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Testosterone deficiency and the metabolic syndrome

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Abstract
Evidence is presented to link components of the metabolic syndrome to testosterone deficiency and obesity. Testosterone deficiency in hypogonadism or testosterone deprivation in normo-gonadotropic men increases fat mass as well as fasting insulin levels. Testosterone supplementation (TS) in a dose dependent manner, increase lean body mass (LBM), reduces fat mass, body mass index (BMI) and waist hip ratio in both young and elderly hypogonadal men. A negative association between T and insulin resistance as well as impaired glucose intolerance has been demonstrated and in type 2 diabetic men TS improves metabolic parameters. TS improves most components of the metabolic syndrome and also reduces inflammatory cytokines.

Keywords: *metabolic syndrome, testosterone deprivation, obesity, diabetes hypogonadism*

Introduction

A relationship between abdominal obesity and cardiovascular risk factors such as hypertension, dyslipidaemia (elevated levels of cholesterol, triglycerides, low-density lipoproteins (LDL) and low levels of high density lipoproteins (HDL)), impaired glucose tolerance with hyperinsulinaemia, has been established. This cluster is known as the 'insulin resistance syndrome' or 'metabolic syndrome' [1–3].

The contribution of visceral obesity in the pathogenesis of the metabolic syndrome

The association between abdominal obesity and 'insulin resistance syndrome' may be explained by some characteristics that distinguish the visceral fat deposit from the subcutaneous fat stores:

1) Visceral fat deposits have a higher metabolic activity with a high turnover of triglycerides (TG) producing large amounts of free fatty acids (FFA) and altering the secretion of adipocytokines. Low levels of circulating leptin receptors and low circulating adiponectin are found in the obese state. Adiponectin is an anti-inflammatory protein, whereas leptin augments inflammation and fibrogenesis. Disturbed adipocytokine secretion might, therefore, promote atherosclerotic cardiovascular diseases, Type 2 diabetes mellitus, hypertension and dyslipidaemia [4].
2) Visceral fat deposits drain into the portal vein which drains directly into the liver. The liver is unable to handle this high flow of FFA leading to a disturbance in glucose and lipid metabolism. Hepatic uptake of elevated FFA, released through the breakdown of TG by insulin-resistant adipocytes, leads to increased hepatic production of TG, atherogenic small dense low-density lipoprotein (LDL), and reduced high-density lipoprotein (HDL) levels [5].
3) High levels of FFA may reduce insulin clearance leading to hyperinsulinaemia, further enhancing hepatic gluconeogenesis. This may reduce glucose uptake by the muscles resulting in peripheral insulin resistance [6].
4) Prolonged lipid perturbations associated with triglyceride over-storage in β-cells impair β-cell function, induce further insulin secretion, and impair glucose tolerance (a process termed lipotoxicity) [7,8].
5) C-reactive protein (CRP) levels rise proportionately with increasing numbers of components of the metabolic syndrome [9]. The endothelial inflammatory processes induced by sustained dyslipidaemia and abnormal fibrinolytic function ultimately result in atherosclerosis [10] and add to the cardiovascular risks [11]. In response to endogenous fibrinolytic inhibitors such as plasminogen activator inhibitor-1 (PAI-1) [12], endogenous tissue-type plasminogen activator (tPA) is elevated and predicts mortality and

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myocardial infarction [13,14]. It is likely, therefore, that high plasma concentrations of PAI-1 and tPA reflect a state of fibrinolytic dysfunction. Fibrinolytic dysfunction increases the propensity to develop arterial thrombosis, which in turn may increase CVD in people with the metabolic syndrome. This hypothesis is supported by the recent observations that diabetes and abdominal obesity are risk predictors of both venous thrombosis [15] and occlusive arterial disease. Among type 2 diabetic patients specifically, PAI-1 is increased [16] and predicts myocardial infarction and stroke [17,18].

6) Higher levels of plasma renin activity, angiotension-converting enzyme and aldosterone found in centrally obese subjects are believed to perpetuate hypertension [19].

Contribution of declining androgen levels to features of metabolic syndrome in men

Already in 1977 Gerald B. Phillips demonstrated a relationship between serum sex hormones and glucose, insulin, and lipid abnormalities in men with myocardial infarction [20]. Fat mass is strongly, negatively associated with (free) testosterone levels [21,22] and this independently of age, with the negative correlation with fat mass being almost exclusively determined by abdominal fat.

Low T levels predict visceral obesity, as well as the development of the metabolic syndrome and diabetes 7–10 years later [23]. Laaksonen et al. [24] reported that subjects with T levels in the lowest third, after correction for BMI, were 1.7 times more likely to develop metabolic syndrome. Similarly, the association between low endogenous sex hormone levels and increased risk of metabolic syndrome is in line with several observational studies on endogenous sex hormones and cardiovascular risk factors [25–30]. The HIM observational study showed that a significantly higher proportion of hypogonadal patients than eugonadal patients reported a history of hypertension, hyperlipidaemia, diabetes and obesity [31]. Men with metabolic syndrome or diabetes mellitus have low T levels and there is some evidence that low T is associated with insulin resistance [32]. Numerous studies support the biological plausibility of the relationship between sex hormones and metabolic syndrome [33,34]. A decrease in endogenous T is associated with an increase in triglycerides [35]. Research findings suggest a relationship between essential hypertension and impaired T levels in men [8,14,23].

