Mechanism and Effect of Testosterone on Metabolic Diseases

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Abstract: As an important steroid hormone, testosterone plays a key role in male growth, sexual function maintenance and metabolism regulation. In recent years, the prevalence of metabolic diseases has continued to climb, and the two-way relationship between decreased testosterone levels and metabolic diseases has received increasing attention. Numerous epidemiological studies have shown that serum total and free testosterone levels are significantly reduced in men with metabolic syndrome, and testosterone levels decrease in steps with the extent of metabolic abnormalities. Obesity, insulin resistance, dyslipidemia, hypertension, hyperuricemia and other components of metabolic syndrome are closely related to hypotestosteronemia. The association between testosterone deficiency and metabolic diseases involves multi-level pathophysiological mechanisms, mainly including the imbalance of hypothalamus-pituitary-testicular axis regulation, insulin resistance, leptin resistance, chronic low-grade inflammatory state and mitochondrial-endoplasmic reticulum stress. In recent years, UGT2B-mediated enhanced mechanisms of hepatic testosterone clearance have provided new perspectives for understanding hormone depletion in metabolic diseases. At the intervention level, lifestyle interventions (weight loss, exercise) can significantly raise testosterone levels and improve metabolic status, while testosterone replacement therapy has shown to improve insulin sensitivity, lower blood glucose, and improve the potential of lipid profile in patients with metabolic diseases with hypogonadism, but its cardiovascular safety and adaptation population still need to be carefully evaluated. In-depth research on the relationship between testosterone and metabolic diseases will help to reveal the core role of sex hormones in metabolic regulation, and provide new theoretical basis and intervention strategies for the precise prevention and treatment of metabolic diseases.

***Keywords*:** testosterone; metabolic syndrome; insulin resistance; obesity; hypogonadism; testosterone replacement therapy

1. Introduction

Metabolic syndrome is a group of clinical syndromes characterized by abdominal obesity, hyperglycemia and dyslipidemia. Its pathophysiological basis lies in insulin resistance and chronic low-grade inflammation. In China, the prevalence of male metabolic syndrome is about 19.2%, and it shows an upward trend with age. Testosterone, as the most important androgen in the body, plays an indispensable role in the physiological processes of male growth and development, sexual desire maintenance, reproductive function, substance metabolism and aging. The relationship between testosterone deficiency and metabolic diseases is not one-way, but a complex two-way interactive network. On the one hand, metabolic syndrome downregulates testosterone synthesis and secretion through various mechanisms; On the other hand, low testosterone levels themselves can further aggravate metabolic disorders by affecting insulin sensitivity, fat distribution, and energy metabolism. The existence of this bi-directional relationship complicates the problem and also presents a challenge for clinical intervention [1]. This article aims to systematically review the interrelationship between testosterone and metabolic diseases, integrate the latest advances in epidemiological evidence, basic research and clinical interventions, and explore the central role of testosterone in metabolic regulation from a multidimensional perspective, with a view to providing references for further research and clinical practice in this field.

2. Epidemiological association of metabolic syndrome and its components with testosterone levels

2.1 Obesity and testosterone levels

Obesity is the most significant metabolic factor affecting testosterone levels in men. Free testosterone levels were significantly inversely correlated with BMI, and this relationship was widely verified in people of different races and age groups. In the European Male Aging Study, obese men with a BMI above 30 kg/m² had about 30% lower testosterone levels compared to those with a BMI below 25 kg/m², and the prevalence of hypotestosteronemia increased by about 13-fold. In a study of 783 men aged 20 to 29 years, only visceral fat remained independently inversely correlated with free testosterone after adjusting for sex hormone-binding globulin

levels. Furthermore, the clinical significance of the effect of obesity on testosterone levels lies in its impairment of male fertility. Adipose tissue is not only an energy storage organ, but also an active endocrine organ. In the state of obesity, macrophage infiltration of adipose tissue is aggravated, and the levels of secreted pro-inflammatory adipokines such as interleukin-6, interleukin-1 and tumor necrosis factor-α are increased. These cytokines can inhibit the secretion of hypothalamic gonadotropin-releasing hormone and luteinizing hormone, thus inhibiting testosterone synthesis in testicular stromal cells. Simultaneously, aromatase activity in adipose tissue is enhanced, converting testosterone to estradiol, further reducing serum testosterone levels and feedback inhibiting hypothalamic-pituitary-testicular axis function [2].

