Testosterone and the Metabolic Syndrome in Men: Current Knowledge

Nieschlag E, Zitzmann M

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Testosterone and the Metabolic Syndrome in Men: Current Knowledge

M. Zitzmann, E. Nieschlag

Circumstances of life and food supply have changed in developed countries, resulting in an increasing prevalence of overweight. As a consequence, a complex disorder consisting of visceral obesity, dyslipidemia, insulin resistance and hypertension emerges: the so-called metabolic syndrome leads to the manifestation of diabetes type 2 and cardiovascular disease.

In men, testosterone deficiency contributes to the generation of the metabolic syndrome, as demonstrated by epidemiological and intervention approaches. Correspondingly, testosterone substitution in hypogonadal men is able to invalidate the mechanisms of the metabolic syndrome by various pathways. It has reciprocal effects on the generation of muscle and visceral fat tissue by exerting influence on the commitment of pluripotent stem cells. In addition, testosterone inhibits further development of pre-adipocytes. It also enhances insulin sensitivity of muscle cells by augmenting mitochondrial capacity and fostering expression of oxidative phosphorylation genes. Testosterone is also able to break the vicious circle of leptin resistance and generation of new adipose tissue. These effects are exerted by androgen receptor-mediated mechanisms.

As epidemiological studies indicate, testosterone substitution is especially helpful in preventing or attenuating the metabolic syndrome in aging men with late-onset hypogonadism and in Klinefelter patients.

Current Knowledge

Within the last century, life circumstances have changed in developed countries as physical activity has become less frequent and, simultaneously, an oversupply of food is present. This results in an increasing prevalence of overweight and obesity, particularly over the past two decades. As a consequence, a complex disorder consisting of visceral obesity, dyslipidemia, insulin resistance and hypertension emerges with increasing incidence: the so-called metabolic syndrome contributes to a symptomatology which progressively leads to the manifestation of diabetes type 2 and cardiovascular disease. While the pathogenesis of the metabolic syndrome and each of its components is complex and not well understood, central obesity and insulin resistance are acknowledged as important causative factors [1–4]. Persons affected are twice as likely to die from and three times as likely to suffer a heart attack or stroke compared to those free of the metabolic syndrome [5]. They also have a fivefold greater risk of developing type 2 diabetes mellitus, if not already present [6].

The International Diabetes Federation has recently updated the criteria for diagnosis of the metabolic syndrome (Tab. 1).

Table 1. The International Diabetes Federation: updated criteria for the diagnosis of the metabolic syndrome. (Source: http://www.idf.org/webdata/docs/MetSyndrome_FINAL.pdf). Central obesity (defined as waist circumference > 94 cm for Caucasian men and > 80 cm for Caucasian women, with ethnicity-specific values for other groups) plus any two of the following four factors:

- concentrations of fasting triglycerides > 150 mg/dl (1.7 mmol/l), or specific treatment for this lipid abnormality
- concentrations of HDL cholesterol < 40 mg/dl (1.0 mmol/l) in males and < 50 mg/dl (1.3 mmol/l) in females, or specific treatment for this lipid abnormality
- systolic blood pressure > 130 or diastolic blood pressure > 85 mmHg, or treatment of previously diagnosed hypertension
- concentrations of fasting plasma glucose > 100 mg/dl (5.6 mmol/l), or previously diagnosed diabetes mellitus type 2

Epidemiological Approaches

A cross-sectional study in 400 independently living elderly men examined the association between endogenous testosterone concentrations and the prevalence of the metabolic syndrome as well as relations of androgen levels to its sub-components. Logistic regression analyses showed an inverse relationship for circulating total testosterone concentrations with the prevalence of the metabolic syndrome: within the cohort of men, each increase of one standard deviation of total testosterone (5.3 nmol/L) was associated with a 57% reduced risk of having the metabolic syndrome. In agreement, higher testosterone levels were associated with high insulin sensitivity. In addition, the more factors of the metabolic syndrome that were present, the lower the total testosterone concentrations measured [11].

These findings are corroborated by longitudinal epidemiological approaches. In a cohort of 702 middle-aged Finnish men without metabolic syndrome, concentrations of total testosterone and factors related to insulin resistance were determined at baseline and after 11 years. During that time, 147 men had developed the metabolic syndrome. Men with total testosterone in the lower fourth quartile had an increased risk of developing the disorder and subsequent diabetes mellitus type 2. Adjustment for potential confounders such as cardiovascular disease, smoking, alcohol intake, and socioeconomic status did not alter the associations [12]. A similar approach was taken in 950 healthy, aging men during the Massachusetts Male Aging Study. The incidence of the metabolic syndrome was markedly related to lower testosterone concentrations, especially in men with a Body Mass Index (BMI) lower than 25 kg/m². This points to the specific,
adverse role of central adiposity in combination with androgen deficiency, especially in those men with slender extremities compared to generally overweight persons: the latter develop the metabolic syndrome more independently from androgen deficiency [13].

