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Research progress on the relationship between testosterone and cardiovascular disease

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ABSTRACT

Testosterone is the main androgen in human body and has many important effects on cardiovascular system Testosterone deficiency is common in patients with cardiovascular diseases. Many data suggest that low serum testosterone level is related to cardiovascular diseases such as coronary heart disease, heart failure and arrhythmiahowever, the mechanism involved is not completely clearin recent years, the research on testosterone and cardiovascular diseases has attracted much attention. This paper summarizes the pathogenesis and influence of testosterone related cardiovascular diseases.

Keywords: testosterone; heart failure; coronary atherosclerotic heart disease; cardiac electrophysiology; myocardial ischemia/reperfusion

1. Introduction

Cardiovascular disease is caused by heart and vascular diseases, including coronary atherosclerotic heart disease, hypertension, peripheral vascular disease, rheumatic heart disease, congenital heart disease, heart failure, and cardiomyopathy. It has the characteristics of high incidence rate, high mortality, high disability rate, high recurrence rate and many complications.

Cardiovascular disease is one of the main causes of human death[1]. A large number of studies have shown that testosterone at normal physiological level is beneficial to the health of men's cardiovascular system, while testosterone deficiency is related to related metabolic diseases, including obesity, insulin resistance, diabetes and adverse cardiovascular events [such as myocardial infarction (MI) and sudden death][2]. Testosterone therapy is safe and reasonable for patients with symptomatic testosterone deficiency[3,4]. However, the testosterone replacement therapy for cardiovascular diseases is still controversialas the cause or inducement of related cardiovascular diseases, testosterone level is often ignored in clinical practicetherefore, study the effect of testosterone level on heart failure.

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2. Testosterone overview

Testosterone is the main androgen in human body. The biosynthesis and secretion of testosterone in serum are mainly controlled by hypothalamus pituitary gonadal axis[5,6]. Hypothalamus can release gonadotropin releasing hormone (GnRH) to stimulate the release of luteotropic hormone (LH) and follicular stimulating hormone (FSH) In testis, LH mainly stimulates testicular stromal cells to synthesize testosterone, while FSH stimulates testicular Sertoli cells to promote spermatogenesis. Androgen is a hormone that promotes the maturation of male accessory sexual organs and the emergence of secondary sexual characteristics. It can also maintain normal sexual desire and produce the occurrence and development of cardiovascular diseases such as coronary heart disease and arrhythmia. It has important reproductive function[7]. Male hormone is mainly testosterone (testosterone) secreted by testis, which belongs to steroid hormone. Testosterone is transported by carrier protein sex hormone binding globulin. Only 1%–2% of testosterone circulates in the blood as free "free" testosterone, which has strong biological activity[8]. Dihydrotestosterone is the most bioactive androgen. It is synthesized by 5A reductase and plays its role through androgen receptor family. The endogenous level of serum testosterone is fluctuant in circadian rhythm. In some acute diseases, such as sudden drop in testosterone level, acute diseases such as myocardial infarction, septicemia, trauma, etc., low testosterone level is also associated with some chronic diseases, such as diabetes, renal failure, malignant tumor, hypertension, dyslipidemia and so on[9,10]. Symptoms of testosterone deficiency include decreased sexual desire, erectile dysfunction, decreased energy, depression, irritability, decreased happiness, etc. Testosterone deficiency risk includes male chronic heart failure, type 2 diabetes, obesity, chronic obstructive pulmonary disease, acquired immunodeficiency syndrome and chronic opioid use, etc.[11].

Research shows that testosterone deficiency is related to bone loss, low body weight, obesity, low energy in the body, physical state, sexual function and other states[12,13]. Testosterone levels reach the highest level in men aged 30-40, and then decline steadily at the level of 1%–2% per year[10], which is related to the increased risk of mortality and cardiovascular events[14]. Epidemiological studies have also found that the low level of serum testosterone is related to cardiovascular diseases such as atherosclerosis, coronary heart disease/arrhythmia[15]. Studies have proved that men have a higher rate of cardiovascular diseases such as myocardial infarction than women, and believe that they play an important role in related cardiovascular diseases[16].

