Journal of Steroid Biochemistry & Molecular Biology 114 (2009) 40–43

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

# The role of testosterone in the metabolic syndrome: A review☆

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ARTICLE INFO

*Article history:*
Received 28 November 2008
Accepted 31 December 2008

*Keywords:*
Testosterone
Metabolic syndrome
Cardiovascular risk factors
Insulin sensitivity
Diabetes mellitus type 2

ABSTRACT

Over the last three decades it has become apparent that testosterone plays a significant role in the maintenance of bone and muscle mass, in erythropoiesis, and in mental functions. But testosterone is also a key player in glucose homeostasis and lipid metabolism. The metabolic syndrome is a clustering of risk factors predisposing to late onset diabetes mellitus, atherosclerosis and cardiovascular morbidity and mortality. The main components of the syndrome are visceral obesity, glucose intolerance, raised blood pressure and dyslipidaemia (elevated triglycerides, low levels of high-density lipoprotein cholesterol), and a pro-inflammatory and thrombogenic state. Cross-sectional epidemiological studies have reported a direct correlation between plasma testosterone and insulin sensitivity, and low testosterone levels are associated with an increased risk of type 2 diabetes mellitus, dramatically illustrated by androgen deprivation in men with prostate carcinoma. Lower total testosterone and sex hormone-binding globulin (SHBG) predict a higher incidence of the metabolic syndrome. There is now evidence to argue that hypotestosteronaemia should be an element in the definition of the metabolic syndrome. Administration of testosterone to hypogonadal men reverses the unfavorable risk profile for the development of diabetes and atherosclerosis. Testosterone should be regarded as a pivotal hormone for men's health.


Obesity is a condition that is reaching epidemic proportions in both the developed and the developing world (Ogden et al. [45]). Approximately 80% of obese adults suffer from at least one, and 40% from two or more of the diseases associated with obesity, such as type 2 diabetes, hypertension, cardiovascular disease, gallbladder disease, cancers and diseases of the locomotor system, such as arthrosis.

Although it appeared relatively suddenly, obesity in its epidemic form – largely manifest in industrialized societies but now rapidly spreading to the rest of the world – is the result of an interaction between human biology and human culture over the long period of human evolution. Similar to other mammals and primates, humans have the capacity to store body fat when opportunities to consume excess energy present themselves. But during the millions of years of human evolution such opportunities were rare, transient and unpredictable. More commonly mankind was confronted with food scarcity and, at the same time, high levels of physical activity were required to survive. In a modern environment, individuals still possessing the ancestral energy-conserving genes are at great risk for overweight and obesity and associated chronic diseases. The prevalence of obesity has doubled in 20 years (for review: Bellisari [8]). Obesity has become an enormous financial burden to the health care system. One study found that obesity has roughly the same association with chronic health conditions as twenty years of aging, exceeding the association of smoking and alcohol abuse (Sturm [58]).

## 1. The metabolic syndrome

A closer examination of obesity has revealed that a preferential accumulation of fat in the abdominal region is associated with an increased risk of non-insulin dependent diabetes mellitus (NIDDM) and cardiovascular disease, not only in obese subjects but even in non-obese subjects (Kannel et al. [23]). A large number of cross-sectional studies have established a relationship between abdominal obesity and cardiovascular risk factors such as hypertension, dyslipidaemia (elevated levels of cholesterol, of triglycerides, of low-density lipoproteins and low levels of high-density lipoproteins), impaired glucose tolerance with hyperinsulinaemia, a cluster known as the 'insulin resistance syndrome' or 'metabolic syndrome' (Bjorntorp and Rosmond [9]; Carr and Brunzell [12]; Grundy et al. [17]; Gans [15]). The term metabolic syndrome is now preferred. The main components of the metabolic syndrome are abdominal obesity, insulin resistance, hypertension and dyslipidaemia. There is a debate in the literature

☆ Lecture presented at the 18th International Symposium of the Journal of Steroid Biochemistry and Molecular Biology, 18–21 September 2008, Seefeld, Tyrol, Austria.