The Rancho Bernardo study, following 294 elderly men over a period of 8 years, demonstrated that low total testosterone (TT) levels, but not bioavailable testosterone levels, corrected for BMI and systolic blood pressure, predicted diabetes mellitus (odds ratio 2.7; 95% C.L.: 1.1–6.6) [36]. In addition, data obtained from the Massachusetts Male Aging Study, a population-based prospective cohort of 1709 men over a period of 15 years showed that low serum Sex Hormone Binding Globulin (SHBG), low TT and clinical androgen deficiency (AD) are associated with an increased risk of developing metabolic syndrome over time and suggest that low SHBG and/or AD may provide early warning signs for cardiovascular risk and an opportunity for early intervention [37].

Furthermore, the San Antonio Heart Study, a population-based study of diabetes and cardiovascular disease, demonstrated a less atherogenic lipid and lipoprotein profile with increased T concentrations [38] and that increased T and Dehydro-epi-androsterone sulfate (DHEAS) are associated with lower insulin concentrations in men [39]. A cross-sectional study of 400 men aged 40–80 years showed that higher levels of serum T were associated with better insulin sensitivity and a reduced risk of metabolic syndrome, independently of insulin levels and body composition suggesting that T may protect against the development of metabolic syndrome [40].

Effects of testosterone deprivation on components of the metabolic syndrome

Within three months of induced hypogonadism with GnRH agonists, fasting insulin levels increase significantly and simultaneously with fat mass [41]. Furthermore, older persons who receive GnRH agonists for prostate cancer (PCa) have a very high incidence of diabetes mellitus [42]. Braga-Basaria [43] in a cross-sectional study evaluated 58 men, including 20 with PCa undergoing androgen deprivation therapy (ADT) for at least 12 months, 18 age-matched men with non-metastatic PCa who had received local treatment and 20 age-matched controls. Metabolic syndrome was present in more than 50% of the men undergoing long-term ADT, predisposing them to higher cardiovascular risk. Abdominal obesity and hyperglycemia were responsible for this higher prevalence.

Dockery et al. measured arterial stiffness (or 'compliance') in 16 men (71 ± 9 years, mean $\pm$ SD) prior to, and three months after, complete androgen suppression with gonadotrophin-releasing hormone analogues as treatment for prostate cancer. Fifteen control men (70 ± 7 years) also had arterial stiffness studies at baseline and three months later. After three months of testosterone suppression, there was a significant fall in systemic arterial compliance (SAC), which was not seen in the controls. Aorto-femural pulse wave velocities (PWVs) tended to increase in the androgen-suppressed men. After testosterone suppression, fasting insulin levels increased from 6.89 ± 4.84 m-units/l to 11.34 ± 8.16 m-units/l (mean $\pm$ SD), total cholesterol increased from 5.32 ± 0.77 mmol/l to 5.71 ± 0.82 mmol/l, and high-density lipoprotein cholesterol increased from 1.05 ± 0.24 mmol/l to 1.26 ± 0.36 mmol/l; $P < 0.005$ for all [44].

Effects of testosterone supplementation on components of the metabolic syndrome

Testosterone supplementation shows a decrease of body fat and an increase in muscle mass in subjects with hypogonadism [45–52]. In a double-blind, placebo-controlled, crossover study in 24 hypogonadal men with type 2 diabetes, T supplementation therapy, reduced insulin resistance and improved glycaemic control [53].

Obesity, insulin resistance and glucose homeostasis have been reported to improve with T therapy in middle-aged men [54,55]. Testosterone supplementation is effective in reducing fat mass, by inducing lipolysis, and increasing muscle mass and strength by increasing muscle protein synthesis and growth through greater expression of insulin-like growth factor-1 [56]. Plasma T levels in men are also inversely associated with circulating leptin concentrations, even after adjusting for fat mass [57], and T therapy reduces leptin levels [58].

Conclusion

Given the fundamental role of sex hormones in the regulation of body composition and homeostasis in humans, more emphasis should be placed on the potential role of androgen dysregulation in the pathophysiology of different obesity phenotypes and the metabolic syndrome. Physicians must be mindful to evaluate metabolic syndrome in all men diagnosed with hypogonadism and hypogonadism in all men diagnosed with metabolic syndrome. Testosterone therapy may not only treat hypogonadism, increasing muscle mass and preventing osteopenia, but may also have tremendous potential to slow or halt the progression from metabolic syndrome to overt diabetes or cardiovascular disease via beneficial effects on insulin regulation, lipid profile and blood pressure. Furthermore, the use of testosterone to treat metabolic syndrome may also lead to the prevention of urological and sexual complications commonly associated with these chronic disease states, such as neurogenic bladder and erectile dysfunction. For optimal effects hormone treatment in the prevention or management of metabolic syndrome should be complemented with optimal nutrition and exercise.

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