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THE RELATION BETWEEN METABOLIC SYNDROME AND TESTOSTERONE LEVEL

Prashant Goel [1,✉], ***Amorin R. Popa*** [2]

[1] University of Oradea, Romania
[2] Department of Diabetes and Internal Medicine, County Hospital Oradea, Romania

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Abstract

Metabolic syndrome is a group of conditions that increases the risk of developing diabetes and cardiovascular diseases. The most important pathogenic factors for metabolic syndrome are insulin resistance and obesity. The clinical presentation of this syndrome results from its influence on glucose and fat metabolism. Testosterone deficiency has a prevalence of up to 50% in men with metabolic syndrome and type 2 diabetes mellitus. A low level of testosterone is a factor for cardiovascular diseases and predictor of metabolic syndrome and, on the other hand, the components of metabolic syndrome can lead to low testosterone. This article reveals the bidirectional link between low testosterone level or hypogonadism and metabolic syndrome.

key words: *metabolic syndrome, testosterone, obesity, hypogonadism, insulin resistance*

Introduction

Metabolic syndrome (MS) represents a major clinical threat developing worldwide in the 21st century. The components of metabolic syndrome are the risk factors for atherogenic cardiovascular diseases involving central obesity, impaired fasting glucose, insulin resistance, elevated triglycerides, reduced high-density lipoprotein cholesterol and hypertension.

In 1923, the Swedish physician, Kylin, described for the first time the metabolic syndrome as a clinical association of hypertension and gout. Later, in 1988, Reaven proposed the insulin resistance as a primary pathology of metabolic syndrome [1].

In 2003, American Association of Clinical Endocrinologists, used the term Insulin Resistance Syndrome by insulin resistance as a primary pathology and obesity as a major criterion [2]. After that, in 2006, International Diabetes Federation (IDF) published new criteria which includes: central obesity (waist circumference based on ethnicity or body mass index >30kg/m^2), elevated blood pressure (>130/85mmHg), high triglycerides (>150 mg/dl), reduced high density lipoprotein (HDL) (<40mg/dl in men & <50mg/dl in women) and fasting glycemia (>100mg/dl or type 2 diabetes).

Approximately one-quarter of world population suffers from metabolic syndrome [3]. The increasing prevalence of metabolic syndrome significantly affects women between 20-39 years. In US, according to National Cholesterol Educational Program definition, the prevalence of MS is 34.5% respectively 39%

✉ Str. Roman Ciorogariu nr.62, Oradea Zip code 410009, Bihor, Romania. Tel: 0040727794800
corresponding author e-mail: drpg22@gmail.com

based on IDF definition [4]. The prevalence of MS is higher in India and South Asian countries [5]. Insulin resistance is a dominant factor and it is responsible for the vascular and metabolic problems, whereas obesity is the significant clinical manifestation. Insulin resistance is defined as inability to perform its action and affecting glucose, fat and protein metabolism and cellular growth and differentiation. There is an increased prevalence of MS in obese persons, but not all obese persons develop this MS and, on the contrary, even lean persons can also have insulin resistance [6].

Testosterone

Testosterone is a steroid hormone that stimulates the development and maintenance of male reproductive system, including primary male sex organs and the development of secondary sexual characteristics. Testosterone is an anabolic-androgenic steroid hormone which is synthesized in testes in men and in ovaries in women. The levels of bioavailable testosterone are positively correlated to muscle strength and bone density and negatively correlated to fat mass. Friedrich Johann Butenandt and Leopld Ruzicka shared the noble prize in 1939 for the discovery of synthesizing testosterone from cholesterol [7].

Testosterone is one of the major androgens, characterized by four ring C18 steroid structure and secreted by Leydig cells found in the interstitium of the testes between seminiferous tubules. The daily average production of testosterone by a normal male is about 5-7 mg, with the highest level in the morning and the lowest in the evening. The testosterone production is regulated by the hypothalamic-pituitary-testicular axis. Out of the total circulating testosterone, only 1-2% testosterone circulates free, while the rest of it is bound to sex hormone bound globulin (60-80%) and albumin (20-40%). Testosterone deficiency is associated with many chronic health conditions, including type 2 diabetes mellitus (T2DM) and other metabolic disorders.