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doi:10.1016/j.jsbmb.2008.12.022

whether combining these components or conditions has an added diagnostic or prognostic value. Meanwhile, there are three main definitions of the metabolic syndrome. These definitions overlap but differ in the points of emphasis of the components. The definition of the National Cholesterol Education program places equal emphasis on the various components of the metabolic syndrome [1]. The definition adopted by the WHO assigns greater value to insulin resistance as a required component of the metabolic derangements (Lakka et al. [33]). Increasingly, professional organizations have now proposed definitions. The International Diabetes Federation has drafted a singly unifying definition in April 2005. The main emphasis in this definition is central obesity defined by waist circumference: waist circumference in Europids ≥ 94 cm and in Asians > 90 cm and two or more of the following four factors: elevated triglycerides: ≥1.7 mmol/L (≥150 mg/dL), reduced HDL-cholesterol: <1.03 mmol/L (<40 mg/dL), elevated blood pressure systolic ≥130 mmHg, diastolic ≥ 85 mmHg (or treatment), and dysglycaemia (raised fasting plasma glucose): ≥5.6 mmol/L (≥100 mg/dL) (or type 2 diabetes) (Ford [14]), (http://www.idf.org/webdata/docs/MetSyndrome_FINAL.pdf).

## 2. The metabolic syndrome and testosterone

Both cross-sectional and longitudinal epidemiological studies have convincingly established that low plasma testosterone/low SHBG are correlated with/predict the metabolic syndrome(Laaksonen et al. [30]; Blouin et al. [10]; Kalme et al. [21]; Muller et al. [41]; Kupelian et al. [29]). Numerous studies have found inverse associations between the severity of features of the metabolic syndrome and plasma testosterone (Mohr et al. [39]; Rodriguez et al. [48]) (Allan et al. [2]; Kaplan et al. [24,25]; Allan et al. [4]; Kalyani and Dobs [22]). There is an inverse relationship between waist circumference, a reliable indicator of visceral obesity, and testosterone levels over all age groups (Svartberg et al. [60]).

Adiposity with its associated hyperinsulinism suppresses SHBG synthesis and therewith the levels of circulating testosterone (Eckel et al. [13]; Kaufman and Vermeulen [27]). It also may affect the strength of LH signaling to the testis (Lima et al. [35]). Further, insulin (Pitteloud et al. [47]) and leptin (Isidori et al. [20]) have a suppressive effect on testicular steroidogenesis. So, there are reasons to believe that adiposity is a significant factor in lowering circulating levels of testosterone.

While it is clear that disease, and in the context of this contribution, in particular the metabolic syndrome suppress circulating testosterone levels, it has also been documented that low testosterone induces the metabolic syndrome (Stellato et al. [56]; Laaksonen et al. [32]). Low testosterone and SHBG levels appeared strongly associated not only with components of the metabolic syndrome, but also with the metabolic syndrome itself, independently of body mass index. Furthermore, sex hormones were associated with inflammation and body iron stores. Even in the absence of late-stage consequences such as diabetes and cardiovascular disease, subtle derangements in sex hormones are present in the metabolic syndrome, and may contribute to its pathogenesis (Laaksonen et al. [31]).

The relative contributions of each of the individual National Cholesterol Education Program Adult Treatment Panel III components of the metabolic syndrome to low serum testosterone in aging men has been examined using multiple linear regression modeling. Based on these analyses the presence of diabetes or fasting serum glucose greater than 110 mg/dL, body mass index 30 kg/m$^2$ or greater, and triglycerides 150 mg/dL or greater each appeared to have a clinically relevant association with low serum testosterone (Kaplan [24,25]).

The role of testosterone is dramatically demonstrated by findings in men with prostate cancer who undergo androgen ablation therapy (Basaria et al. [7]; Smith [32]), particularly in the longer-term (Braga-Basaria et al. [11]). Another study showed convincingly that acute androgen deprivation reduces insulin sensitivity in young men (Yialamas et al. [63]) and strongly impairs glycemic control of men with diabetes mellitus (Haidar et al. [18]). Visceral fat cells secrete a large number of cytokines, which impair testicular steroidogenesis (Lyon [36]; Trayhurn [61]; Eckel et al. [13]).

