

Testosterone deficiency and testosterone replacement therapy

Dr. Ethan D. Grober

Assistant Professor, Department of Surgery, Division of Urology, University of Toronto
Mount Sinai & Women's College Hospital, Toronto, ON, Canada

Let's start with the basics: What is testosterone?

Testosterone is the main “male hormone” or androgen in men. As you get older, the levels of testosterone in your body tend to gradually decline about 1% each year. This change usually affects your sex drive or erections. In some men, however, low concentrations of testosterone are associated with important health problems and an overall decreased quality of life. In recent years, we've studied the aging male and the impact that levels of testosterone can have on a man's health.

About 25–45% of men between the ages of 40–80 have low levels of testosterone. In Canada, over 660,000 men suffer from testosterone deficiency. Despite this, the percentage of men receiving appropriate management for testosterone deficiency syndrome is small in comparison to the frequency of the condition.

More and more doctors are realizing the potential benefits of men maintaining healthy levels of testosterone and are discussing the variety of treatment options to replace lost testosterone.

What is testosterone deficiency syndrome?

Many names have been used to characterize the phenomena of decreasing testosterone levels in men as they age: *Andropause*, *Androgen Deficiency in the Aging Male (ADAM)*, *Late Onset Hypogonadism* and more recently *Testosterone Deficiency Syndrome*. Regardless of the term, this syndrome includes:

- 1) Low measured concentrations of testosterone within the blood and
- 2) Recognizable signs and symptoms associated with low testosterone levels.

The Canadian Society for the Study of the Aging Male defines testosterone deficiency syndrome as:

A biochemical syndrome associated with advancing age and characterized by a deficiency in serum testosterone levels, which may result in significant alternations in the quality of life and negatively affect the function of multiple organ systems.

Where does testosterone come from?

In men, the testicles produce most of the testosterone (90%). Small glands on top of the kidneys called the adrenal glands produce the other 10%. The cells within the testicles responsible for testosterone production are called Leydig cells. The brain has the ability to sense whether testosterone levels are high, low or normal. Production and regulation of testosterone within the testicles by the Leydig cells is controlled by signals from the brain that travel to the testicles within the blood. The main signal from the brain is the hormone called LH or luteinizing hormone. Take a look at Figure 1 for an overview of this process.

Within the blood, most (98%) of the testosterone travels to the various tissues and organs throughout the body attached to proteins. When testosterone is bound to a protein it has a relatively weak influence in men. The most powerful form of testosterone is not attached to a protein at all – it’s “free” – and has a greater ability to affect functions within of the body. When testosterone is linked to proteins, it’s almost like the proteins act as sponges soaking up the testosterone and preventing their actions.

As men age, several key changes occur within the body that can help explain why testosterone levels decline.

1. The strength and frequency of the hormone signals from the brain are diminished.
2. There are fewer testosterone producing cells within the testicles.
3. There is less of the most powerful form of testosterone (free testosterone) within the body.
4. Testosterone breakdown is increased.
5. The target organs which respond to testosterone become less sensitive.

How is testosterone deficiency diagnosed?

The diagnosis typically requires both the presence of the common symptoms associated with testosterone deficiency coupled with evidence of low or borderline levels of testosterone in the blood.

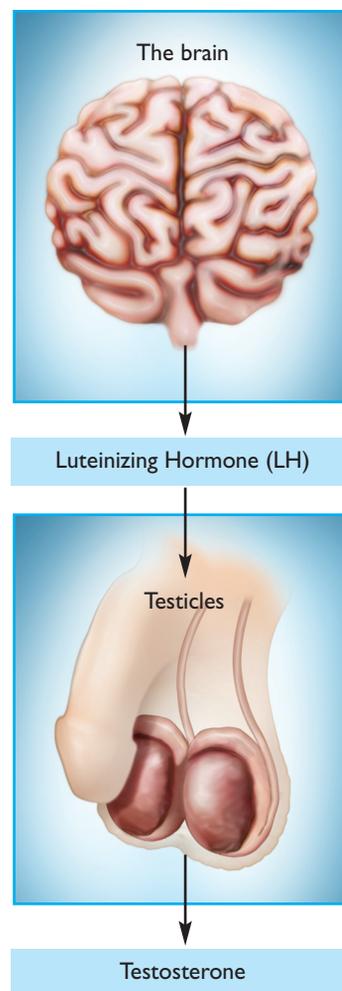


Figure 1. Overview of how testosterone is produced in the body

History

Screening questionnaires:

Several questionnaires for patients have been developed to help determine whether your symptoms are related to testosterone deficiency. This is usually the first step. The most common questionnaire is the called the ADAM (Androgen Deficiency in the Aging Male) questionnaire – see Table 1.

Table 1. The ADAM Questionnaire

1. Do you have a decrease in libido? (yes/no)
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Do you have a decreased enjoyment of life?
5. Are you sad?
6. Are you grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to play sports?
9. Are you falling asleep earlier after dinner?
10. Has there been a recent deterioration in your work performance?

If you've answered YES to questions 1, 7 or any 3 other questions, you may have a testosterone deficiency.

If your doctor suspects testosterone deficiency, you'll be examined and your doctor may focus on the following signs and symptoms:

- Decreased libido or sex drive
- Erectile dysfunction
- Loss of energy
- Increasing fatigue or sleepiness
- Lack of motivation
- Irritability
- Depressed mood
- Inability to concentrate
- Sleep disturbances
- Hot flashes
- Decreased muscle mass
- Weight gain or increased body fat
- Reduced bone mineral density (fragile bone structure)

Physical Exam

If you have symptoms of testosterone deficiency, you may be a candidate for testosterone replacement therapy. If so, you'll undergo a complete physical exam, with particular attention to the following testosterone dependant tissues and organs.

- Testicles: size, firmness, location
- Penile length
- Prostate size and consistency by performing a digital rectal examination (DRE)
- Secondary sex characteristics: facial and body hair, changes with puberty
- Breast tissue development (gynecomastia)
- Weight and fat distribution
- Muscle and bone structure and function

Blood Tests

If your physical signs and symptoms suggest testosterone deficiency, the level of testosterone in your body can be measured with a simple blood test. It's possible to measure the total amount of testosterone in the blood, as well as the proportions of testosterone that are free and protein-bound. Your testosterone level tends to be highest in the morning between 8-11 am, so it's best to try and perform the blood test during this time.

If your testosterone levels are low or borderline on the initial blood test, your doctor may suggest that your testosterone be measured again. If your testosterone levels are consistently low, you'll need a more complete hormone assessment and additional blood tests to determine the reason for the testosterone deficiency and to make sure it's safe to consider testosterone replacement. These tests may include:

- Pituitary function tests: LH, FSH, prolactin, TSH
- Prostate health: PSA (prostate specific antigen – a screening test for prostate cancer)

What are the Potential Benefits of Testosterone Replacement Therapy?

If you're experiencing the symptoms of testosterone deficiency and blood tests confirm low levels of testosterone, you may be offered testosterone therapy. The ultimate goals of testosterone replacement therapy are to maintain or regain the highest quality of life, minimize the symptoms of low testosterone and to prevent major illness. Table 2 highlights important medical conditions commonly associated with testosterone deficiency.

An overview of the steps to the diagnosis of testosterone deficiency is illustrated in Figure 2.