3. Testosterone related cardiovascular diseases

Testosterone, heart failure and heart failure (HF) are clinical symptoms of impaired systolic and/or diastolic functions of the heart and insufficient blood perfusion of the circulatory system, which are manifested as pulmonary and/or systemic blood stasis More and more attention has been paid to the role of testosterone in the pathogenesis of heart failurethere is evidence that chronic heart failure is associated with testosterone deficiency in 25% of men, and it is considered that testosterone deficiency is closely related to the occurrence and development of heart failure[4]. In some chronic diseases, the level of testosterone often decreases. In addition, patients with heart failure combined with liver congestion can increase the level of sex hormone binding globulin and further reduce the level of free testosterone[17]. The study also found that the decrease of testosterone level was related to the severity of heart failure[18]. Testosterone deficiency is associated with cardiomyopathy, the occurrence and development of heart failure and the decrease of insulin sensitivity. It can lead to muscle fatigue through the impaired glucose uptake of muscle cells, which can provide a theoretical basis for correcting testosterone deficiency in heart failure and is expected to become a treatment method[4].

Several researchers have discussed the role of testosterone treatment in patients with heart failure and found that intravenous testosterone can increase cardiac output and reduce peripheral vascular resistance. Chronic long-term treatment can reduce circulating inflammatory mediators and may reduce left ventricular fibrosis[14,15]. Meta analysis found that testosterone supplementation in patients with heart failure is related to the use of 6-minute walking test to improve motor function and metabolic parameters such as fasting blood glucose, fasting insulin and insulin resistance[19]. The symptoms of heart failure are determined by many factors, not just the degree of myocardial dysfunction. Therefore, other mechanisms of skeletal muscle dysfunction, such as insulin resistance, which leads to the inability of glucose to enter skeletal muscle, have been proposed[20]. The link between testosterone deficiency and insulin resistance, as well as other metabolic disorders, once again makes testosterone treatment an attractive treatment option, which needs further research.

Testosterone and coronary atherosclerotic heart disease in the 1970s and 1980s, epidemiological studies showed that the 10-year mortality of men suffering from myocardial infarction and cardiovascular disease was higher than that of women, so it was speculated that testosterone played an important role in cardiovascular disease An in-depth study of the relationship between testosterone and cardiovascular disease shows that atherosclerosis in men is more common in men with low testosterone concentration[16]. Some researchers reported that men with low endogenous testosterone levels are more likely to develop coronary atherosclerotic heart disease (coronary heart disease)[10]. The severity of coronary heart disease was also studied as a function of serum testosterone concentrationlower serum testosterone levels are associated with more severe coronary heart disease, while higher serum testosterone levels reduce the severity of coronary heart disease[21]. The study found that compared with women, men have a three times higher risk of coronary heart disease[2,22]. A grouping study was conducted on 138 male patients with testosterone deficiency over 65 years old, which confirmed that testosterone had an inhibitory effect on coronary plaque[23]. Intravenous infusion of physiological concentration testosterone in patients with coronary heart disease shows significant vasodilation[24]. Long term administration of testosterone in patients with chronic stable angina pectoris can reduce the occurrence of muscle ischemia and ST segment depression in the maximum exercise test center[25]. In men without coronary heart disease, there is no conclusive data on whether testosterone injection is beneficial or harmful.

In women with polycystic ovary syndrome, there is no increase in the incidence of coronary heart disease In a woman's lifetime, high levels (but within the physiological range) of free testosterone and androstenedione are associated with a low prevalence of atherosclerosis and a low incidence of cardiovascular events[26,27]. A prospective cohort study found that in postmenopausal women, high androgen levels did not increase the risk of coronary heart disease in postmenopausal women[28]. Compared with men, the decrease of fatal cardiovascular events in women is due to the interaction between androgen and estrogen, which has internal cardioprotective effect and explains this gender dimorphism[28,29]. In addition, in vitro studies have found that testosterone can inhibit L-type calcium channel, and the action site is the same as that of nifedipine. Therefore, it is considered that it may be the mechanism of testosterone's anti ischemic effect. However, whether testosterone deficiency will aggravate coronary heart disease is unknown[10,25]. The study also found that testosterone can improve the myocardial ischemia state of male coronary heart diseasetestosterone is an arterial vasodilator in coronary circulation and other vascular beds (including pulmonary vessels), which can reduce systemic peripheral vascular resistance There is evidence that testosterone mediates this effect on vascular reactivity through calcium channel blockade (L-calcium channel), and stimulates potassium channel opening through a direct non genomic mechanism[30]. If it can be further confirmed that low serum testosterone level can be used as an independent predictor of mortality in patients with coronary heart disease, it is of great significance to reduce the mortality and prognosis of coronary heart disease.

