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LETTER

Negative health effects of low testosterone concentrations in older adults

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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 as < 350 ng/dL (12 nmol/L). The aim is to review the latest work on testosterone treatments, including their advantages and disadvantages, and to address important issues in testosterone therapy.

Keywords: Metabolic syndrome, cardiovascular risk, testosterone replacement therapy, blood testosterone concentration, obesity in the elderly

Introduction

According to studies, men over the 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 the degree of testosterone deficiency, ranging from mild to severe, showing signs of low libido, lack of vitality, fatigue, mood changes, insomnia, anemia, delayed ejaculation, hot flashes, erectile dysfunction, muscle atrophy, and abdominal fat accumulation. The American Urology Association (AUA) considers low blood testosterone to be less than 350 ng/dL in adults. However, some researchers and health care providers disagree and consider levels below 250 ng/dL to be low. Providers also consider symptoms when diagnosing low testosterone. Possible conditions and symptoms of low serum testosterone include obesity in 52% of reported cases (BMI > 30 kg/m^2), type 2 diabetes, long-term opioid analgesic use in 53% of reported cases (74% with long-acting regimens), osteoporotic fractures, and rapid weight loss. Other symptoms may include testicular atrophy, generalized weakness, low bone mass (osteoporosis), and facial, axillary, and perineal hair loss [1, 2]. Low testosterone increases the risk of metabolic syndrome and cardiovascular disease in older patients, which is an important message. Current evidence on testosterone therapy in patients with hypotestosteronism does not support that testosterone supplementation increases the risk of cardiovascular disease. However, testosterone therapy will increase erythropoietin (EPO) production and lead to an increase in hematocrit; therefore, hematocrit must be closely monitored during treatment to avoid exceeding normal levels, especially in elderly patients and those with cardiovascular disease [1].

Cause of hypotestosterone

Side effects of medications such as chemotherapy, testicular injury or cancer, *etc*. Problems with the glands in the brain (hypothalamus and pituitary) that control hormone production or low thyroid function. Other risk factors such as: (1) age, (2) obesity, and (3) diabetes are all associated with lower blood testosterone levels. Low testosterone levels due to obesity and diabetes can often be categorized as primary (testicular hypofunction) and secondary (pituitary hypofunction), affecting two organs and implying a bidirectional influence on each other [3, 4]. Other causes include mumps infection, orchiditis, testicular trauma, testicular torsion, orchiectomy, and factors such as radiation damage, environmental toxins, *etc*., all of which lead to decreased testosterone production by the testes. Many

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factors, including external, environmental, and internal, influence testosterone levels. Undoubtedly, nutritional deficiencies, especially of such nutrients as zinc, magnesium, vitamin D, along with low intake of polyphenols, affect the hypothalamic-pituitary-gonadal (HPG) axis. On the other hand, trauma to the pituitary gland, hemorrhage, and even brain tumors and brain metastases from other malignant tumors are among the most common causes of acquired secondary hypogonadism [5, 6]. Common acquired causes of the primary form of the disease are age (such as menopause) and long-term use of certain drugs that interfere with testosterone synthesis (such as the antifungal drug ketoconazole, the immunosuppressant cyclosporine, and the chemotherapy drug cisplatin).

Primary and secondary hypotestosteronism

Primary hypogonadism differs from secondary hypogonadism in two ways. Primary hypogonadism is more likely to be associated with a decrease in sperm production rather than testosterone production. Although many testicular diseases affect both the seminiferous tubules and the Leydig cells, they usually cause more damage to the seminiferous tubules. As a result, the sperm count may be low and the serum follicle-stimulating hormone (FSH) concentration may be normal or high. In contrast, in secondary hypogonadism, there is a proportional reduction in testosterone and sperm production. Primary hypogonadism is more likely to be associated with gynecomastia, presumably due to the stimulatory effect of supranormal serum FSH and luteinizing hormone (LH) concentrations on testicular aromatase activity. This results in increased conversion of testosterone to estradiol and increased testicular secretion of estradiol relative to testosterone. Primary hypogonadism is associated with low testosterone levels and high normal to high LH and FSH levels. Secondary hypogonadism is associated with low testosterone levels and normal to low LH and FSH levels. Primary hypogonadism is caused by testicular failure and is characterized by low serum testosterone and high levels of LH and FSH. For this reason, primary hypogonadism is also known as hypergonadotropic hypogonadism. Low blood testosterone concentrations in obese patients are associated with adipocyte hypertrophy and dysfunction [6].