### 2.1. The effects of normalization of testosterone levels on features of the metabolic syndrome.

#### 2.1.1. Effects on fat distribution/body composition

So, it is clear now that low testosterone levels are a factor in the etiology of common ailments of elderly men such as the metabolic syndrome and its associated diseases such as diabetes mellitus and atherosclerotic disease. The question arises then whether testosterone treatment has a role to play in the treatment of the metabolic syndrome and its sequelae such as diabetes mellitus type 2 and cardiovascular disease. There is increasingly evidence of a beneficial effect of testosterone treatment on visceral fat and other elements of the metabolic syndrome. Changes in visceral fat appeared to be a function of changes in serum total testosterone (Allan et al. [3]). The beneficial effects of androgens on (visceral) fat have been confirmed in other studies (Munzer et al. [43]; Schroeder et al. [49]). A recent study, not yet published, investigated the effects of normalization of circulating testosterone levels in men with subnormal testosterone levels receiving treatment with parenteral testosterone undecanoate and found favorable effects on body composition (waist circumference) (Gooren [16]). In another as yet unpublished study 32 hypogonadal (plasma testosterone <12 nmol/L) men with the metabolic syndrome, with newly diagnosed type 2 diabetes mellitus were single-blindly randomized to diet and exercise alone ($n$ = 16) or to diet and exercise in combination with testosterone gel 50 mg once daily ($n$ = 16) and treated for 52 weeks. No glucose lowering agents were administered prior to or during the study period. Addition of testosterone significantly further improved these measures compared to diet and exercise alone on waist circumference (Heufelder et al. [19]).

#### 2.1.2. Effects on lipids

In a large epidemiological study (The Telecom Study) there appeared to be an association of testosterone and cardiovascular risk factors in healthy, non-diseased, adult men. Serum triglycerides, total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, fasting and 2-h plasma insulin were higher and values of serum high-density lipoprotein cholesterol were lower in men with lower serum testosterone levels (Simon et al. [52]).

That testosterone is a significant factor in this difference in risk profile is demonstrated by observations in men receiving androgen ablation treatment for prostate carcinoma, resulting in a rather acute and profound decline of serum testosterone. In these men there is an increase of serum cholesterol, LDL-cholesterol and triglycerides and a decrease in HDL-cholesterol (Haidar et al. [18]). The role of testosterone is further corroborated by the favorable effects of administration of testosterone on lipid profiles in a study of men with newly diagnosed diabetes mellitus and the metabolic syndrome (Heufelder et al. [19]). Observations in men treated with parenteral testosterone undecanoate for up to 9.5 years showed that these effects are persistent over time (Zitzmann and Nieschlag [64]).

#### 2.1.3. The association between plasma levels of testosterone and blood pressure

There is evidence from epidemiological studies of the metabolic syndrome that there is an inverse relationship between circulating levels of testosterone and blood pressure. Lower levels of

testosterone in men are associated with higher blood pressure, left ventricular mass, and left ventricular hypertrophy (Svartberg et al. [59]). Part of the explanation may be the stiffening of large arteries as observed in men who receive androgen ablation treatment with GnRH-agonists for prostate cancer and who experience a drastic decrease of circulating testosterone levels (Smith et al. [53]). The first study to demonstrate a favorable effect of testosterone treatment on blood pressure in abdominally obese men was published by Mårin et al. [38]. Another study investigating the effects of testosterone treatment of men with osteoporosis found also a beneficial effect on blood pressure levels (Anderson [5]). In a study of 122 men receiving treatment with parenteral testosterone undecanoate over 15 months both systolic and diastolic blood pressure decreased (Yassin and Saad [62]). The maximum effect was attained after nine months of testosterone administration. A single-blind randomized study of testosterone administration to men with the metabolic syndrome and recent onset of diabetes mellitus established also beneficial effects of testosterone on blood pressure over and above the effects of diet and exercise (Heufelder et al. [19]). These effects are persistent as demonstrated in a study of men receiving testosterone treatment up to 9.5 years (Zitzmann and Nieschlag [64]).