Testosterone and myocardial ischemia/reperfusion myocardial ischemia/reperfusion injury (MIRI) is a phenomenon of vascular state change and further aggravation of dysfunction after myocardial ischemia/reperfusion, which is one of the pathogenesis of cardiac ischemic diseases Recent studies have shown that factors such as large production of oxygen free radicals, calcium overload, myocardial energy metabolism disorder, apoptosis, neutrophil activation and vascular endothelial cell injury may jointly participate in the pathogenesis of Miri The study found that the level of testosterone in patients with ST segment elevation myocardial infarction or those with microvascular disorder confirmed by angiography or ECG was lower than those without microvascular disorder[31]. Relevant studies suggest that testosterone can induce coronary artery relaxation[32]. The patients with ischemic cardiomyopathy complicated with low testosterone level were given testosterone replacement therapy for one month. The results showed that the time of ST segment falling by 1mm in Bruce treadmill test was improved, and the total cholesterol and serum tumor necrosis factor were reduced-α (TNF-α) Horizontal[14]. In the subsequent study, the researchers examined the effect of testosterone replacement therapy on myocardial ischemia after 12 months. The results showed that long-term testosterone treatment once again increased the time of ischemia on the treadmill (129 seconds for testosterone treated patients vs 12 seconds for placebo patients)[25]. Some experimental animal studies have shown that testosterone administration may reduce the area of myocardial infarction The researchers found that testosterone administration started one week before myocardial infarction had a neutral effect on the size of myocardial infarction, but shortened the QT interval for correcting heart rate[33]. More follow-up studies are needed to determine whether testosterone has potential therapeutic potential against ischemia and angina pectoris.

Testosterone and atherosclerosis (as) are the main causes of coronary heart disease, cerebral infarction and peripheral vascular diseasesthe disorder of lipid metabolism is the pathological basis of atherosclerosis, which is characterized in that the lesions of the affected arteries start from the intima, generally followed by the accumulation of lipids and compound sugars, bleeding and thrombosis, followed by fibrous tissue hyperplasia and calcium deposition, and the gradual metamorphosis and calcification of the middle layer of the artery, resulting in the thickening and hardening of the arterial wall and the stenosis of the vascular cavitycarotid intima-media thickness (CIMT) is an index to evaluate the degree of atherosclerosis[30]. Testosterone deficiency has a potential effect on lipid metabolismin testosterone deficiency, due to poor control of fat and blood glucose and insufficient storage capacity of subcutaneous fat bank, excessive fat deposition may lead to fat "overflow" into internal organs. At the same time, testosterone deficiency and elevated circulating sugar and lipid cause metabolic imbalance in visceral adipose tissue, which leads to fat accumulation with the metabolic action of liver and muscle. This ectopic lipid accumulation in the liver (steatosis) and arterial wall (atherosclerosis) will lead to corresponding pathological consequences (see **Figure 1**)[30]. In a 12-month experiment to study the effect of testosterone on the volume of coronary plaque in men with hypogonadism older than 65 years old, it was found that testosterone treatment was related to the increase of non calcified plaque volume. The clinical inference of this change was not clear, and there was no change in coronary artery calcification score in each group. Exploratory analysis of plaque components found that compared with placebo, testosterone treatment significantly increased the volume of fibrous plaque, and the change of non calcified coronary plaque volume was not related to the change of total testosterone level after treatment[34]. In some clinical trials, the reason for the decrease of LDL cholesterol after testosterone replacement therapy is not completely clear In testicular deficient mice, testosterone replacement therapy increased the mrna expression of cholesterol and cell transporter ABCA1 and apo E protein[35]. There is evidence that testosterone stimulates cholesterol efflux from THP-1 monocyte macrophage system, which is related to the transport of ABCA-1 transporter to cell membrane, but the effect of high density lipoprotein cholesterol (HDL-C) is not clear[36]. In healthy men and type 2 diabetes, HDL-C was positively correlated with testosterone serum level[37]. Animal experiments have found that in the aorta of animals rich in cholesterol and

rich diet, testosterone deficiency promotes the formation and development of lipid plaque, which is the first stage of atherosclerotic plaque. Testosterone replacement therapy has been proved to protect and improve the occurrence and development of early plaque[38,39].