Disease related to hypotestosteronism

Low testosterone is known to cause many chronic diseases, such as leptin resistance: fat cells secrete leptin to cause central leptin resistance and reduce kisspeptin signaling in the hypothalamus, which in turn reduces gonadotropin releasing hormone (GnRH) and LH secretion, where Leydig cells of the testis interfere with LH action and further reduce testosterone production; estrogen action: The adipocyte aromatase enzyme (aromatase enzyme-CYP19A1) catalyzes the conversion of androstendione and testosterone to estrone (E1) and estradiol (E2), which negatively feedback to the hypothalamic-pituitary pathway to reduce testosterone production [7]; and proinflammatory cytokines: fat cells produce more tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 as these cytokines begin to interfere with the kisspeptin signal in the hypothalamus and reduce GnRH secretion, which many studies have also shown to reduce insulin sensitivity, cause tissue inflammation, and produce insulin resistance [8]. Other conditions may also develop, such as decreased muscle differentiation, increased tissue inflammation, decreased mitochondrial function, and impaired lipoprotein lipolytic enzymes to produce free fatty acids for increased fat accumulation in muscle, liver, and pancreas. These mechanisms all contribute to reduced insulin sensitivity and place the patient in a state of insulin resistance. Hyperinsulinemia also reduces kisspeptin signaling, leading to hypogonadism and a hypotestosterone state. Previous animal studies in mice have shown that mice with removed androgen receptors have increased fat accumulation, increased blood triglycerides, and increased body weight because 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 Rating Scale, Aging Males Symptoms (AMS) Rating Scale or Androgen Deficiency in Aging Men (ADAM) questionnaire and body composition analysis, as well as tests such as sex hormone detection and insulin resistance to screen obese or overweight patients with hypogonadism, all helped the physician determine the most appropriate treatment regimen of testosterone supplementation for these subjects to reduce insulin resistance, which 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 may be used to diagnose hypogonadism in patients who have persistent symptoms of testosterone deficiency despite having testosterone levels in the normal range. It is important to note that blood samples are typically obtained between 7:00 a.m. and 11:00 a.m., when blood testosterone concentrations are highest. If the blood testosterone concentration is below the target threshold and the patient is experiencing symptoms, the case is immediately diagnosed as low testosterone. As men age, circulating testosterone concentrations decline while the prevalence of cognitive impairment and dementia increases. Epidemiologic studies of middle-aged and older men have shown an association between lower testosterone concentrations and a higher prevalence and incidence of cognitive decline and dementia, including Alzheimer's disease. In observational studies, men with prostate cancer treated with androgen deprivation therapy had an increased risk of dementia. A randomized, placebo-controlled trial of one year of testosterone treatment showed an improvement in sexual function but no improvement in

cognitive function [9, 10]. There is a known association between diabetes and the risk of dementia. A randomized, placebo-controlled trial of two years of testosterone treatment in 1,007 men aged 50-74 years, waist circumference ≥ 95 cm, baseline testosterone ≤ 14 nmol/L, showed an effect of testosterone in reducing the risk of type 2 diabetes (T2DM). This study did not include cognitive endpoints. Further research is warranted, but at this time, lower testosterone concentrations in aging men should be considered a biomarker rather than a proven therapeutic target for reducing the risk of cognitive decline and dementia, including Alzheimer's disease [11].