Summarizing these non-interventional findings, there are strong indications that a testosterone deficiency in men might contribute to the prevalence of the metabolic syndrome. This applies especially to elderly persons with an age-related decline of hypothalamic-pituitary-testicular functionality, which is referred to as late-onset hypogonadism [14, 15]. Nevertheless, non-interventional studies cannot fully elucidate cause and effect in this regard: the metabolic syndrome leading to vascular and endocrine disturbances might as well initiate hypogonadism, an effect known from other chronic disorders [16]. There are indications that such an effect exists, as a Finnish cohort study involving 651 men demonstrates: after 11 years of surveillance, the odds ratio was 3 to be diagnosed with total testosterone concentrations below 11 nmol/L for men with the metabolic syndrome compared to non-affected persons [17].

**Interventional Studies**

Interventional approaches altering testosterone concentrations are able to further illuminate these questions.

**Androgen Ablation**

Pharmacological deprivation of testosterone is a treatment option in men with prostate cancer. A study in such patients assessed the effects of short-term GnRH agonist treatment on insulin sensitivity within the setting of a prospective 12-week study involving 25 men without evidence of diabetes mellitus at baseline. Leuprolide depot and bicalutamide were used for testosterone ablation. The mean percentage of body fat mass as well as mean HbA1c increased significantly, while insulin sensitivity decreased markedly [18].

The results are corroborated by a cross-sectional study in 53 men, including 18 men with prostate carcinoma who received androgen ablation for at least 12 months prior to the onset of the study, 17 age-matched men with non-metastatic prostate carcinoma, who had undergone prostatectomy and/or received radiotherapy and who were not receiving androgen ablation therapy, and 18 age-matched controls. None of the men had a known history of diabetes mellitus. Men in the treatment group had a higher BMI compared with the other groups as well as higher fasting levels of glucose, insulin and leptin. The homeostatic model assessment for insulin resistance demonstrated markedly higher values for men with decreased testosterone concentrations [19].

Consistently, a placebo-controlled study in healthy men receiving short-term testosterone deprivation by a GnRH-receptor antagonist demonstrated incremental effects on concentrations of insulin and leptin after 3 weeks within a condition of marked hypogonadism [20].

**Androgen Substitution in Hypogonadal Men**

In a well-designed, double-blind study, 30 middle-aged men with abdominal obesity were treated with transdermal preparations of testosterone, dihydrotestosterone or placebo. In the group treated with testosterone, visceral fat mass decreased (measured by computerized tomography) without significant changes in other depot fat regions. In addition, the glucose disposal rate, measured with a euglycemic hyperinsulinemic clamp, was markedly augmented. Plasma triglycerides, cholesterol, and fasting blood glucose concentrations as well as diastolic blood pressure decreased [21].

Corresponding effects were seen in 24 hypogonadal men with diabetes mellitus type 2 involved in a double-blind placebo-controlled crossover study. The men received an intramuscular testosterone preparation or placebo for 3 months in random order, followed by a washout period of 1 month before the alternate treatment phase. Testosterone therapy improved fasting insulin sensitivity. HbA1c levels were reduced correspondingly, as were fasting blood glucose levels. Testosterone treatment resulted in a reduction in visceral adiposity as assessed by waist circumference. Total cholesterol decreased with testosterone therapy but no effect on blood pressure was observed (Fig. 1) [22].

These studies are supported by a larger, cross-sectional observation in elderly men: these were either untreated hypogonadal men (n = 24), treated hypogonadal men (n = 61) or healthy eugonadal men (n = 60). In eugonadal men, serum testosterone levels decreased with advancing age while BMI, total body fat content and leptin increased significantly. In untreated hypogonadal patients, an increase in BMI and total fat mass was also observed with advancing age. However, in substituted hypogonadal patients, no age-dependent change in BMI, body fat content, or serum leptin was found [23] (see Fig. 2).

The decreasing effects of testosterone treatment on visceral adipose tissue are most likely dose-dependent, as demonstrated by a study in men receiving various doses of intramuscular testosterone [24].

**Pathophysiological Considerations**

Visceral fat tissue plays a central role within the metabolic syndrome, acting as a source of inflammatory, anti-insulinergic and atherogenically relevant cytokines such as TNF-α and IL-6 [25, 26]. Fat tissue also functions as an endocrine organ: its product adiponectin plays an important role in metabolism and is related to cardiovascular risk factors. It is produced by fat cells in large quantities, yet its levels are inversely associated with total body fat
mass, which is most likely caused by auto-/paracrine down-regulation via inflammatory cytokines. Improvement of insulin sensitivity and inhibition of various atherogenic processes within the vessel wall are direct effects of adiponectin (e. g. [27]). Leptin is another hormone secreted by fat cells. Hypophagia to reduce fat mass is supported by leptin signals, but adipose tissue fosters further food intake by facilitating leptin resistance at the hypothalamic level via afferent-nerve signals [28]. A vicious circle is thus induced as leptin resistance increases further adipocyte-related production of this hormone. There are indications that high levels of leptin can mitigate testosterone secretion [29, 30].

