

Testosterone levels and type 2 diabetes in men: current knowledge and clinical implications

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Abstract: The relationship between testosterone and diabetes is an important issue, given the fact that diabetes is becoming a fast-growing epidemic, the morbidity associated with which is more disabling than the disease itself. Various studies have demonstrated the increasing prevalence of hypogonadism in diabetic subjects, but whether this is a cause or effect is still an area of active research. The past couple of decades have witnessed an increasing rate of testosterone prescriptions, even though the relationship between testosterone therapy and cardiovascular effects is still not conclusive. The studies done in this regard have shown conflicting results, and there is still a dearth of long-term, follow-up studies in this field. This paper reviews in brief the postulated mechanisms, observational studies, and interventional data regarding the adverse effects of testosterone therapy in type 2 diabetes mellitus, stressing the cardiovascular risks.

Keywords: testosterone, hypogonadism, type 2 diabetes, cardiovascular events, quality of life

Introduction

Diabetes is a growing epidemic, with 328 million people worldwide having diabetes, and this number is expected to rise to 592 million by the year 2035.^{1,2} Cardiovascular events are the single most important cause of morbidity in patients with diabetes. A number of epidemiological studies have suggested an association of obesity, metabolic syndrome, and dysglycemia with low serum testosterone and poor quality of life in type 2 diabetes.¹⁻⁷ This association is of clinical significance because low total testosterone in men has been reported to be associated with increased cardiometabolic risk factor burden, including a greater prevalence of dyslipidemia³ and atherosclerosis,⁶ and an overall increase in mortality.⁷ This paper reviews the current literature on the underlying mechanism, and observational studies and interventional data evaluating the relationship between serum testosterone levels and cardiovascular risk parameters in patients with type 2 diabetes.

Low testosterone and diabetes

A meta-analysis by Ding et al in 2006⁸ showed that men with diabetes had significantly lower levels of serum testosterone when compared with men without diabetes. The mean pooled difference between the two groups was -76.6 ng/dL (95% confidence interval -99.4 to -53.6 ng/dL). They also found that men with higher total testosterone concentrations (449.6 – 605.2 ng/dL) had a 42% lower risk of type 2 diabetes than those with lower concentrations (213.2 – 446.7 ng/dL).

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Another meta-analysis by Corona et al⁹ similarly showed that men who had lower baseline total testosterone had an increased incidence of incident diabetes in comparison with controls. In the Third National Health and Nutrition Examination Survey,¹⁰ the investigators studied a cohort of 1,413 adult men, 101 of whom had diabetes, and found that men in the lowest tertile of free testosterone had an approximately four-fold increased risk of having diabetes when compared with men in the highest tertile of free testosterone, even after adjustment for age, ethnicity, and adiposity.

In another cross-sectional study of 1,292 men by Brand et al,¹¹ it was shown that diabetic men had not only lower testosterone but also lower levels of sex hormone binding globulin (SHBG) when compared with non-diabetic men. In another cross-sectional survey of 574 men with type 2 diabetes and 69 men with type 1 diabetes by Grossmann et al,¹² testosterone deficiency was found to be more common in men with diabetes, regardless of type of diabetes.

The Hypogonadism In Males study of 1,849 men (1,451 non-diabetic and 398 diabetic) showed that testosterone levels were also influenced by the presence of obesity in the study subjects, as they found a negative correlation between testosterone and body mass index, irrespective of whether the subjects had diabetes or not, although diabetic men had a higher prevalence of low free testosterone across all body mass index categories.¹³

Potential mechanisms

Role of sex hormone binding globulin

Several prospective studies have showed that diabetes and metabolic syndrome are more strongly predicted by low SHBG than by low testosterone.^{14–20} Ding et al²¹ showed that low SHBG levels are associated with a higher risk of type 2 diabetes in men and women. High levels of SHBG are associated with lower risk of diabetes. Similar findings were also reported by Perry et al.²² Lakshman et al¹⁹ showed that even after adjusting for free testosterone or total testosterone, SHBG was a strong predictor of incident diabetes. Many studies have found that the negative relationship between testosterone and insulin resistance/metabolic syndrome is independent of SHBG.^{12,23–25} However, the interrelationship between SHBG, testosterone, and insulin resistance is complex and yet to be fully clarified. It is likely that many other undetermined factors also play an important role.