Testosterone replacement therapy

Men can take testosterone replacement therapy (TRT) orally, via intramuscular injections and implants, or via transdermal patches, oral 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 supplementation in obese men reduced fat and improved lean body composition and was associated with improved hemoglobin A1c and β-cell function. The supplement is effective in reducing total fat, and the effect is quite profound, which may be due to the fact that testosterone can inhibit lipoprotein lipase, regulate adipocyte differentiation, and reduce the distribution ratio of visceral fat. For an individual with obesity and severe symptoms of low testosterone (such as suffering from erectile dysfunction), testosterone supplementation with weight loss exercise can significantly improve symptoms. Most importantly, these include beneficial effects on mood, energy levels and patient 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 interrelated and can 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 the risk of cardiovascular disease [11]. TRT was a useful clinical tool for managing ischemic events in this subgroup of patients, while potentially having a positive impact on their mobility and overall quality of life. This study recommended that, with careful monitoring, testosterone-deficient patients with T2DM and cardiovascular risk may benefit from TRT. Other observational studies of pooled analyses in obese hypogonadal men with T2DM found that TRT significantly reduced fasting blood glucose and HbA1c levels; reduced total cholesterol, low-density lipoprotein cholesterol, triglycerides, and levels of inflammatory markers, suggesting a reduction in the inflammatory response; increased high-density lipoprotein cholesterol levels; and improved systolic and diastolic blood pressure. TRT in obese, diabetic men improves glycemic control and lipid profiles and may prove useful in reducing the risk of cardiovascular disease.

Discussion

Low testosterone levels have adverse effects on multiple organs of the body, leading to a decline in quality of life, including changes in sexual function, overt 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 with chronic diseases may sometimes have relatively low blood testosterone concentrations, especially with comorbidities such as osteoporosis, erectile dysfunction, metabolic syndrome, *etc*., as well as abnormal body fat distribution and insulin resistance. Clinically, if a man experiences sexual dysfunction and given his age, as a sign of possible menopause, it is recommended to test serum testosterone concentration to rule out hypotestosterone syndrome [12-14]. It has long been believed that higher levels of testosterone increase the risk of prostate cancer or cause rapid cancer growth, while low levels of testosterone have a protective effect. Prostate-specific antigen (PSA) is often used as a marker of prostate health, and several studies have examined this relationship and how TRT affects PSA. Most of these studies have found that elevated testosterone, even over the long term, does not affect PSA or that its effect is negligible. A prostate saturation hypothesis may explain these findings, suggesting that when androgen receptors on the prostate become "saturated", the prostate becomes insensitive to further increases in serum testosterone, such as those seen with TRT. An increase in serum testosterone and dihydrotestosterone when men were on TRT for 6 months; however, when biopsied before and after TRT, there was no change in androgen levels within the prostate tissue. PSA is not the perfect marker for prostate cancer, so several studies have tried to clarify whether TRT increases the incidence of prostate cancer. A plethora of studies have not shown testosterone concentrations to be higher in men with prostate cancer compared to those without cancer. Reports have shown that hypogonadal men with normal PSA levels do not have lower cancer rates than the general healthy population. Testosterone supplementation and daily lifestyle changes can help older men with low testosterone, with or without obesity, especially in the following areas 1. Loss of muscle mass and hip BMD due to weight loss; 2. Improved aerobic capacity (increase in peak oxygen consumption, VO_2 peak) as an important indicator for the elderly to maintain an independent lifestyle [12]; 3. Improved sexual function such as erection, orgasm, libido, and intercourse for greater life satisfaction; and 4. Restoration of normal 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 at a gradual pace of progression.

Conclusions

Testosterone deficiency is associated with adverse effects on body composition, bone density, sexual function, and mood, and may also increase insulin resistance, fatty liver, and worsening of cardiovascular risk factors. Numerous studies have demonstrated the benefits of open-label testosterone in hypogonadal men. There are several possible routes of administration for testosterone treatment. Each approach has advantages and disadvantages, and the choice of replacement method is often determined by patient preference or co-medication. Although new developments are promising, it appears that of the available treatments, only the transdermal gel and the long-acting injectable have demonstrated pharmacokinetic behavior that results in steady-state levels within the physiological range.

Declarations

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