Testosterone and the metabolic syndrome

Keywords

Testosterone levels

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Abstract

There is convincing evidence that abdominal obesity, a key factor in the metabolic syndrome, is associated with low testosterone levels and, conversely, low levels of testosterone are a risk factor for development of the metabolic syndrome, thus producing a vicious circle. The mechanisms by which the metabolic syndrome induces hypogonadism are increasingly being elucidated. It is now clear that insulin resistance decreases Leydig cell responsiveness to stimulation with human chorionic gonadotropin.

Androgen depletion in men with prostate cancer has demonstrated an impressive increase in insulin resistance and the risk of developing type 2 diabetes mellitus. Androgens have direct (membrane) effects on pancreatic β-cells thus stimulating insulin production.

The relationship between circulating testosterone levels and the metabolic syndrome has been demonstrated in elderly men, but, paradoxically, there is a lack of effect of testosterone insulin sensitivity or glucose tolerance in healthy young men.

Interventions with testosterone in men with the metabolic syndrome lead to improvements of body composition (decreasing fat mass and increasing lean body mass) and improve insulin sensitivity.

The metabolic syndrome is an insulin resistance syndrome with simultaneous occurrence of abdominal obesity, impaired fasting glucose, impaired glucose tolerance or overt type 2 diabetes, dyslipidemia and hypertension. Other medical disorders are also associated with this cluster of symptoms, and most importantly, the syndrome results in a severe increased morbidity and mortality. The incidence of metabolic syndrome increases rapidly both in the western world and even more so in developing countries. Although the metabolic syndrome currently receives wide attention, it was described more than 80 years ago [1] and the significance of abdominal obesity was already noted 60 years ago [2].

Central or visceral obesity causes increases inflow of free fatty acids into the liver via portal venous drainage and induces metabolic disorders due to a perturbation of liver metabolism [3].

Endocrine factors and the metabolic syndrome

Endocrine factors influence fat accumulation and distribution. Corticosteroids are known to increase accretion of fat intra-abdominally, while growth hormone and sex steroids may prevent such accretion [4]. In men testosterone seems to play a role in counteracting accretion of abdominal fat. Thus in men there appears to be a negative correlation between testosterone levels and abdominal fat mass, or its surrogate measure abdominal circumference. A decline of circulating testosterone brings on further accretion of the abdominal fat pool [5].

Abdominal obesity is a key risk factor for development of impaired fasting glucose, impaired glucose tolerance and type 2 diabetes. As low testosterone levels are associated with accretion of abdominal fat and abdominal fat increases the risk for disturbed glucose metabolism, it is not surprising that approxi-

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mately 30% of men with type 2 diabetes have testosterone levels in the hypogonadal range [6].

Endogenous sex hormones have a clearly predictive value for the risk of development of type 2 diabetes mellitus [7].

A further indication for a close relation between low testosterone levels and development of type 2 diabetes can be derived from longitudinal epidemiological data indicating that a −1 SD decrease in testosterone leads to a 1,5 times increased diabetes risk [8] while men with + 1SD in testosterone have a 50% reduced diabetes risk [9]. Another aspect of the relation between testosterone and type 2 diabetes is the observation that men with metabolic syndrome are more likely to develop hypogonadism over time (Laaksonen et al 2003). This implies that there might be a vicious circle: i.e low testosterone facilitates development of metabolic syndrome which, in turn, causes further supression of testosterone levels.

In addition to the association between low testosterone levels and development of insulin resistance, cross sectional data also demonstrate a positive correlation between a healthy blood lipid profile (high HDL and low LDL cholesterol levels) and serum testosterone [10]. Moreover, in this study there was also a clear negative correlation between testosterone and body mass index (BMI), waist circumference and indices of insulin resistance. This also supports the idea that low blood testosterone is related to an unfavourable metabolic situation.

Insulin resistance and Leydig cell function

Testosterone (in males) mainly originates from testicular Leydig cells and its synthesis and secretion is controlled by pituitary secretion of luteinizing hormone (LH). Serum testosterone levels are positively correlated to insulin sensitivity (measured with hyperinsulinemic euglycemic clamp technique) [11]. Leydig cell responsiveness to stimulation with LH can be assessed by measurement of serum testosterone levels prior to and after 48–72 hours following an injection of human chorionic gonadotropin (hCG), a hormone with similar biological effect as LH. Earlier observations have shown diminished testosterone responses to hCG with increasing BMI [12] and in a recent study it was shown that the crucial factor affecting Leydig cell responsiveness is insulin sensitivity [13]. Thus insulin resistance affecting Leydig cell secretory capacity causes further decline in serum testosterone levels. Another important observation on the relation between testosterone and insulin resistance is derived from studies of men with prostate cancer who have undergone total androgen blockade (Matthew et al 2006). In this group of men the radical lowering of circulating testosterone results in impaired fasting glucose and gradual development of type 2 diabetes. This further supports the idea of a vicious circle –insulin resistance, lowered testosterone levels, increased insulin resistance etc. Experimental *in vitro* data further indicate that testosterone has a direct effect on pancreatic beta cells and induces insulin release of the same order of magnitude as the classical oral anti-diabetic drug tolbutamid [14]. Extrapolations from *in vitro* data must be done with caution, but the findings open a new vista linking testosterone with glucose metabolism.

Although increasing circulating testosterone levels in men with abdominal obesity and metabolic syndrome seem to improve glucose tolerance and insulin sensitivity, there appears to be no relation between testosterone levels and insulin sensitivity in young normal weight healthy men [15].

The clinical feature of the metabolic syndrome resembles the catabolic state encountered in patients with hypercortisolism. Many of the features of the metabolic syndrome, such as abdominal obesity, insulin resistance, hypertension and dyslipidemia, are also present in states of hypercortisolism. In males declining testosterone levels cause a shift towards catabolism and thus a relative state hypercortisolism. As testosterone regulates body composition (lean mass versus fat mass) a loss of testosterone makes it more difficult to maintain an adequate amount of lean tissue and relative hypogonadism may facilitate development of both general obesity and abdominal obesity.

Results from intervention studies

We conducted recently a randomized placebo-controlled study of testosterone administra-