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**Testosterone supplementation for older men with low testosterone levels**

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**Abstract**

The effects of testosterone include sex differentiation, muscle formation, increase in bone density, promotion of erythropoiesis, erectile function, etc. With aging, the concentration of testosterone in serum decreases at a rate of 0.4-2.6% per year. Hypotestosterone is a well-studied disease and the deficiency is defined as a clinical syndrome associated with increasing age and comorbidities. It is characterized by the level of testosterone in the blood and its correlation with other complicating conditions. Low testosterone is defined by a value <300 ng/dL (12nmol/L). Men’s testosterone levels have dropped 20% in the last 20 years and more and more younger men are suffering the effects of low testosterone. The low level of testosterone will have adverse effects on multiple organs of the body, leading to a decline in the quality of life, including change in sexual function, apparent obesity (men with low testosterone and women with excessive testosterone), abdominal obesity (indicated by excessive waist circumference and other potential metabolic and cardiovascular diseases. Patients of chronic diseases may sometimes suffer with relatively lower concentration of testosterone in their blood, especially showing related symptoms like osteoporosis, erectile dysfunction, metabolic syndrome, etc., as well as abnormal body fat distribution and insulin resistance. The aim of testosterone replacement therapy is to improve symptoms and signs of testosterone deficiency including decreased libido, erectile dysfunction, depressed mood, anaemia, loss of muscle and bone mass, by increasing serum testosterone levels to physiologic range.

**Keywords:** Metabolic syndrome; Cardiovascular risk; Testosterone replacement therapy; Blood testosterone concentration; Obesity in the elderly.

