The relationship between sex hormones and the metabolic syndrome

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Abstract. 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 (MetS). Physicians must be mindful to evaluate MetS in all men diagnosed with hypogonadism and hypogonadism in all men diagnosed with MetS. Thus, clinical screening for obese patients should include the assessment of waist circumference, testosterone levels, body mass index and physical inactivity. The side effects of Androgen deprivation therapy (ADT) for prostate cancer patients may delay mortality from prostate cancer but , it is undeniable that the effects induced by this treatment have serious consequences. ADT should be considered and discussed between physicians and patients when making treatment decisions. If the decision is to initiate ADT, proper monitoring, preventive strategies and management of weight, insulin resistance, diabetes hyperlipidemia, sexual function and Osteopenia is essential. (www.actabiomedica.it)

Key words: Metabolic syndrome, testosterone, androgen deprivation, diabetes

Introduction

It is estimated that in U.S. men aged 40-69 years, there are about 481,000 new cases of hypogonadism per year. Overall, approximately 2.4 million U.S. men suffer from the condition (1) Hypogonadism (HG) results from a deficiency in testosterone secretion that may occur naturally with increasing age, or as a result of disorders of the hypothalamus, pituitary glands or testes. Men with HG can experience reduced libido and sexual function, reductions in energy and body strength, changed physique, alterations in well-being, and reduced quality of life (2, 3). Low T levels predict visceral obesity and a decrease of lean body mass (LBM) This can be explained in part by the reciprocal effects of Testosterone on the generation of muscle and visceral adipose tissue by influencing the commitment of pluripotent stem cells and by inhibiting the development of pre-adipocytes. Changing lifestyles and an excess of food supply in industrialized nations further increases the prevalence of overweight and obesity. Furthermore a relationship between abdominal obesity and cardiovascular risk factors such as hypertension, dyslipidemia elevated levels of cholesterol, triglycerides, low-density lipoproteins (LDL) and low levels of high density lipoproteins (HDL)], exists. Insulin sensitivity of muscle cells is increased by augmenting mitochondrial capacity and fostering expression of oxidative phosphorylation genes. This results in impaired glucose tolerance with hyperinsulinemia,. The cluster of all the above mentioned pathologies is known as the 'insulin resistance syndrome' or 'MetS (4-6).The prevalence of MetS increases with age and up to 70 years it is more common in men then women (7).

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

MetS has been the focus of great amount of research for most of the 20th century because of the major morbidity and mortality implications of cardiovascular disease. Already in 1977 Gerald B. Phillips (8) demonstrated a relationship between serum sex hormones and glucose, insulin, and lipid abnormalities in men with myocardial infarction. Fat mass is strongly, negatively associated with (free) testosterone levels (9) and this is independent of age. Furthermore, the negative correlation with fat mass is almost exclusively determined by abdominal fat.

Since the 1998 Banting lecture (10), a number of new candidates for the MetS/insulin resistance syndrome/"syndrome X" have been recognized. These additional candidates have included a group of novel risk factors including elevated C reactive protein (CRP) levels, plasminogen activator inhibitor-1 (PAI-1), and fibrinogen. The potential lipotoxic effect of accumulation of fatty acids in non-adipose tissues is thought to be a major component in the development of insulin resistance. Chronic exposure to high concentrations of free fatty acids in the blood affects pancreatic β cell function, insulin secretion and lipid synthesis in the liver, and storage in adipose tissue the Maintaining normal levels of fatty acids requires coordinated regulation between the liver, adipose tissue and skeletal muscle. 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:

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 dyslipidemia (11) Laaksonen et al reported (12) that low T levels predict visceral obesity, as well as the development of the

MetS and diabetes 7-10 years later. and that subjects with T levels in the lowest third quartile, after correction for BMI, were 1.7 times more likely to develop the MetS. 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. The HIM observational study (13) showed that a significantly higher proportion of hypogonadal patients than eugonadal patients reported a history of hypertension, hyperlipidemia, diabetes and obesity.

