make sure the patient is a good candidate for treatment.

TRT can harm patients with certain health issues. For instance, men with prostate cancer, breast cancer, or high red blood cell count (erythrocytosis) can be harmed by TRT. These people should not receive TRT. Other people may have health issues that need to be treated before TRT starts. A doctor should discuss all the benefits and risks of TRT with the patient before starting treatment.

A patient on TRT usually takes it for life. Once treatment begins, progress should be monitored by the doctor. The goal of treatment is normal levels of testosterone. If this goal is reached, it shows that treatment is working to raise levels. But symptoms should also improve. Hormone levels and symptoms should be looked at 3 to 6 months after starting TRT and then once each year.

How Laboratory Testing can Help
Quest Diagnostics offers tests that can help identify low T and its causes. Tests are also offered that help with treatment.

- **Diagnosing low T:** Tests can help confirm a man has low T.
- **Determining the cause:** Tests can help figure out what is causing low T.
- **Identifying candidates for TRT:** Tests can help a doctor know if treatment will be safe for the patient.
- **Monitoring TRT:** Tests can help a doctor know if treatment is raising hormone levels. They can also help a doctor know if treatment is causing side effects, such as high red blood cell count.\(^2,3\)

References