COMMENTARY

The relationship between testosterone and metabolic syndrome

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Coronary artery disease and diabetes are major causes of morbidity and mortality in the Western countries. Unfortunately, by the time these chronic diseases present clinically, irreversible vascular damage has already occurred. Thus, it is critical to identify upstream determinants of disease and target them for preventive measures. The metabolic syndrome is characterized by dyslipidemia, hyperglycemia, hypertension and central obesity. It has been established as a precursor state in which patients are at significantly increased risk of developing cardiovascular disease. Aging is associated with a gradual decline of testosterone levels in men.¹ This decrease is accompanied by changes in body composition including increases in adipose mass and decreases in lean body mass, dyslipidemia, insulin resistance and glucose metabolism dysregulation.

Epidemiological studies have established that low testosterone/low sex hormone-binding globulin can predict the development of the metabolic syndrome.² A number of studies have found an inverse relationship between the severity of the metabolic syndrome and plasma testosterone.³ These previous studies agree with the results of Akishita *et al.*⁴ Adiposity and hyperinsulinemia may suppress sex hormone-binding globulin synthesis and therefore circulating testosterone levels.⁵ Furthermore, insulin and leptin have a suppressive effect on testicular steroidogenesis.^{6,7} Thus, there is evidence that adiposity is a significant factor in lowering circulating levels of testosterone. Conversely, low testosterone and sex hormone-binding globulin themselves may induce metabolic

syndrome.⁸ Thus, the question arises whether testosterone therapy could have a role in the treatment of the metabolic syndrome. There is increasing evidence that testosterone treatment has beneficial effects on visceral fat mobilization and other elements of the metabolic syndrome.⁹ Changes in visceral fat appeared to be a function of changes in total serum testosterone.

Serum triglycerides, total cholesterol, low-density lipoprotein cholesterol and fasting insulin levels were higher and high-density lipoprotein cholesterol levels lower in men with lower serum testosterone levels.¹⁰ In fact, men with prostate carcinoma who receive androgen ablation are prime examples of this phenomenon. In these men, there is increased total serum cholesterol, low-density lipoprotein cholesterol and triglycerides, and decreased high-density lipoprotein cholesterol. Low testosterone level in men is also associated with higher blood pressure, left ventricular mass and left ventricular hypertrophy.¹¹ Testosterone treatment also has beneficial effects on the blood pressure of abdominally obese men.¹²

There is an association between serum testosterone and insulin resistance.¹⁰ In other studies, testosterone levels are frequently low in men with type 2 diabetes, and the majority of these men have symptoms of hypogonadism. Obesity is associated with low testosterone levels in diabetic men.¹³ As indicated above, androgen deprivation in men with prostate carcinoma leads to deterioration in insulin sensitivity and therefore increases the risk of developing type 2 diabetes mellitus.¹⁴ A single-blind randomized study of testosterone administration in men with the metabolic syndrome and recent onset of diabetes established the beneficial effects of testosterone on blood glucose control over and above the effects on diet and

exercise.¹⁵ After 1 year, there were significantly more men in the testosterone-treated group who no longer met the criteria for metabolic syndrome.¹⁵ In randomized control trials, testosterone treatment improved insulin sensitivity in middle-aged abdominally obese men,¹⁶ although the findings have not been completely consistent.¹⁷

Testosterone itself may contribute to the pathogenesis of insulin resistance and diabetes by increasing skeletal muscle mass at the expense of fat mass and decreasing abdominal obesity through inhibition of lipoprotein lipase activity.¹⁶ There is a close relationship between low testosterone levels, insulin resistance and abdominal obesity. Experimental studies have shown that testosterone affects fat metabolism largely through stimulation of β -adrenergic-induced lipolysis.¹⁸ In addition, testosterone has been shown to inhibit lipoprotein lipase activity in abdominal adipose tissue, leading to decreased triglyceride uptake in central fat depots.¹⁹

Both overall and abdominal obesity may decrease testosterone levels. The effects of weight loss on testosterone and sex hormone-binding globulin have been consistent, and both overall and abdominal obesity increase glucocorticoid turnover and production. This increase results in abnormal control of the hypothalamic–pituitary–adrenal axis and possibly in mild hypoandrogenism in men.²⁰ Obesity is also associated with abnormally increased expression and activity of the enzyme 11β -hydroxysteroid dehydrogenase type 1 in adipose tissue. This enzyme determines local glucocorticoid concentrations through interconversion of cortisol and its inactive counterpart cortisone.²¹ Thus, it is likely that the relationship between sex hormones and metabolic syndrome is, to some degree, bidirectional, with low sex

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hormone levels being predictive of the development of metabolic syndrome, which in turn is associated with a further decline in sex hormone levels.

Recent epidemiological reports have found that low testosterone levels are a predictor of mortality in elderly men.²² The results of Araujo *et al.*²³ did not confirm this relationship between plasma testosterone and overall mortality. The study did support, however, that low testosterone levels are predictive of mortality from coronary heart disease.²³

A deficiency of testosterone causes serious deterioration in men's health. The diagnosis of metabolic syndrome often leads to cardiovascular disease and diabetic complications. Thus, testosterone has even more effects on men's health than previously thought and should be regarded as an important hormone in health maintenance.

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