**Introduction**

Testosterone deficiency is a growing epidemic. According to studies, men over age of 45 can develop hypogonadism and the rate of insufficient testosterone concentration is as high as 38.7%[1]. The test is taken at around 9am due to the release time of testosterone in the body (known as the circadian rhythm). This is the time when testosterone blood levels are at their highest. Testosterone levels can differ by about 10-20% throughout the day, depending on the individual and their age (older men have less of a difference)[2]. The low level of testosterone can be specified as degree of testosterone deficiency, ranging from mild to severe, showing signs of low libido, lack of vitality, fatigue, mood changes, insomnia, anemia, delayed ejaculation, flushing, erectile dysfunction, muscle atrophy, and fat accumulation in the abdominal cavity[2,3]. Other symptoms may also include testicular atrophy, general weakness, insufficient bone mass (osteoporosis), and hair loss on the face, underarms, and perineum. Risk factors like: (1)seniority, (2)obesity, and (3)diabetes are all related to decreased concentration of blood testosterone. The low level of testosterone due to obesity and diabetes can often categorized as primary (testicular hypofunction) and secondary (pituitary hypofunction), affecting two organs and implying a bidirectional influence on each other. Common acquired causes of the primary type of the disease are age (such as the menopause) and long-term use of specific drugs that interfere with testosterone synthesis (such as the mycoinhibitor, Ketoconazole; the immunosuppressant, Cyclosporin; and the chemotherapy drug, Cisplatin). Other causes may include mumps infection, orchiditis, testicular trauma, testicular torsion, orchiectomy, and factors like radiation damage, environmental poison, etc., all of which lead to decreased production of testosterone by the testicles. On the other hand, trauma to the pituitary gland, hemorrhage, and even brain tumors and brain metastases of other malignant tumors are one of the common causes of acquired secondary hypogonadism. The low concentration of testosterone in the blood of obese patients is related to hypertrophy and dysfunction of adipocytes[2-4]. Low testosterone is known to cause many chronic diseases, such as Leptin resistance: fat cells secreting leptin to cause leptin resistance in the center and reduce the kisspeptin signal in the hypothalamus that in turn reduces GnRH (gonadotropin releasing hormone) and Luteinizing hormone (LH) secretion, where the Leydig cells of the testis interfere with LH action and further reduce the testosterone production; Estrogen action: adipocyte aromatase enzyme (aromatase enzyme-CYP19A1) catalyzes the conversion of androstenedione and testosterone into estrone (E1) and estradiol (E2), which negatively feedback on the hypothalamic-pituitary pathway to reduce the production of testosterone; and Proinflammatory cytokines: fat cells produce more tumor necrosis factor-α (TNF-α), interleukin-1 (interleukin, IL-1) and interleukin-6, as these cytokines start interfering with the kisspeptin signal in the hypothalamus and reducing GnRH secretion, for which many studies also showed these to reduce the sensitivity to insulin, cause tissue inflammation, and produce insulin resistance. Other conditions may also develop, like decreased muscle differentiation, increased tissue inflammation, decreased mitochondrial function, and affected lipoprotein lipolytic enzymes to produced free fatty acids for more fat accumulation in muscles, liver, and pancreas. These mechanisms are all contributing to reduced insulin sensitivity and associating the patient with the condition of insulin resistance. Hyperinsulinemia also reduces the kisspeptin signaling, leading to hypogonadism and hypotestosterone condition. Previous animal experiments on mice have found that mice with removed androgen receptors have increased fat accumulation, increased blood triglycerides and body weight, as they would also develop resistance to leptin and insulin[5-8]. The study found that testosterone supplement to obese men did reduce fat and improved lean body composition, as well as being associated with improved hemoglobin A1c and β-cell function. The supplement is effective in reducing the total amount of fat and the effect is quite profound, which may be attributed to the fact that testosterone can inhibit lipoprotein lipase, regulate adipocyte differentiation, and reduce the distribution ratio of visceral fat [9-11]. For an individual of obesity and severe symptoms of low testosterone (such as suffering from erectile dysfunction), testosterone supplement with weight loss exercise may improve symptoms significantly. In summary, low testosterone, obesity, and insulin resistance are mutually correlated and may lead a person into a vicious cycle of deterioration. Low testosterone can also affect men’s body composition, quality of life, emotional stability, bone density, and sexual dysfunction, while it is also known to increase cardiovascular disease risk [12-15]. In the practice of weight loss clinics, medical history and symptom inquiries by adopting questionnaires such as the low male hormone assessment scale, AMS rating scale (Aging males symptoms rating scale) or ADAM questionnaire (Androgen Deficiency in Aging Men questionnaire ADAM) and body composition analysis (body Composition), as well as tests like sex hormone detection, and insulin resistance to screen obese or overweight patients with hypogonadism, all helped physician to find the most appropriate treatment regimen of testosterone supplement for these subjects to reduce insulin resistance that will improve their physical and mental health. It is worthy to note that blood is usually drawn between 7a.m. and 11a.m. when the blood testosterone concentration is the highest. If the blood testosterone concentration is lower than the target threshold and the patient shows symptoms, the case is immediately diagnosed as low testosterone [1,4,7,16].

**Testosterone supplement**

The goal of testosterone replacement therapy (TRT) is to restore blood testosterone to normal levels. According to the currently published guidelines, it is recommended that the concentration of testosterone is restored to the mid-normal range (International Society for Sexual Medicine) or to the middle tertile of the normal reference range (American Urological Association). Supplementing testosterone and adjusting lifestyle do help the elderly of low testosterone with or without obesity in the following areas: 1. Loss of muscle mass and hip BMD from weight loss; 2. Improved aerobic capacity (increase peak oxygen consumption, VO2 peak), which is an indication of the elderly capable of living independently; 3. Improved sexual function such as erection, orgasm, libido and sexual intercourse to get more satisfaction in life; and 4. Restoration to normal testosterone level. After treatment, it is recommended that focus is directed towards assessing whether the serum testosterone level has reached the normal range and whether symptoms have improved. Some of these signs and symptoms can be caused by other factors, including medication side effects, obstructive sleep apnea, thyroid problems, diabetes and depression. It's also possible that these conditions cause low testosterone levels, so treatment might result in increase of testosterone levels.