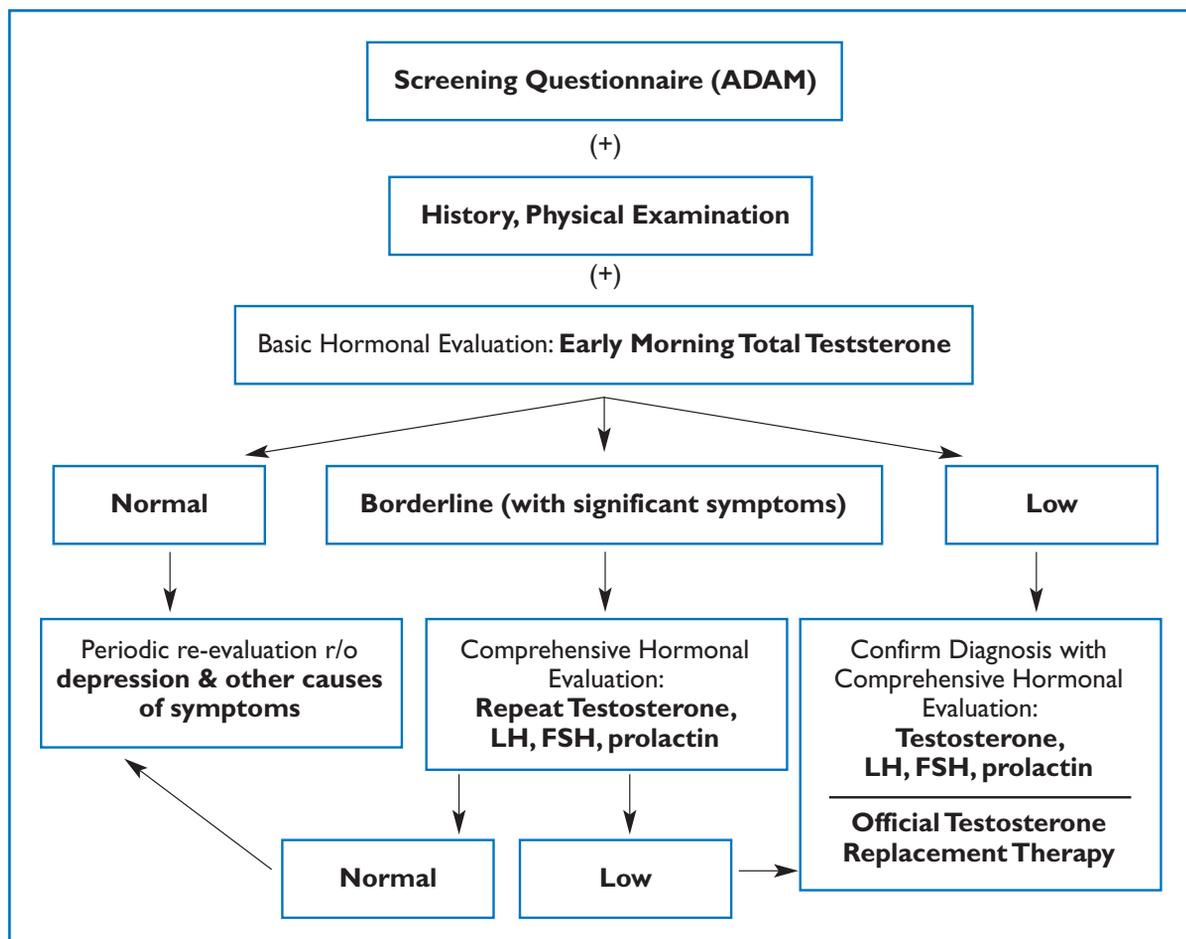


Figure 2. Summary of the Evaluation for Testosterone Deficiency.

Table 2. Clinical disorders or conditions associated with a high prevalence of low testosterone levels

- Type II diabetes mellitus
- Metabolic syndrome
- Human immunodeficiency virus (HIV)
- Treatment with opioids (pain killers), glucocorticoids or ketoconazole
- Osteoporosis (weak bone structure)
- Severe kidney disease
- Chronic obstructive pulmonary disease (lung disease)
- Infertility
- Brain tumours/masses, radiation or trauma
- Use of street drugs
- Liver disease

When you're treated with testosterone, you'll start to see:

- Improved libido, sexual arousal and motivation
- Improved erectile function
- Increased energy levels
- Improved mood and sense of well-being
- Increased muscle mass and strength
- Decreased fat accumulation
- Increased alertness and cognition
- Increased bone mineral density
- Improved control of blood sugar levels

Other important benefits we're currently investigating include:

- Improvements in cholesterol levels
- Decreased risk of heart disease
- Improvements in blood pressure

Testosterone replacement therapy options

The main goal of testosterone therapy is to restore your testosterone levels to “normal” biological concentrations. The method of testosterone replacement therapy depends on availability, safety, effectiveness, potential side effects and preference (patient and physician).