Role of visceral adiposity

Visceral obesity is projected to be an important risk factor for the development of insulin resistance and type 2 diabetes. Free

testosterone levels have been reported to be low and correlate inversely with the degree of obesity in obese individuals.^{26,27} It has been suggested that increased visceral adipose tissue in hypogonadal men leads to a further reduction in testosterone concentrations through increased conversion to estradiol by aromatase, which has a direct inhibitory effect on the hypothalamic-pituitary-gonadal axis. Visceral fat produces inflammatory cytokines, adipokines, biochemical modulators, and other proinflammatory factors, including interleukin-6, interleukin-1 β , plasminogen activator inhibitor-1, tumor necrosis factor (TNF)- α , angiotensinogen, vascular endothelial growth factor, and serum amyloid A which contribute to systemic and peripheral vascular inflammation and dysfunction.²⁸ Release of free fatty acids is one of the mechanisms via which visceral adiposity and inflammatory response modulate insulin sensitivity. By activating nuclear factor- κ B pathways, free fatty acids lead to increased synthesis of TNF- α . Further activation of lipolysis by TNF- α and increased synthesis of interleukin-6 and macrophage chemoattractant protein-1 increases recruitment of more macrophages and modulates insulin sensitivity. Increased production of TNF- α also augments expression of adhesion molecules in both endothelial and vascular smooth muscle cells. TNF- α also contributes to the dysregulation of insulin modulation of endothelin-1-mediated vasoconstriction and nitric oxide-mediated vasodilation, hence promoting vasoconstriction.

Role of leptin

Low total and free testosterone and low SHBG levels are seen in men with obesity, metabolic syndrome, and type 2 diabetes, as shown in previous studies. Whether this is a cause or effect is still unclear, with hypogonadism-induced obesity and obesity-induced androgen deficiency both plausibly contributing to a bidirectional effect on disease pathology.^{29–32} Visceral obesity is believed to cause these changes through increased proinflammatory cytokines.^{29–32}

The hypogonadal-obesity-adipocytokine hypothesis explains why the body cannot increase the production of testosterone by increased gonadotrophin secretion to stimulate the testis in response to low testosterone levels.³³ Estradiol, TNF- α , and interleukin-6 suppress hypothalamic production of gonadotropin-releasing hormone which leads to decreased release of luteinizing hormone and follicle-stimulating hormone from the pituitary, hence leading to decreased gonadal stimulation. This in turn leads to decreased testosterone release, causing a state of hypogonadotrophic hypogonadism. Leptin, well known to have a role in regulation of body weight and food intake, also stimulates hypothalamic

gonadotropin-releasing hormone neurons that induce the release of luteinizing hormone under normal conditions. Leptin probably causes these changes by acting on the leptin receptor expressed on kisspeptin neurons, as no leptin receptors are seen on gonadotropin-releasing hormone neurons.³⁴ In obesity, although adipocytes are releasing increased amounts of leptin, the hypothalamic-pituitary axis becomes leptin-resistant.³⁵ Secondly leptin also directly suppresses the stimulatory action of gonadotrophins on the Leydig cells of the testis to reduce testosterone production; therefore, elevated leptin levels in obesity may further diminish androgen status.

In a study of 60 men of mean age 60.5 years, testosterone levels correlated with insulin sensitivity measured by hyperinsulinemic-euglycemic clamp studies, suggesting a relationship between decreased testosterone and impaired mitochondrial function.²⁴ Moreover, increasing insulin resistance assessed by glucose tolerance test and hypoglycemic clamp was shown to be associated with a decrease in testosterone secretion by Leydig cells.³⁶