Common symptoms of hypotestosterone syndrome include easy fatigue, decreased bone density, emotional instability, decreased activity and motor function, decreased muscle mass, decreased libido, sexual dysfunction, infertility, etc., but with these signs progressing at a gradual pace. Diseases and symptoms in association with low serum testosterone include obesity in 52% of reported cases (BMI > 30 kg/m2), type 2 diabetes, long-term use of analgesic opioids in 53% of reported cases (74% with long-acting regimen), and osteoporotic fractures from rapid weight loss. Clinically, if a male experiences sexual dysfunction at the age of “menopause”, it is recommended to test the serum testosterone level to differentiate hypotestosterone syndrome. However, it is recommended that treatment goals are established to achieve an appropriate level of testosterone (e.g., 3-5 ng/mL) rather than subjective symptom improvement [17-20]. The goal of testosterone replacement therapy (TRT) is to return serum testosterone levels to within physiologic range and improve symptoms in hypogonadal people. Although some men believe they feel younger and more vigorous if they take testosterone medications, there's little evidence to support the use of testosterone in healthy people. Guidelines from the American College of Physicians indicate that testosterone therapy might improve sexual function somewhat in some men, but there's little evidence that it improves other functions, such as vitality and energy. What are the risks of testosterone therapy for normal aging? Testosterone therapy has various risks, including: Worsening sleep apnea- a potentially serious sleep disorder in which breathing repeatedly stops and starts, and also causing acne or other skin reactions. But elevated testosterone will raise LDL (bad cholesterol levels), and can thus lead to heart health issues such as potentially resulting in a heart attack, cardiovascular disease, or stroke. Risk of sleep apnea and infertility is also heightened if you have high testosterone levels. So if the human body's testosterone concentration is too high, it is also harmful to the body.

**Conclusion**

Testosterone levels generally peak during adolescence and early adulthood. As you age, your testosterone level gradually declines — typically about 1% a year after age 30 or 40. For older men, it's important to determine if a low testosterone level is due to normal aging or if it is due to hypogonadism. Hypogonadism hampers the ability to produce normal amounts of testosterone due to a problem with the testicles or with the pituitary gland that controls the testicles. Testosterone replacement therapy, in the form of injections, pellets, patches or gels, can improve the signs and symptoms of low testosterone in these men. Supplementing testosterone and adjusting daily life can help the elderly of low testosterone with or without obesity, particularly in the following areas: 1. Loss of muscle mass and hip BMD due to weight loss; 2. Improved aerobic capacity (increase peak oxygen consumption, VO2 peak), as an important indicator of the elderly to maintain independent lifestyle; and 3. Improved sexual function such as erection, orgasm, libido and sexual intercourse for more satisfaction with life; and 4. Restoration to normal testosterone level. Common symptoms of hypotestosterone syndrome include easy fatigue, decreased bone density, emotional instability, decreased activity and motor function, decreased muscle mass, decreased libido, sexual dysfunction, infertility, etc., but at a gradual pace of progression[21-23]. The possible diseases and symptoms of low serum testosterone include obesity in 52% of reported cases (BMI > 30 kg/m2), type 2 diabetes, long-term use of analgesic opioids in 53% of reported cases (74% with long-acting regimen), osteoporotic fractures and rapid weight loss. When testosterone replacement therapy used to treat with hypogonadism, it may also result in other benefits: 1.improved sexual desire and erectile function, 2.improved energy, mood, and vitality, 3.increased lean body mass, 4.reduced waist circumference, 5.reduced total body fat mass, 6.increased bone mineral density(BMD), 7.increased insulin sensitivity, 8.reduced blood glucose and hemoglobin A1c, and 9.increased muscle strength. So clinically, if a male experiences sexual dysfunction and given the age as a sign of possible menopause, it is recommended to test the serum testosterone concentration to rule out hypotestosterone syndrome [24-27].

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The author contributed solely to the article.

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**Conflicts of interest**

All authors declared that there are no conflicts of interest.

**Ethical approval and consent to participate**

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**Consent for publication**

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