Low Testosterone Level and Metabolic Syndrome in the Elderly

**Abstract**

The effects of testosterone include sex differentiation, muscle formation, increase in bone density, promotion of erythropoiesis, erectile function, etc. 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). 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 (men with low testosterone and women with excessive testosterone), abdominal obesity (indicated by excessive waist circumference and other potential metabolic and cardiovascular diseases. Patients with chronic diseases like osteoporosis, erectile dysfunction, metabolic syndrome, etc., may sometimes suffer from low concentration of testosterone in their blood.

**Keywords**:

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

**Introduction**

According to studies, men over age of 45 can develop hypogonadism and the rate of insufficient testosterone concentration is as high as 38.7%. 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 [1]. 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[2]. 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, orchitis, 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[3-6].

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, interleukin-1 (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 produce 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 [7]. 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 [4,6-8]. 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 [9-13]. For an individual of obesity and severe symptoms of low testosterone (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 [14-16]. In the practice of weight loss clinics, medical history and symptom inquiries by adopting questionnaires such as the low male hormone assessment scale. Aging Males Symptoms rating scale (AMS rating scale) or Androgen Deficiency in Aging Men questionnaire (ADAM questionnaire). Other conditions such as body composition analysis, 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. to 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 [1,6,9,18]. Serum levels of testosterone vary dramatically over time and even during the course of a day. In addition, what may seem like a symptom of testosterone excess may actually be unrelated to this hormone. In fact, most of what we know about abnormally high testosterone levels in men comes from athletes who use anabolic steroids, testosterone or related hormones to increase muscle mass and athletic performance. Problems associated with abnormally high testosterone levels in men include: heart muscle damage and increased risk of heart attack; prostate enlargement with difficulty urinating; liver disease; acne; fluid retention with swelling of the legs and feet; weight gain, perhaps related in part to increased appetite; high blood pressure and cholesterol; insomnia; headaches; increased muscle mass; increased risk of blood clots; stunted growth in adolescents; mood swings, euphoria, irritability, impaired judgment, delusions; among women, perhaps the most common cause of a high testosterone level is polycystic ovary syndrome (PCOS). This disease affects 6% to 10% of premenopausal women.

**Testosterone supplement**

Testosterone is the major sex hormone in males and plays a number of important roles, such as: the development of the penis and testes; the deepening of the voice during puberty; the appearance of facial and pubic hair starting at puberty; later in life, it may play a role in balding; muscle size and strength; bone growth and strength; sex drive (libido); sperm production. Testosterone therapy may make sense for elder who have low testosterone levels and symptoms that might be due to testosterone deficiency. It's not clear if low levels without symptoms are meaningful; treatment risks may outweigh benefits. However, the wisdom and effectiveness of testosterone treatment to improve sexual function or cognitive function among elderly is unclear [19]. People with normal testosterone levels are sometimes treated with testosterone at the recommendation of their doctors or they obtain the medication on their own. Some have recommended it as a remedy for aging; for example, a study from Harvard Medical School in 2003 found that even among men who started out with normal testosterone results noted loss of fat, increased muscle mass, better mood, and less anxiety when receiving testosterone therapy. Similar observations have been noted among women. However, the risks and side effects of taking testosterone when the body is already making enough still discourages widespread use [20,21]. Testosterone therapy have various risks, including worsening sleep apnea – which is a potentially serious sleep disorder in breathing repeatedly stops and starts, and it is causing acne or other skin reactions or stimulating growth of the prostate(benign prostatic hyperplasia) and growth of existing prostate cancer. 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. 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[22-24]. 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. 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[25-29].

**Conclusion**

There is a clear link between metabolic syndrome and hypotestosteronism. Obesity appears to be a significant factor and can cause endocrine disorders in the body, including testosterone. There are three possible reasons; first when there is more adipose tissue in the body, leptin will increase in the serum level, and leptin may interfere with the function of LH and inhibit the production of testosterone. Second obese people will produce more cortisol which inhibits the hypothalamus upward and indirectly inhibits the production of testosterone; third the adipose cells convert more estrogen, thus inhibiting the production of testosterone through negative feedback. Therefore, obesity reduces the concentration of testosterone, which in turn leads to the proliferation of adipose cells, forming a vicious cycle. Many studies have shown that supplementing adequate testosterone can reduce total cholesterol, low-density cholesterol (LDL) and triglyceride, and can increase the concentration of high-density cholesterol (HDL). Some studies have also shown that adequate testosterone supplementation can improve patients' insulin sensitivity and blood sugar control. Sufficient testosterone supplementation can not only improve the symptoms of low testosterone but also related symptoms may also have the possibility of improvement in metabolism. However, the current evidence is not enough to recommend that all patients with metabolic syndrome or diabetes should be given testosterone supplementation when low testosterone is not confirmed. This still requires future large-scale and rigorous studies to confirm its efficacy. In summary, there is a close correlation between hypotestosteroneism and metabolic syndrome. Low testosterone can lead to metabolic syndrome, and metabolic syndrome can lead to low testosterone. Because both of these will increase the risk of diabetes and cardiovascular disease; therefore, for our medical staff, when a patient is clinically found to be suffering from low testosterone, we also need to be vigilant and conduct a detailed evaluation to see whether he also has metabolic syndrome, and vice versa. For patients suffering from low testosterone, in addition to evaluating and considering supplementary treatment with testosterone, patients must also be advised to make changes in their daily routine, such as exercise, weight loss, and diet control to reduce the risks associated with metabolic syndrome.