Other research findings suggest a relationship between essential hypertension and impaired T levels in men. The Rancho Bernardo study (14), following 294 elderly men over a period of 8 years, demonstrated that low total testosterone levels, but not low bioavaiable testosterone levels, when corrected for BMI and systolic blood pressure, predicted diabetes mellitus (odds ratio 2.7; 95% C.L.: 1.1-6.6).) (15) Hypogonadotrophic hypogonadism (HH) is associated with obesity in patients with type 2 diabetes. Furthermore, recent data show that HH is not associated with type 1 diabetes. C-reactive protein concentrations have been shown to be elevated in patients with HH and are inversely related to plasma testosterone concentrations. This inverse relationship between plasma free testosterone and C- reactive protein concentrations in patients with type 2 diabetes suggests that inflammation may play an important role in the pathogenesis of this syndrome. This is of interest since inflammatory mechanisms may have a cardinal role in the pathogenesis of insulin resistance. In a meta-analysis of testosterone levels and type 2 diabetes involving 6,427 men, cross-sectional studies showed that testosterone levels were significantly lower in men with diabetes (-77 ng/dL); similar results were seen in the prospective studies, with a 42% lower risk of diabetes in men with high testosterone levels (450-605 ng/dL; 15.6 - 21.0 nmol/L) compared with those with lower levels (213-447 ng/dL; 7.4 - 15.5 nmol/L

Data obtained from the Massachusetts Male Aging Study (17), a population-based prospective cohort of 1709 men followed over a period of 15 years showed that low serum SHBG, low total testosterone and clin-

ical androgen deficiency are associated with increased risk of developing MetS over time. These results suggest that low SHBG and/or androgen deficiency may provide early warning signs for cardiovascular risk and an opportunity for early intervention. Osuna et al correlated (18) waist circumference, body mass index (BMI), insulin, and homeostatic model assessment of insulin resistance (HOMAIR) to T levels and, in each case, found a significant negative correlation.

Effects of testosterone deprivation (ADT) on components of the metabolic syndrome

Lage et al (2007) found that the estimated risk of incident diabetes associated with receiving ADT was 1.36, and that these patients were more likely to develop diabetes within 1 year, even when correcting for the factors of older age, poorer health, and increased likelihood of other medical cofactors, especially hypertension. Several other studies have documented unfavorable perturbations in body composition as a result of ADT .In a prospective study of 79 men undergoing ADT for 12 months, percentage FM significantly increased by 11% whereas LBM decreased by 3.8% (19). In another study, 32 men with no metastatic PCa on GnRH agonist experienced a 2.7% reduction in LBM and an increase of 9.4% in FM (20). Most of the increase in FM was due to accumulation of subcutaneous abdominal fat. Similarly, a cross-sectional study confirmed these findings (21).

In this study, three groups of men were studied: (1) men on ADT for at least 12 months, (2) men with PCa not on ADT and (3) healthy age-matched controls. The authors noted higher FM in the extremities and the trunk in men on ADT. This study also reported reduced upper body muscle strength in the ADT group. MetS was present in more than 50% of the men undergoing long-term ADT, predisposing them to higher cardiovascular risk.

Within 3 month of induced hypogonadism with GnRH agonists, fasting insulin levels increase significantly and simultaneously with fat mass. In a 12-week prospective study, whole body Insulin Sensitivity Index (ISI) decreased by 12.9%+7.6% (p=0.02),while fasting insulin levels increased by 25.9%+9.3%

(p=0.04) in men on ADT (22). Fasting glucose levels remained unchanged. In another study, median serum fasting insulin levels were 11.8 mU/l, 15.1 mU/l (p=0.02) and 19.3 mU/l (p=0.02) at baseline, 1 month and 3 months into ADT, respectively. In addition, the authors also noted a direct association between fasting insulin levels with the change in FM (r=0.56, p=0.013), suggesting that hyperinsulinemia and insulin resistance is closely linked to obesity (23). On the other hand Yialamas et al (23) demonstrated that acute sex steroid withdrawal for 2 weeks reduced insulin sensitivity in young healthy men with idiopathic Hypogonadotrophic hypogonadism, suggesting that T modulates insulin sensitivity directly and further suggesting that this pathway is not mediated by changes in body composition. Furthermore, older men who receive GnRH agonists for prostate cancer (PCa) have a very high incidence of diabetes mellitus. MetS was present in more than 50% of the men undergoing long-term ADT, predisposing them to higher cardiovascular risk. Dockery et al (24) measured arterial stiffness (or 'compliance') in 16 men (71+/-9 years, mean+/-S.D.) prior to, and 3 months after, complete androgen suppression with GnRH analogues as treatment for PCa. After 3 months of testosterone suppression, there was a significant fall in systemic arterial compliance, which was not seen in the controls. Aorto-femoral pulse wave velocities 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+/-S.D.), 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. In an other study, median serum fasting insulin levels were 11.8 mU/l, 15.1 mU/l (p=0.02) and 19.3 mU/l (p=0.02) at baseline, 1 month and 3 months into ADT, respectively (25).