Role of androgen receptor polymorphism in metabolic syndrome

In a cross-sectional study,³⁷ testosterone levels showed a negative relationship with obesity and leptin, but were positively associated with androgen receptor (AR) CAG repeat polymorphism length (AR CAG). These associations of AR CAG with obesity and leptin were independent of testosterone, estradiol, and gonadotropin levels, as well as age. A less sensitive receptor associated with the longer AR CAG probably results in higher testosterone and luteinizing hormone levels. Men with less transcriptionally active ARs achieve higher testosterone levels that have the potential to offset the clinical effects of the receptor polymorphism. However, in the face of the low testosterone levels seen in patients with diabetes, this polymorphism becomes clinically significant. Higher testosterone levels seen in men with a less sensitive receptor are not truly compensatory as they may have effects via mechanisms other than the classical AR. Future research with emerging selective AR modulators might help to decipher the effects of AR stimulation from the overall effects of testosterone. Experimental studies in mice have been conducted to study the role of the AR in insulin resistance. Progressively reduced insulin sensitivity and impaired glucose tolerance were seen in AR knockout ($AR^{-/-}$) mice with advancing age. Aging $AR^{-/-}$ mice were shown to have accelerated weight gain, hyperinsulinemia, and hyperglycemia, and also exhibited increased triglyceride content in skeletal muscle and liver that was attributed to the loss

of ARs in these mice. The AR knockout mice also showed increased serum levels of leptin, and weight loss could not be stimulated with exogenous leptin, pointing to leptin resistance as a possible pathology. These AR knockout mice did not show any improvement in their metabolic abnormalities or insulin resistance with exogenous dihydrotestosterone replacement.³⁸

Various explanations have been offered for the decreased insulin sensitivity in AR knockout mice. Decreased peroxisome proliferator-activated receptor- α expression in skeletal muscle, decreased hepatic lipid metabolism, and subsequent alterations in expression of genes that stimulate adipocyte differentiation, and lipid accumulation were found in these mice. In another study, peroxisome proliferator-activated receptor- α null mice were shown to have impairment in hepatic lipid oxidation which resulted in elevated circulating free fatty acid levels and hepatic steatosis. An alternative explanation is that the altered release of adipokines in AR knockout mice could lead to skeletal muscle and hepatic insulin resistance. Another possible mechanism is leptin resistance, which leads to ectopic deposition of triglycerides in non-adipocytes, such as skeletal muscle and liver, which in turn leads to insulin resistance and adipogenic type 2 diabetes.³⁹

Testosterone replacement

Several interventional trials have reported improvement in visceral obesity, insulin resistance, glycemic control, and lipid profile after short-term testosterone therapy.^{40–43} In the TIMES2 (Testosterone replacement In hypogonadal men with either MEtabolic Syndrome or type 2 diabetes) study,⁴³ the investigators found improvement in certain cardiovascular risk factors including insulin resistance, cholesterol, lipoprotein(a), body fat composition, and sexual function after transdermal testosterone therapy in men with type 2 diabetes and/or the metabolic syndrome. In a study of 581 diabetic males who were followed up for a mean (standard deviation) of 5.8 ± 1.3 years, Muraleedharan et al⁴⁴ found that patients in a low testosterone group had a high mortality rate of 41/238 (17.2%) as compared with 31/343 (9%) in a normal testosterone group. They also showed that testosterone therapy might improve survival in this group. In a double-blind, placebo-controlled, crossover study,⁴¹ 30 patients with type 2 diabetes and hypogonadism were given testosterone therapy which reduced their homeostatic model assessment index, glycated hemoglobin, and fasting plasma glucose. Conflicting results were seen in another study⁴⁵ of 22 men aged 25–50 years with type 2 diabetes mellitus and hypogonadism in which exogenous testosterone supplementation had a neutral effect on the homeostatic

model assessment index and markers of glycemic control. Rebuffé-Scrive et al⁴⁶ demonstrated a reduction in waist/hip ratio and abdominal lipoprotein lipase activity with moderate doses of testosterone in moderately obese middle-aged men. Hence, the effects of testosterone therapy have been shown to be inconsistent in the various studies and further trials will clarify the situation. Testosterone therapy seems to have better effects in obese men with lower basal testosterone levels when testosterone is maintained at mid-normal levels for a longer time with replacement therapy.