#### *2.1.4. The association between insulin resistance, glycaemic control, and type 2 diabetes*

In epidemiological studies in healthy adult men there appears to be an association between serum testosterone and insulin resistance: fasting and 2-h plasma insulin were higher in the men with lower testosterone. After adjustment for both body mass index and waist/hip ratio, fasting and 2-h plasma insulin levels remained significantly different between the two groups (Simon et al. [52]). In another study total testosterone and SHBG concentrations were lower in the obese group compared with normal and overweight subjects. The mean insulin concentration was significantly higher in the obese group compared with the other groups. Total testosterone was negatively correlated with the body mass index, waist circumference, leptin, insulin and also with the HOMA-IR (Osuna et al. [46]).

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 (Kapoor et al. [26]).

As indicated above with other components of the metabolic syndrome, androgen deprivation of men with prostate carcinoma leads to a deterioration of insulin sensitivity and therewith increase the risk of developing diabetes mellitus type 2 and atherosclerotic disease (Smith et al. [54,55]). Acute withdrawal of testosterone administration to men with hypogonadotropic hypogonadism reduces insulin sensitivity in young healthy men with idiopathic hypogonadotropic hypogonadism. The acuity of the resulting hypogonadism, with a too short period of time to induce changes in body mass index or leptin levels, suggests that sex steroids modulate insulin sensitivity in the absence of apparent or detectable changes in body composition (Yialamas et al. [63]).

It appears that there is a vicious circle: insulin resistance is associated with a decrease in testosterone secretion by the Leydig cell (Pitteloud et al. [47]) perpetuating the problem of low testosterone inducing/aggravating features of the metabolic syndrome. In men with hypogonadotropic hypogonadism testosterone treatment resulted in an improvement of body composition (decrease of fat mass/increase of lean body mass) and of glycaemic control (Naharci et al. [44]). A decrease of 1% in levels of $HbA_{1c}$ leads to a significant reduction of the risk of complications (Stratton et al. [57]).

A single-blind randomized study of testosterone administration to men with the metabolic syndrome and recent onset of diabetes mellitus established beneficial effects of testosterone on glycaemic control and on $HbA_{1c}$ levels over and above the effects of diet and exercise. After 1 year there were significantly more men in the testosterone-treated group who no longer met the criteria for suffering of the metabolic syndrome (Heufelder et al. [19]). Also markers of inflammation and coagulation had significantly more improved in the men who had received testosterone.

## 3. New perspectives on testosterone

In recent times the understanding and thinking about the (patho)physiological functions of testosterone have undergone a revolutionary development. It was well-known that hypogonadism in men usually resulted in loss of libido and potency which could be restored by androgen administration. While the significance of testosterone for male reproductive/sexual functioning has been obvious to most physicians, they now need to familiarize themselves with the insight that testosterone is a key player in glucose homeostasis and lipid metabolism.

Physicians will have to make a change of their mind-set that testosterone, rather being a dangerous companion to a man's life, bringing joy but exacting its toll, is a vital hormone for men's health, from early prenatal development to the end of a man's life. Earlier it has been questioned whether testosterone has an essential role to play in male physiology. Recent epidemiological studies have found that low testosterone levels are a predictor of mortality in elderly men (Shores et al. [51]; Shores et al. [50]; Khaw et al. [28]; Laughlin et al. [34]) (Maggio et al. [37]). Another study could not confirm this (Araujo et al. [6]), but, while disagreeing on the relationship of plasma testosterone and over-all mortality, the latter study agreed that a low testosterone level was predictive of mortality from ischemic heart disease.

Obviously, epidemiological studies cannot unravel cause-relationships but the evidence is convincing that the decline in testosterone levels with aging is accounted for rather by (age-related) disease than the calendar age of men (Muller et al. [40]; Mulligan et al. [42]). Intervention studies provide potential answers to the causality of the relationship. It is no exaggeration to say that in modern medicine and endocrinology testosterone is no longer a marginal hormone. Neither is it a life-style hormone for those men seeking eternal youth. Its deficiency leads to a serious deterioration of the health of men expressing itself in the metabolic syndrome and its sequelae: diabetes mellitus type 2 and atherosclerotic disease, osteoporosis and sarcopenia, all strongly limiting physical independence in old age and accelerating morbidity and mortality.

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