Hypoandrogenism is defined as androgen deficiency with serious consequences. Its clinical presentation, depending on age, includes loss of libido, erectile dysfunction, depression, muscle loss, increased body fat mass, weight gain and decreased bone density. Other associated comorbidities include obesity, hypertension, dyslipidemia and even diabetes. Hypotestosteronenemia is associated with an atherogenic lipid profile, increases of insulin resistance and high systolic and diastolic blood pressure.

The testosterone levels in men decline progressively with aging at a rate of 1% per year [8]. The declining rate varies depending upon chronic affections such as obesity, stress and medications. Low testosterone levels also impair insulin sensitivity and it is negatively correlated to insulin resistance. The prevalence of testosterone deficiency is about 40% in males with T2DM and it has been reported that patients with metabolic syndrome have lower total and free testosterone than those without metabolic syndrome [9].

The influence of Metabolic Syndrome on testosterone level

Numerous studies have shown abdominal obesity linked with low testosterone levels, while others have proven that low testosterone is associated with visceral fat accumulation [10]. The prevalence of hypogonadism in obese patients is around 57.7% and 35.6% using cut-offs total testosterone <317ng/mL and free testosterone < 78ng/mL [11], while in diabetic patients it ranges from 24.5% to 43% [12] respectively in metabolic syndrome patients ranging from 30-35% [13].

Obesity is characterized by an increase of the both adipocytes number and hypertrophy. There has been a bidirectional relationship between obesity and low testosterone levels as a result of interaction between adipocytokines and hypothalamic-pituitary hormones [14].

In 1999, Cohen presented the hypogonadal-obesity cycle hypothesis. Testosterone inhibits adipocytes lipoprotein lipase activity, enzyme that breaks triglycerides to free fatty acids [15]. Low testosterone levels lead to the development of central obesity and intra-abdominal fat deposition. The hypothesis suggests that low testosterone resulting from high aromatase activity increases adipocytes and fat deposition, gradually lowering testosterone levels further. Estradiol, adipocytokines and other factors inhibit hypothalamic-pituitary-testicular axis, leading to hypogonadotrophic hypogonadism state [16]. The reduction of gonadotropins leads to the reduced stimulation of testosterone production.

On the other hand, obesity leads to low testosterone levels. In the obese patients, abdominal adipose tissue is an important source of inflammatory cytokines. There are certain adipokines secreted and considered to be the possible markers of MS: leptin, adiponectin and resistin.

Leptin is secreted by adipocytes and it is also known as a satiety hormone [17], which controls the energy exchange and the body weight. It has been observed that obese patients have a higher level of leptin. Hyperleptinemia, along with increased aromatase activity in adipose tissues which increases the secretion of estradiol, develops insulin resistance by activating lipolysis in visceral fat and leads to accumulation of free fatty acids that inhibit the release of insulin from beta-cells of pancreas [18]. The relation between leptin and insulin remains controversial as some authors believe that increasing the insulin level above physiological level can increase leptin concentration, while others think that variations in levels of leptin and insulin are negatively correlated. Hyperleptinemia plays an important role in hypogonadism in obese men by inhibiting directly the Leydig cell steroidogenesis [19].

Adiponectin, secreted from adipocytes, regulates the carbohydrates and fat metabolism. It increases fatty acid oxidation, glucose uptake in muscle and reduces hepatic glucose production. Therefore, its deficiency leads to insulin resistance, obesity, T2DM and eventually atherosclerosis [20]. Many studies have proven that hypoadeponectin state leads to the development of chronic heart failure in obesity.

Resistin, secreted by preadipocytes, is considered to neutralize the inhibitory effect of insulin on hepatic glucose production and to reduce the glucose uptake by skeletal muscles. Some authors believe that the increased resistin level is associated with obesity, insulin resistance T2DM, while others disapprove. Thus, the role of resistin remains unclear.