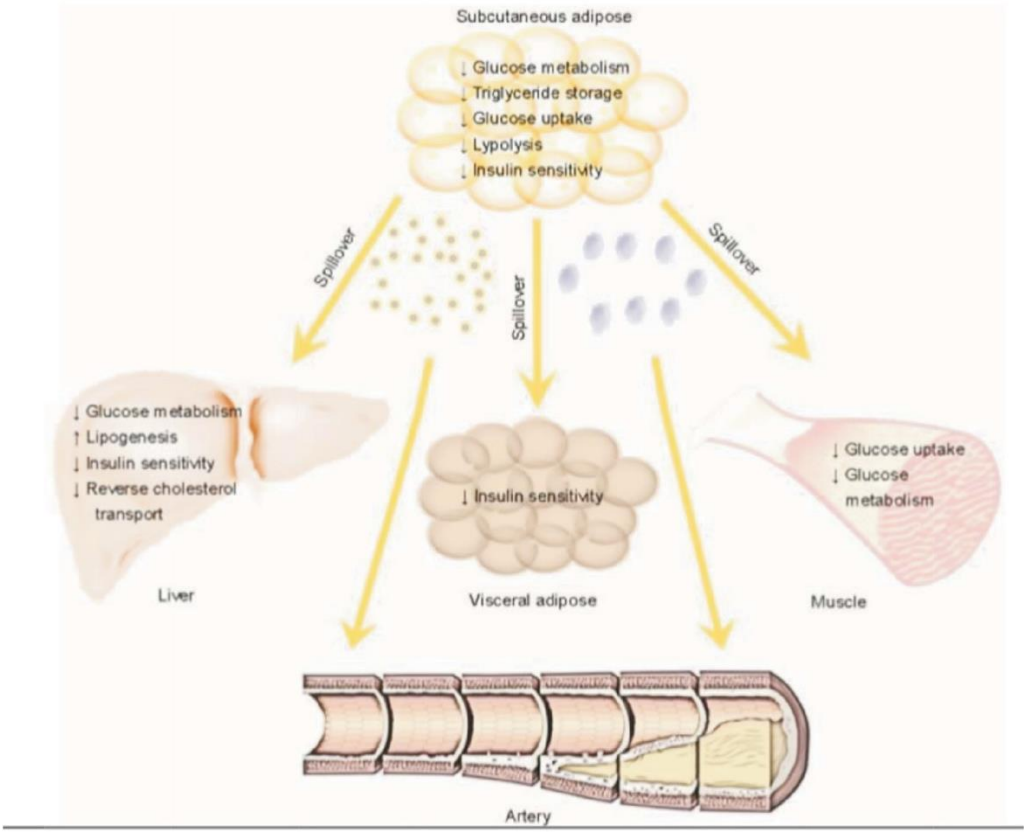

Figure 1. Lipid metabolism and related pathological consequences.

4. Testosterone and the risk of death from cardiovascular disease

Cardiovascular disease has become one of the major factors threatening human health and survival rate. The research on testosterone and the risk of death from cardiovascular disease has a long history. Most studies have revealed the important relationship between low-level testosterone and mortality, and believe that the increase of serum testosterone has a protective effect on the cardiovascular system. With the significant increase of testosterone hormone therapy in the past decade, the impact of testosterone deficiency on health and the potential risk of treatment have attracted more and more attention[40]. The relationship between testosterone deficiency and cardiovascular health, especially cardiovascular mortality, is an important topic in this field A European prospective survey in Europe showed that the mortality of cardiovascular disease was negatively correlated with the concentration of serum testosterone[41,42]. A 30-year study has also shown that low levels of testosterone represent an increase in cardiovascular risk and overall mortality, and are associated with acute coronary disease and atherosclerosis[43,44]. Patients with cardiovascular disease treated with testosterone have a lower incidence of cardiovascular events than untreated patients[45,46]. Low testosterone levels are associated with chronic disease status, such as metabolic syndrome, diabetes mellitus, dyslipidemia, hypertension, renal failure, malignancy and cardiovascular events. Studies have found that high levels of testosterone are associated with a reduced risk of cardiovascular events in men over the age of 70, but this phenomenon does not include young men[47]. A meta-analysis including 18 studies and more than 22,000 subjects showed that the overall mortality of cardiovascular disease was related to testosterone level. Therefore, the researchers concluded that although there was great heterogeneity in the study, low testosterone level was