2.2 Abnormal glucose metabolism and testosterone levels

The association of abnormal glucose metabolism with hypotestosteronemia has been confirmed in several large-scale clinical studies. Studies have shown that the main driver of low testosterone in diabetics is insulin resistance, not islet beta cell hypofunction or glycated hemoglobin levels. Important evidence in support of this idea comes from intervention studies: the use of rosiglitazone to improve systemic insulin resistance resulted in a significant increase in testosterone levels in patients with elevated blood sugar. From the site of action, the effect of abnormal glucose metabolism on testosterone is mainly localized at the hypothalamic level. After gonadotropin-releasing hormone (GnRH) stimulation in diabetic patients, the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) was normal, and the level of testosterone was increased, suggesting that impaired hypothalamic function in hyperglycemic environment was the key link leading to abnormal secretion of gonadotropin-releasing hormone.

2.3 Dyslipidemia and Testosterone Levels

With the change of dietary structure and improvement of living standard, the prevalence of hyperlipidemia in China is increasing year by year. The survey and analysis of male residents over 40 years old showed that serum triglyceride, total cholesterol and low density lipoprotein cholesterol were significantly negatively correlated with serum testosterone levels. High-fat diet-induced hyperlipidemia reduces testosterone synthesis through lipotoxic mechanisms and severely interferes with normal male reproductive function. The mitochondrial structure of testicular mesenchymal cells in mice with high triglyceride diet was damaged, the inner and outer mitochondrial membranes were abnormally separated, and the interstitial space of some mitochondrial membranes was slightly expanded. At the same time, free cholesterol accumulated in the testicular interstitium of high cholesterol-fed rats, and the expression of endoplasmic reticulum stress marker protein was significantly increased.

2.4 Hyperuricemia and Testosterone Levels

In recent years, hyperuricemia has been increasingly identified as an important component of metabolic syndrome. Its pathogenesis mainly stems from the decrease in uric acid excretion caused by hyperinsulinemia caused by insulin resistance, while visceral fat accumulation promotes increased uric acid synthesis by increasing the influx of free fatty acids to the liver. Possible mechanisms by which elevated uric acid levels affect testosterone levels include: impairment of testicular mesenchymal cell function by inducing oxidative stress; Interferes with the normal regulation of the hypothalamic-pituitary-testicular axis through inflammatory pathways; And affecting testicular blood supply by reducing nitric oxide bioavailability.

2.5 Metabolic liver disease and testosterone levels

The liver is the primary site for testosterone metabolism and clearance. Testosterone is mainly metabolized in hepatocytes through two pathways: one is converted into dihydrotestosterone (DHT) through 5 α-reductase, which has a higher affinity with androgen receptors; Second, it is catalyzed by members of the uridine diphosphate-glucuronyltransferase (UGT) family (mainly the UGT2B subfamily), and combines with glucuronic acid to form water-soluble metabolites, which are excreted through bile and urine. In the NASH stage, liver inflammation and fibrosis are key factors determining prognosis [3]. Testosterone can inhibit inflammatory response through a variety of mechanisms: first, it inhibits NF-κ B and TLR4 signaling pathways and reduces the production of pro-inflammatory factors such as TNF-α, IL-6 and IL-1 β; The second is to promote the polarization of Kupffer cells to M2 type and enhance the release of anti-inflammatory mediators. In liver fibrosis, testosterone can inhibit the activation of hepatic stellate cells (HSCs).

3. Molecular mechanism of bidirectional association between testosterone and metabolic diseases

3.1 Hypothalamic-pituitary-testicular axis regulation imbalance

The hypothalamic-pituitary-testicular (HPT) axis is the core endocrine pathway that regulates testosterone synthesis.

The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which promotes adenopituitary synthesis and secretes FSH and LH, where LH acts on testicular interstitial cells to regulate testosterone synthesis. Obese patients with metabolic syndrome have increased adipokines, impaired kisspeptin signaling, and impaired GnRH neuron function, which in turn leads to hypogonadism. Both hypothalamic leptin resistance and insulin resistance in obese patients can impair kisspeptin signaling, thereby reducing testosterone levels.

3.2 Bidirectional association of insulin resistance

There is a complex two-way relationship between testosterone and insulin sensitivity. The study found that serum testosterone levels were positively correlated with insulin sensitivity in men, with hypogonadism men having about twice as much insulin resistance as normal men. Lipotoxic mechanisms play an important role in the association of testosterone with insulin resistance [4]. Low testosterone levels can directly affect ectopic lipid accumulation, and high-fat diet accelerates hepatic testosterone metabolic clearance by activating the AHR-UGT2B pathway, leading to protective hormone depletion, thus affecting the mechanism of insulin resistance and type 2 diabetes. It was further confirmed that low testosterone levels are closely related to ectopic lipid accumulation, a process that plays a central role in the development of insulin resistance. Insulin resistance can also indirectly affect total testosterone levels by reducing SHBG levels.