Due to the excess of adipose mass, there is a high aromatase activity, which increases the secretion of estradiol. Estradiol suppress the hypothalamic-pituitary axis, reducing the luteinizing hormone which further decreases the testicular production of testosterone. Another important feature noticed in obese patients is that there is attenuated pulse of luteinizing hormone (LH), while the frequency of LH pulse is unaffected [21]. The increased accumulation of free fatty acid leads to insulin resistance. The hyperinsulinic state leads to a further decrease in testosterone secretion by the Leydig cells, mediated by the presence of insulin receptors on the Leydig cells. Therefore, all the changes occurring during obesity at the level of adipocytes and pituitary hormones contribute to

the pathogenesis of the metabolic syndrome and to the reduction of the testosterone secretion.

Non-alcoholic fatty liver disease (NAFLD) is referred to liver damage from simple steatosis to nonalcoholic steatohepatitis. NAFLD is considered as hepatic indication of MS and is referred as fat accumulation in liver exceeding 5-10% by weight [22]. The prevalence of NAFLD in metabolic patients is about 70-90%. A study done in coastal eastern India showed that in NAFLD patients, insulin resistance is not only associated with fatty liver, but also with other histological severe diseases [23].

Testosterone presents an inverse relationship with body mass index and waist circumference. Another predictor for low testosterone is waist-to- height ratio. As a result of a study, it was shown that the total testosterone level for waist-to-height ratio of 0.5, 0.6 and 0.7 was approximately 461 ng/dL, 375 ng/dL respectively 288 ng/dL. Therefore, waist-to-height ratio above 0.5 is considered to be a predictor for low testosterone level [24]. According to Tromso Study, testosterone levels are inversely associated with anthropometrical measurements and with systolic blood pressure [25].

In a Finnish Study, based on middle-aged men, free testosterone and SHBG were 11% and 18% lower in men with metabolic syndrome [26], whereas The Massachusetts Male Aging Study demonstrated that lower testosterone level in non-obese population was a predictor for the later development of metabolic syndrome among the men with BMI <25kg/m^2 [27].

Another meta-analysis of 21 clinical reports confirmed that there is a high prevalence of low testosterone levels in men with diabetes and/or metabolic syndrome [28], while Kapoor and colleagues showed that in men with T2DM overt hypogonadism was present in 17% of the studied cohort [29]. Dandona et al showed that hypogonadism in men with type 1 diabetes was 6%, while in men with T2DM was 26% [30]. They also demonstrated the inverse correlation between testosterone and body mass index.

Chubb et al showed that lower sex hormone binding globulin is more strongly associated with metabolic syndrome than low testosterone [31]. Another small study done on chronic heart disease patients showed that testosterone administration improved metabolic parameters [32].

As the number of MS components increases, there is a decrease in testosterone level, suggesting that it plays a protective role against MS. According to the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE): weight loss therapy by caloric restriction and more physical activity is necessary in men with hypogonadism and with increased abdominal circumference [33], while the surgical approach could improve hypogonadism in men with obesity (BMI > 50kg/m^2). Bariatric surgery also improves BMI, triglycerides, HOMA-IR and even restores sexual function and fertility [34].

There has been evidence that testosterone replacement therapy improves HOMA-IR and reduces HbA1c [35] by approximately 0.7% within a period of 18 months in men with MS and T2DM.

Conclusion

Based on the literature review of the studies done, modifications appearing in obese or in men with low testosterone level develop the same clinical features as in MS. This shows the existence of an inverse relationship between MS and low testosterone levels. MS, along with obesity and insulin resistance, decreases testosterone level through induction of primary or secondary hypogonadism whereas low testosterone is a predictor for the development of

MS and even T2DM. Therefore, it is strongly recommended to screen obese men for hormone profile.

Conflict of interest: author has declared no conflict of interest.

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