Risk-benefit ratio of testosterone therapy

Various studies have been done in the recent past to assess the risk-benefit ratio of testosterone therapy, with conflicting results. A retrospective national cohort study⁴⁵ that studied hypogonadal men who had undergone coronary angiography reported an increased risk of Kaplan–Meier estimated cumulative percentages, with events of 25.7% at 3 years in a testosterone therapy group versus 19.9% in a no therapy group.

Another study⁴⁷ has similarly reported a substantial increase in risk of myocardial infarction after initiation of testosterone therapy. Many potential explanations have been given to account for this increase in cardiovascular events after testosterone therapy, including a rise in platelet thromboxane A2 receptor density and platelet aggregation, a role of dihydrotestosterone in enhancing monocyte activation in the endothelium via smooth muscle proliferation, and expression of vascular cell adhesion molecule-1.⁴⁸ Further studies are required to confirm or refute these plausible mechanisms.

Calof et al⁴⁹ performed a meta-analysis of randomized clinical trials to determine the risks of adverse events associated with testosterone replacement in men ≥ 45 years of age. They found that the combined rate of all prostate events was significantly greater in testosterone-treated men than in placebo-treated men, and the testosterone-treated group was found to have higher hematocrit. They did not find a difference in frequency of cardiovascular events, sleep apnea, or death between the two groups. A similar meta-analysis conducted by Fernández-Balsells et al⁵⁰ revealed no significant effect on mortality, prostate, or cardiovascular outcomes in the testosterone-treated group, although there was a significant increase in hemoglobin and hematocrit and a fall in high-density lipoprotein cholesterol in this group.

A study by Mathur et al⁵¹ in which 13 men were studied over a period of 12 months (seven were treated with testosterone and six with placebo) showed that testosterone increased

the time to exercise-induced ischemia, and reduced body mass index and triglycerides. Mathur et al⁵¹ also showed a decrease in carotid intima-media thickness, although the changes in absolute terms were small, the technique being highly observer-dependent. The concept of testosterone being an attractive option for treatment of heart failure was supported by Caminiti et al in a double-blind, placebo-controlled, randomized trial including 70 elderly patients with chronic heart failure in whom they found that intramuscular testosterone supplementation on top of optimal therapy improves functional exercise capacity, muscle strength, glucose metabolism and baroreflex sensitivity.⁵²

Current knowledge suggests that testosterone replacement is safe, and possibly beneficial, in men who do not have a history of atherosclerotic vascular disease. The benefits should be weighed against the risks in men with a history of atherosclerotic vascular disease.

Conclusion

It has now been proved beyond reasonable doubt that testosterone deficiency in type 2 diabetes is associated with increased occurrence of metabolic syndrome, dyslipidemia, atherosclerosis, and cardiovascular events. Testosterone therapy in general has been found to be beneficial in this cohort of individuals. However, further study is needed to examine the risk of a variety of specific serious adverse cardiovascular events in relation to testosterone dose and duration, and to assess if the risks of testosterone therapy vary by level of serum testosterone and presence or absence of hypogonadal disease. Given the rapidly increasing use of testosterone therapy, the conflicting results of the recent studies, and the morbidity associated with the low testosterone syndrome in type 2 diabetes, further adequately powered studies are required to assess the range of benefits and risks suggested for such therapy. Until that time, clinicians might be well advised to include serious cardiovascular events in their discussions of potential risks with patients, particularly for men with existing cardiovascular disease. Patients should also be informed of the effect of testosterone on hemoglobin and prostate events, and the need for regular follow-up and monitoring before commencing testosterone therapy. Having considered the risks and benefits of testosterone therapy, the question of who should be prescribed testosterone in the hypogonadal diabetic group is still unanswered. The Endocrine Society has not made any recommendations regarding supplementation of testosterone to improve survival in patients with cardiac comorbidities. Until specific

guidelines in this regard are available and supported by adequately powered, long-term studies, testosterone therapy should be cautiously used based on individual case scenarios and risk factors.

Disclosure

The authors report no conflicts of interest in this work.

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