In Canada, we have several treatment options available.

- *Testosterone gels:* A testosterone gel can be applied daily to the skin. You apply it like a lotion to the upper arms and shoulders each morning after a shower.
- *Testosterone patch:* Like gels, you apply the patch to the skin each day, allowing testosterone to be absorbed through the skin and into the blood.
- *Injections:* Testosterone can be absorbed into the blood by injecting it directly into a large muscle – typically the shoulder, thigh or buttock. This is the least expensive treatment option, but typically requires a nurse or doctor to administer the injection about every 3 weeks.
- *Oral pills:* Like traditional medications, testosterone pills or tablets can be taken orally throughout the day.

Testosterone Medications

Generic name

Trade name

Intramuscular Injections

Testosterone Cypionate

Depo-testosterone

Testosterone Enanthate

Delatestryl

Oral Medications

Testosterone Undecanoate

Andriol

Generic name

Trade name

Transdermal (Skin) Agents

Testosterone Patch

Androderm

Testosterone Gel

AndroGel

Testosterone Gel

Testim

Testosterone Gel

Axiron

What are the side effects of testosterone replacement therapy?

Testosterone replacement is generally safe and effective. Serious side effects are uncommon provided your doctor regularly monitors your treatment.

If you have known or suspected cancer of the prostate or breast, you should not be treated with testosterone. The side effects of testosterone therapy depend on the treatment method. The most common side effects include:

- Skin rash or irritation
- Abnormal blood test
- Acne or oily skin
- Headache
- Breast development
- Hair loss
- Sleep disturbances

These side effects are reported in 5% or less of patients receiving treatment.

Potentially serious side effects include:

- Increased red blood cell production causing thickening of the blood
- Prostate disorders
- Liver problems
- High blood pressure
- Cholesterol abnormalities
- Decreased sperm production and fertility
- Fluid retention
- Worsening of sleep apnea or heart failure

Often side effects can be minimized or eliminated altogether with dose adjustment, switching to another form of therapy or stopping it completely.

Prostate health

We know that prostate health depends on testosterone. We used to think that testosterone therapy would lead to prostate cancer. We based this on the fact that most patients with advanced prostate cancer can be controlled by significantly reducing testosterone concentrations.

Recently, we've learned that the risk of prostate cancer is not increased in otherwise healthy men receiving testosterone replacement. It is generally recommended that men over 50 be checked every year for prostate cancer with a digital rectal examination (DRE - feeling the prostate) and PSA test. This holds true regardless of whether or not a man is receiving testosterone.

In terms of prostate size and voiding symptoms, testosterone replacement therapy does not seem to cause any significant negative effects.

Follow-ups

If you have started testosterone replacement, you'll need to be monitored regularly by a qualified physician. Symptom severity, testosterone and PSA levels and digital rectal examination status should be recorded before starting treatment. Follow-up evaluations are generally arranged about three months after the start of testosterone replacement therapy and include a review of symptoms changes, testosterone levels and prostate health (PSA & DRE).

Depending on the type of testosterone replacement, your doctor may perform other tests. Once symptoms and testosterone levels have normalized, further monitoring can be scheduled at intervals of six to 12 months. Once established, testosterone replacement therapy is frequently lifelong and requires a commitment to follow-up from the patient and treating physician.

Important points to remember

- Testosterone deficiency is common and can negatively affect your overall health, sexual function and quality of life.
- Low testosterone is associated with serious medical conditions like diabetes, obesity and metabolic syndrome.
- Testosterone replacement is indicated for men who have signs and symptoms of testosterone deficiency and low levels of testosterone in the blood. These men require medical supervision to identify possible side effects.
- Testosterone supplementation can provide important health and quality of life benefits to men with testosterone deficiency.