Although several short-term prospective studies noted the development of hyperinsulinemia as early as 3 months into ADT, Basaria et al. conducted across-sectional study investigating the long-term effects of ADT on metabolic parameters in three groups of men: (1) men with PCa on ADT for at least 12 months, (2) men with PCa not on ADT and (3)

healthy, age-matched men [32]. After adjusting for age and BMI, men on ADT had higher fasting insulin levels (45.0+7.25 m U/ml) compared with non-ADT (24.0+7.24 m U/ml, p=0.05) and healthy age-matched controls (19.0+7.39 m U/ml, p=0.02). Insulin resistance, as measured by HOMAIR, was also higher in ADT (17+2.78), compared to non-ADT (6.0+2.77, p50.01) and controls (5.0+2.83, p=0.01). The novel finding of the study was that fasting glucose levels were also elevated in men on ADT (131+7.43 mg/dl) compared to non-ADT (100+7.42 mg/dl) and healthy controls (99+7.58mg/dl) (23) Keating et al. (26) in an observational study confirmed these findings and showed that men on ADT have an increased risk of incident diabetes. Although ADT can improve overall survival in certain cohorts of patients, it is undeniable that the effects induced by this treatment have serious consequences. The side effects of ADT should be considered and discussed between physicians and patients when making treatment decisions. If the decision is to initiate ADT, proper monitoring and management of weight, insulin resistance, diabetes and hyperlipidemia should be practiced (27).

Effects of testosterone supplementation on components of the metabolic syndrome

Testosterone supplementation showed decrease of body fat and increase in muscle mass in subjects with hypogonadism (28-30). Testosterone supplementation is effective in reducing fat mass, by inducing lipolysis, and increasing muscle mass by increasing muscle protein synthesis and growth through greater expression of insulin-like growth factor-1.Furthermore Testosterone has a protective effect on pancreatic beta cells, which is possibly exerted by androgen-receptor-mediated mechanisms and influence of inflammatory cytokines (31). In a double-blind placebo-controlled crossover study in 24 hypogonadal men with type 2 diabetes testosterone supplementation reduced insulin resistance and improved glycaemic control (32). Furthermore obesity, insulin resistance and glucose homeostasis had also been reported to improve with testosterone therapy in mid-dle-aged men (33). In a single blind, 52-week randomized clinical trial, the effects of supervised diet and exercise (D&E) with or without transdermal testosterone administration on components of the MetS in hypogonadal men with the MetS and newly diagnosed T2D were assessed.. All D&E plus testosterone patients reached the HbA(1c) goal of less than 7.0%; 87.5% of them reached an HbA(1c) of less than 6.5%.Testosterone treatment improved insulin sensitivity, adiponectin, and high-sensitivity C-reactive protein. The authors conclude that addition of testosterone to supervised D&E results in greater therapeutic improvements of glycemic control and reverses the MetS after 52 weeks of treatment in hypogonadal patients with the MetS and newly diagnosed T2D then D%E alone (34). Also Naharci et al (2007) (35) demonstrated that long-term T therapy improved insulin sensitivity and reduced body fat mass..They also showed that the higher the delta in T, the greater the insulin sensitivity. These finding are consistent with observations by Pitteloud et al (36) in which they demonstrated such a dose relationship. This is particularly important because it points to the need to achieve high normal T levels rather than low normal T levels.

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 MetS. Physicians must be mindful to evaluate MetS in all men diagnosed with hypogonadism and hypogonadism in all men diagnosed with MetS. 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 of MetS to overt diabetes or cardiovascular disease via beneficial effects on insulin regulation, lipid profile and blood pressure. For the optimal effects hormone treatment in the prevention or management of the MetS should be complemented with optimal nutrition and exercise.

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