3.3 Leptin resistance and testosterone synthesis

Leptin is a hormone secreted primarily by adipose tissue and plays a dual role in regulating energy balance and reproductive function. Chronic elevated leptin levels caused by obesity can lead to central leptin resistance and impaired leptin signaling pathways. Under normal circumstances, leptin can directly act on the hypothalamus to promote GnRH secretion, and can also stimulate the pituitary gland to secrete LH and FSH. However, in the obese state, the leptin released by adipocytes increased significantly, but the responsiveness of HPT axis to leptin decreased, and the expression of Kisspeptin gene was down-regulated, which produced an inhibitory effect on HPT axis, ultimately leading to hypogonadotropic hypogonadism.

3.4 Chronic low-grade inflammation and decreased testosterone

Obesity-related chronic low-grade inflammation plays a key role in testosterone decline. CRP levels were significantly higher in men with hypogonadism than in men with normal testosterone levels, suggesting that low testosterone status is closely related to increased systemic inflammatory burden. In the obese state, macrophage infiltration of adipose tissue is significantly increased, and the levels of secreted inflammatory factors including IL-6, IL-1, and TNF-α are elevated. From the molecular level, TNF-α and IL-1 play an important role in maintaining testicular function under normal physiological conditions, but their imbalance in the state of chronic inflammation can have a damaging effect. Studies have shown that TNF-α and IL-1 β can inhibit GnRH and LH secretion in animals and in vitro experiments, and can also indirectly lead to hypogonadism by inducing insulin resistance. IL-6 can directly act on the testis, inhibit the production of testosterone in interstitial cells, and play a negative regulatory role on male reproductive function.

4. Improvement of testosterone level and metabolic status by intervention measures

4.1 Lifestyle Interventions

Lifestyle interventions are a fundamental strategy to improve low testosterone associated with metabolic syndrome and include a controlled diet, weight loss, and a regular exercise program. Studies have shown a clear dose-relationship between weight loss and increased testosterone levels. In morbidly obese adults, bariatric surgery reverses hypogonadism and returns testosterone levels to normal. The mechanism of increased testosterone levels after weight loss may involve multiple aspects: decreased aromatase activity due to fat loss; Increase gonadotropin release by restoring neuronal leptin sensitivity; Positive effects of improved insulin sensitivity on the function of the hypothalamic-pituitary-testicular axis. Exercise itself can increase testosterone levels even without weight loss [5]. An aerobic exercise program designed for 16 normal weight men and 28 overweight or obese men showed significant increases in serum testosterone levels in overweight/obese men after regular exercise, along with significant improvements in body mass index and lipid profile.

4.2 Testosterone replacement therapy

Testosterone replacement therapy (TRT) in patients with metabolic syndrome complicated with hypogonadism can significantly improve insulin sensitivity, fasting blood glucose and dyslipidemia. TRT can bring significant and long-lasting weight loss, prevent the progression of prediabetes, and may induce disease remission in some patients with type 2 diabetes. In men with type 2 diabetes with hypogonadism, TRT decreases fasting blood glucose and glycated hemoglobin levels and reduces cardiovascular events and all-cause mortality. In addition, TRT inhibits spermatogenesis, so special caution should

be taken for men who still have childbearing needs. The problems of TRT in cardiovascular safety also require long-term follow-up evaluation [6].

5. Conclusion

In summary, there is a complex and tight bi-directional relationship between testosterone and metabolic diseases. Epidemiological evidence consistently shows that the serum testosterone level of patients with metabolic syndrome, especially those with obesity, insulin resistance and dyslipidemia, is significantly reduced, and the degree of testosterone deficiency is positively correlated with the severity of metabolic disorders. At the molecular level, the newly discovered UGT2B-mediated enhanced hepatic testosterone clearance mechanism provides an important new perspective for understanding endogenous protective hormone depletion in metabolic diseases. In terms of clinical management, lifestyle interventions (weight loss and exercise) are the basic treatment for improving low testosterone associated with metabolic syndrome, resulting in significant testosterone level boosts and metabolic improvements. The application of TRT in rigorously screened patients with hypogonadism can improve insulin sensitivity, blood glucose and lipid profiles, but it needs to be implemented within a framework of weighing individual benefits and risks, with close attention to safety issues. Large-scale randomized controlled trials and long-term follow-up studies should be strengthened in the future to clarify the efficacy and safety of TRT in different metabolic disease subtypes. Systematic study of the interaction between testosterone and metabolic diseases from the perspective of endocrine regulation will open up a new path for the precise prevention and treatment of metabolic diseases [7].

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