**Reference**

1. Giagulli VA, Castellana M, Lisco G, Triggiani V. Critical evaluation of different available guidelines for late‐onset hypogonadism. Andrology 2020, 8(6), 1628-1641.
2. Ishay A, Tzemah S, Nitzan R, Jehassi A, Cohen M. Testosterone management in aging males: surveying clinical practices of urologists and endocrinologists in Israel. Sexual Medicine 2019, 7(4), 409-417.
3. Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Prac. 2006 Jul;60(7):762-9.
4. Kelly DM, Jones TH. Testosterone: a metabolic hormone in health and disease. J Endocrinol. 2013;217:R25–45.
5. Rasouli N, Kern PA. Adipocytokines and the metabolic complications of obesity. J Clin Endocrinol Metab. 2008;93: S64–73.
6. Liu CC, Wu WJ, Lee YC, Wang CJ, Ke HL, Li WM, et al. The prevalence of and risk factors for androgen deficiency in aging Taiwanese men. J Sex Med 2009; 6:936-46
7. da Silva Rosa SC, Nayak N, Caymo AM, Gordon JW. Mechanisms of muscle insulin resistance and the cross‐talk with liver and adipose tissue. Physiological Reports 2020, 8(19): e14607.
8. Rao PM, Kelly DM, Jones TH. Testosterone and insulin resistance in the metabolic syndrome and T2DM in men. Nat Rev Endocrinol. 2013;9(8):479–93.
9. Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones TH. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. J Clin Endocrinol Metab 2004; 89: 3313-8.
10. Clarke H, Dhillo WS, Jayasena CN. Comprehensive review on kisspeptin and its role in reproductive disorders. Endocrinol Metab (Seoul). 2015;30:124–41.
11. Harter CJ, Kavanagh GS, Smith JT. The role of kisspeptin neurons in reproduction and metabolism. J Endocrinol. 2018;238:R173–R183.
12. Barnouin Y, Armamento-Villareal R, Celli A, Jiang B, Paudyal A, Nambi V, et al. Testosterone replacement therapy added to intensive lifestyle intervention in older men with obesity and hypogonadism. The Journal of Clinical Endocrinology & Metabolism 2021; 106(3): e1096-e1110.
13. Lee CH, Kuo SW, Hung YJ, et al. The effect of testosterone supplement on insulin sensitivity, glucose effectiveness, and acute insulin response after glucose load in male type 2 diabetics. Endocr Res 2005; 31:139-48.
14. Reckelhoff JF, Yanes LL, Iliescu R, Fortepiani LA, Granger JP. Testosterone supplementation in aging men and women: possible impact on cardiovascular-renal disease. Am J Physiol Renal Physiol 2005; 289: F941-F948.
15. Grossmann M. Testosterone and glucose metabolism in men: current concepts and controversies. J Endocrinol. 2014; 220: R37–55.
16. Ng Tang Fui M, Hoermann R, Prendergast LA, Zajac JD, Grossmann M. Symptomatic response to testosterone treatment in dieting obese men with low testosterone levels in a randomized, placebo-controlled clinical trial. Int J Obes (Lond). 2017;41:420–6.
17. McArdle MA, Finucane OM, Connaughton RM, McMorrow AM, Roche HM. Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies. Front Endocrinol (Lausanne). 2013; 4: 52.
18. Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJ, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. Clin Endocrinol (Oxf) 2010; 73:602-12.
19. Morgentaler A, Caliber M. Safety of testosterone therapy in men with prostate cancer. Expert opinion on drug safety 2019, 18(11), 1065-1076.
20. 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;94:907-13.
21. Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones TH. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. J Clin Endocrinol Metab 2004; 89: 3313-8.
22. Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol 2006; 154: 899-906.
23. Reckelhoff JF, Yanes LL, Iliescu R, Fortepiani LA, Granger JP. Testosterone supplementation in aging men and women: possible impact on cardiovascular-renal disease. Am J Physiol Renal Physiol 2005; 289: F941-F948.
24. Jones TH, Arver S, Behre HM, et al. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). Diabetes Care 2011; 34:828-37.
25. Bolona ER, Uraga MV, Haddad RM, et al. Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc 2007; 82:20-8.
26. Dimitriadis GK, Randeva HS, Aftab S, Ali A, Hattersley JG, Pandey S, et al. Metabolic phenotype of male obesity-related secondary hypogonadism pre-replacement and post-replacement therapy with intra-muscular testosterone undecanoate therapy. Endocrine. 2018; 60: 175–84.
27. Hackett G, Kirby M, Edwards D, Jones TH, Wylie K, Ossei-Gerning N, et al. British Society for Sexual Medicine Guidelines on Adult Testosterone Deficiency, With Statements for UK Practice. J Sex Med 2017;14:1504-23.
28. Lin HY, Xu Q, Yeh S, Wang RS, Sparks JD, Chang C. Insulin and leptin resistance with hyperleptinemia in mice lacking androgen receptor. Diabetes 2005; 54:1717-25.
29. Gupta V, Bhasin S, Guo W, Singh R, Miki R, Chauhan P, et al. Effects of dihydrotestosterone on differentiation and proliferation of human mesenchymal stem cells and preadipocytes. Mol Cell Endocrinol 2008; 296:32-40.