significantly related to the overall mortality and cardiovascular disease mortality[43]. In addition, some researchers screened 1178 articles and found 70. The meta-analysis showed that there was a significant correlation between low testosterone/high estradiol level and cardiovascular disease[48]. Longitudinal research shows that the total mortality and cardiovascular disease mortality of people with low testosterone level are the highest, and the total mortality and cardiovascular disease mortality are negatively correlated with serum testosterone concentration[49]. Testosterone replacement therapy may have clinical benefits related to cardiovascular diseasehowever, whether low testosterone level and increased mortality are only covariates or causality remains to be confirmed.

5. Testosterone and cardiac electrophysiology

Testosterone mainly affects the qtc interval of ECG, which is a standardized value, which corrects the QT variability caused by the change of heart rate. It is well known that the qtc of men is shorter than that of women, but this difference does not exist before puberty[30]. The third national health and Nutrition Examination Survey and multi-ethnic atherosclerosis research report show that there is an inverse relationship between male QT interval and testosterone level[50]. Studies have found that sex hormones and steroids can control human ventricular repolarization and arrhythmia[30] qtc prolongation is a risk factor for ventricular arrhythmia, which is related to the increased risk of torsade de pointe ventricular tachycardia and ventricular fibrillation, which may lead to sudden death[51]. In the study on the difference between sex hormones and steroids and the morphology of ventricular repolarization in men and women, the QT interval in men is shorter than that in women (450 ms vs 470 MS), and the difference can be explained by the difference of testosterone level[30,52]. A shorter QT interval was observed in healthy men of all ages, corresponding to the highest level of serum testosterone from 9 to 50 years old, while the low level of testosterone was related to the prolongation of QT interval[53]. There is evidence that the qtc interval is prolonged in male hypogonadism, including male obesity related hypogonadism. Although not all research results are consistent, estrogen and progesterone do not affect the qtc interval[54]. The QT interval was shortened by intramuscular injection of 240 mg testosterone heptanate in non obese men with hypogonadism; At the same time, it was also found that QT interval was shortened by injecting this dose of testosterone into patients with chronic heart failure[47]. In men with high testosterone levels, the shortened qtc interval can be explained by prolonging the RR interval[55]. The mechanism of testosterone affecting ventricular repolarization remains to be clarified, but it may be related to testosterone activating potassium channel, reducing the activity of L-type calcium channel and accelerating repolarization[56]. In a randomized placebo-controlled trial of 30 male patients with chronic heart failure, it was found that testosterone treatment also shortened QT and qtc intervals[57].

Animal experiments have studied the changes of qtc interval in mice treated with testosterone replacement therapy after orchiectomy and mice not treated with testosterone replacement therapy after orchiectomy. It is found that testosterone replacement therapy can significantly reduce ventricular repolarization rate by increasing ultrafast potassium current I (Kur) in ventricular myocytes by using whole cell voltage and current clamp. I (Kur) is the main current of myocardial repolarization mediated by kv 1.5 potassium channel, and testosterone can increase the protein expression of kv 1.5 potassium channel[30]. Another study found that testosterone is inversely proportional to the duration of action potential and the risk of early depolarization in female mice, and the increase of early depolarization is related to the increased risk of arrhythmia[30]. Testosterone levels drop sharply after myocardial infarction. These studies also raise the question whether low testosterone will increase the risk of arrhythmia after myocardial infarction A large number of scientific studies support clinical trials and prove the potential important role of testosterone as an antiarrhythmic drug Therefore, the study of testosterone and arrhythmia has important clinical value.

6. Outlook

Testosterone is widely involved in cardiovascular diseases. Testosterone deficiency is related to a variety of cardiovascular diseases. Many research data show that testosterone has a good therapeutic effect on cardiovascular diseases, but the testosterone treatment of patients with cardiovascular diseases is still controversial and needs further research. Whether low testosterone level and related cardiovascular diseases are only covariates or causality remains to be further confirmed. The specific action mechanism of testosterone on cardiovascular diseases is not clear, which is very important for the understanding and treatment of testosterone related cardiovascular diseases. The further study on the correlation and action mechanism between testosterone and related cardiovascular diseases is of far-reaching significance for the study of multi-channel treatment of cardiovascular diseases.

Conflict of interest

The authors declare no conflict of interest.

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