Negative health effects of low testosterone concentrations in older adults

Da-Ming Liao[1] , Chieh Chen [2]

[1]Department of Dental, Puli Christian Hospital, Taiwan ROC

[2]Department of family medicine, Hualien Armed Forces General Hospital, ROC

Corresponding author: Chieh Chen
guppy5230@yahoo.com.tw
+886-928-698950

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 <350 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, 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[1]. 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.

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. The American Urology Association (AUA) considers low blood testosterone to be less than 300ng/dL for adults. However, some researchers and healthcare providers disagree with this and feel that levels below 250ng/dL are low. Providers also take symptoms into consideration when diagnosing low testosterone. The possible diseases and symptoms of low serum testosterone include obesity in 52% of reported cases (BMI > 30 kg/m^2), 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. Other symptoms may also include testicular atrophy, general weakness, insufficient bone mass (osteoporosis), and hair loss on the face, underarms, and perineum[1,2]. Low testosterone will increase the risk of metabolic syndrome and cardiovascular disease in elderly patients, which can be regarded as an important message for patient's health. The current evidence about testosterone therapy for patients with hypotestosteronism does not support that testosterone supplementation will increase the risk of cardiovascular disease. However, testosterone therapy will increase the production of erythropoietin (EPO) and lead to an increase in hematocrit; therefore, hematocrit needs to be closely monitored during treatment periods to avoid exceeding normal values, especially in elderly patients and patients with cardiovascular disease.

Cause of hypotestosterone

Medicine side effects, such as chemotherapy, testicle injury or cancer, ect. Problems with glands in the brain (hypothalamus and pituitary) that control hormone production or low thyroid function. Other risk factors such as: (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[3,4]. 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. Many factors, including external, environmental and internal factors, influence testosterone levels. Undoubtedly, nutritional deficiency, and particularly of such nutrients as zinc, magnesium, vitamin

D, together with low polyphenols intake, affects the HPG axis. 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[5,6]. 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).

Primary and secondary hypotestosteronism

1.Primary hypogonadism differs from secondary hypogonadism in two ways.

Primary hypogonadism differs from secondary hypogonadism in two ways. Primary hypogonadism is more likely to be associated with a decrease in sperm production than in testosterone production. Although many testicular diseases both the seminiferous tubules and the Leydig cells, they usually damage the seminiferous tubules to a greater degree. As a consequence, the sperm counts may be low and the serum FSH concentration normal or high. Yet the serum testosterone concentration remains normal; In contrast, in secondary hypogonadism there is a proportionate reduction in testosterone and sperm production. Primary hypogonadism is more likely to be associated with gynecomastia, presumably due to the stimulatory effect of the supranormal serum FSH and LH concentrations on testicular aromatase activity. This results in increased conversion of testosterone to estradiol and enhanced testicular secretion of estradiol relative to testosterone. 2.Primary hypogonadism is associated with low levels of testosterone and high-normal to high levels of LH and FSH. Secondary hypogonadism is associated with low levels of testosterone and normal to low levels of LH and FSH. Primary hypogonadism is caused by testicular failure and is characterised by low serum testosterone and high LH and FSH concentrations. For this reason, primary hypogonadism is also known as hypergonadotropic hypogonadism. The low concentration of testosterone in the blood of obese patients is related to hypertrophy and dysfunction of adipocytes[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[7]; 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[8]. 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.

Differential diagnosis of hypotestosteronism

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. Hypogonadism is diagnosed when the morning serum testosterone level is less than 300 ng/dL. However, clinical judgment can be exercised in the diagnosis of hypogonadism for patients with persistent symptoms of testosterone deficiency despite having testosterone levels are in the normal range. 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. As older men, circulating testosterone concentrations decline, while prevalence of cognitive impairment and dementia increase. Epidemiological studies of middle-aged and older men have demonstrated associations of lower testosterone concentrations with higher prevalence and incidence of cognitive decline and dementia, including Alzheimer's disease. In observational studies, men with prostate cancer treated by androgen deprivation therapy had a higher risk of dementia. A randomised placebo-controlled trial of one year's testosterone treatment, showed an improvement in sexual function, but no improvement in cognitive function[9,10]. There

is a known association between diabetes and dementia risk. A randomised placebo-controlled trial of two year's testosterone treatment in 1,007 men aged 50–74 years, waist circumference $\geq$ 95cm, baseline testosterone $\leq$ 14nmol/L, showed an effect of testosterone in reducing type 2 diabetes risk. There were no cognitive endpoints in that trial. Additional research is warranted but at this stage lower testosterone concentrations in ageing men should be regarded as a biomarker rather than a proven therapeutic target for risk reduction of cognitive decline and dementia, including Alzheimer's disease[11].

Testosterone replacement therapy

People can take TRT (testosterone replacement therapy) orally, via intramuscular injections and implants or transdermal patches, mouth patches, and topical creams or gels. Other options include intranasal gels or pellets. The dosage of supplementation administered clinically depends on the degree of low serum testosterone concentrations. Some options require daily administration, others weekly or monthly and some every three months. 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. 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. Most importantly, these include beneficial effects on mood, energy levels and patients' sense of well-being, sexual function, lean body mass and muscle strength, erythropoiesis and bone mineral density (BMD), cognition and some benefits on cardiovascular risk factors. 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[11].

Conclusion

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[12-14]. 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[12]; 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.

Reference

1. 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.
2. 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.
3. 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.
4. McArdle MA, et al. Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies. Front Endocrinol (Lausanne). 2013; 4: 52.
5. Ng Tang Fui M, et al. 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.
6. Wrzosek, M., Woźniak, J., & Włodarek, D. (2020). The causes of adverse changes of testosterone levels in men. Expert Review of Endocrinology & Metabolism 2020; 15(5): 355-362.
7. Fui MNT, Dupuis P, Grossmann M. Lowered testosterone in male obesity: mechanisms, morbidity and management. Asian journal of andrology 2014; 16(2): 223.
8. Hackett G, et al. British Society for Sexual Medicine Guidelines on Adult Testosterone Deficiency, With Statements for UK Practice. J Sex Med 2017;14:1504-23.
9. Yeap, BB, Flicker, L. Testosterone, cognitive decline and dementia in ageing men. Reviews in Endocrine and Metabolic Disorders 2022, 23(6):1243-1257.
10. Qaseem A, Horwitch CA, Vijan S, Etxeandia-Ikobaltzeta I, Kansagara D, Clinical Guidelines Committee of the American College of Physicians*. Testosterone treatment in adult men with age-related low testosterone: a clinical guideline from the American College of Physicians. Annals of internal medicine 2020, 172(2), 126-133.
11. Grossmann M, et al. Testosterone and glucose metabolism in men: current concepts and controversies. J Endocrinol. 2014; 220: R37–55.
12. Wu FC, Tajar A, Beynon JM, et al. Identification of late onset hypogonadism in

middle-aged and elderly men. N Engl J Med 2010; 363:123-35.

13. Liu PY, Death AK, Handelsman DJ. Androgens and cardiovascular disease. Endocr Rev 2003; 24:313-40.

14. Traish AM, Saad F, Feeley RJ, Guay A. The dark side of testosterone deficiency: III. Cardiovascular disease. J Androl 2009; 30:477-94.