Testosterone seems to have various effects on fat cells and insulin resistance. A study in mouse pluripotent stem cells indicates that testosterone regulates body composition by promoting the commitment of these mesenchymal cells into the myogenic lineage and by inhibiting their differentiation into the adipogenic lineage. This provides a unifying explanation for the reciprocal effects of androgens on muscle and fat mass in men [31]. An inhibiting effect of testosterone has also been described concerning the differentiation of pre-adipocytes: in 3T3-L1 cells that differentiate to form fat cells in adipogenic medium, testosterone inhibits adipocyte differentiation in vitro through an androgen receptor-mediated nuclear translocation of beta-catenin and activation of downstream Wnt signaling (such Wnt signals direct distinct fates of differentiation in precursor cell types) [32]. In addition, testosterone increases lipolysis and the number of adrenoreceptors in male rat adipocytes [33].

Testosterone may facilitate insulin sensitivity both in fat and muscle cells by up-regulating the expression of insulin-induced downstream protein expression. Respective dose-dependent effects of testosterone on insulin receptor substrate-1 and glucose transporter 4 expression were seen in cell models [34]. Recent models of insulin resistance also suggest a pivotal role of mitochondrial function with the decreased transcription of oxidative phosphorylation genes in skeletal muscle of insulin-resistant subjects. This leads to decreased oxidative phosphorylation, decreased lipid oxidation, intracellular accumulation of triglycerides in skeletal muscle, and ultimately insulin resistance [35]. A study in 60 men demonstrated testosterone levels to correlate positively with mitochondrial capacity assessed by measuring maximal aerobic capacity and also expression of oxidative phosphorylation genes [36].

As discussed above, leptin resistance and consequently upregulated adipocyte leptin secretion play a pivotal role in obesity. Testosterone substitution in hypogonadal men is able to reduce leptin secretion of fat cells, probably by an androgen-receptor-mediated pathway (see also below [10]), thus breaking the described vicious circle of leptin resistance and obesity [23, 37–39].

**Role of the Androgen Receptor**

Testosterone effects are mediated by the androgen receptor [40]. It is therefore not surprising that an androgen receptor knock-out model in mice demonstrates effects in agreement with testosterone deficiency: progressively reduced

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**Figure 2:** Relation of age to body fat content, Body Mass Index and testosterone levels in healthy, hypogonadal and testosterone-substituted men. Testosterone administration prevents the age-related increase of adipose tissue and weight. Modified from [23]; author permission granted by E. Nieschlag.
insulin sensitivity and impaired glucose tolerance are seen in these mice with advancing age. Aging androgen receptor knock-out mice display accelerated weight gain, hyperinsulinemia, and hyperglycemia. The loss of the androgen receptor contributes to increased triglyceride content in skeletal muscle and liver in these animals and leptin concentrations are elevated in serum [41].

Apart from complete dysfunctionality of the androgen receptor, modulations of its activity have also been observed and can be assigned to a polymorphic polyglutamine stretch of variable length within the N-terminal domain of the receptor protein. This stretch is encoded by a variable number of CAG-triplets in exon 1 of the androgen receptor gene, which is located on the X-chromosome. The length of the polymorphism is inversely associated with androgen-induced gene transcription [40]. Pathological CAG-triplet elongations (>36) are observed in spinobulbar muscular atrophy, the so-called Kennedy Syndrome. Long before the androgen receptor polymorphism was recognized as cause for the disease [42], an association of the disorder with diabetes mellitus was suspected [43]. As confirmed recently, markedly reduced androgen function indeed leads to pathological glucose metabolism in about 50% of these patients [44]. Also within the normal range of CAG-triplet length (13 to 36 repeats), modulatory effects on androgenic activity are reflected by metabolic parameters: concentrations of insulin and leptin as well as body composition in men are associated with this polymorphism (Fig. 3) [10, 45].

**Perspectives**

Among hypogonadal men, especially the group of Klinefelter patients exhibit an increased prevalence of the metabolic syndrome [46]. Special efforts to detect this under-diagnosed chromosome disorder and to mitigate the increased mortality of these men due to complications of diabetes mellitus and cardiovascular events [47] are necessary. Although approaches examining the effects of testosterone on sub-parameters of the metabolic syndrome have been made (see above), prospective studies investigating its incidence in hypogonadal men receiving testosterone substitution therapy are needed. Such studies should take the modulatory effect of the androgen receptor into account to fully elucidate the putative potential of testosterone to attenuate or prevent the metabolic syndrome in men.

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