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Review

Testosterone deficiency, metabolic syndrome and diabetes mellitus☆

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ABSTRACT

Testosterone deficiency in adult age is associated with a decrease in libido, energy, hematocrit, muscle mass and bone mineral density, as well as with depression. More recently, testosterone deficiency has also been associated with various components of the metabolic syndrome, which in turn is associated with a five-fold increase in the risk of cardiovascular disease. Low testosterone levels are associated with increased insulin resistance, increase in fat mass, low HDL cholesterol, higher triglyceride levels and hypertension. Testosterone replacement therapy in patients with testosterone deficiency and type 2 diabetes mellitus and/or metabolic syndrome has shown reductions in insulin resistance, total cholesterol, LDL cholesterol and triglycerides and improvement in glycemic control and anthropometric parameters.

Déficit de testosterona, síndrome metabólico y diabetes mellitus

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RESUMEN

El déficit de testosterona en la edad adulta se relaciona con depresión, disminución de la libido, energía, hematocrito, masa muscular y de la densidad mineral ósea. En los últimos años, también se ha asociado con diversos componentes del síndrome metabólico, que a su vez se relacionan con un aumento de hasta 5 veces en el riesgo de enfermedad cardiovascular. Así, las concentraciones bajas de testosterona se asocian con una mayor resistencia a la insulina, incremento de la masa grasa, colesterol HDL bajo, triglicéridos elevados e hipertensión arterial. Inversamente, el tratamiento sustitutivo en pacientes con déficit de testosterona y diabetes mellitus tipo 2 y/o síndrome metabólico ha demostrado reducciones en la resistencia a la insulina, colesterol total, LDL y triglicéridos, y una mejoría del control glucémico y los parámetros antropométricos.

Introduction

Male hypogonadism is defined as the reduction of one or two major testicular functions: spermatogenesis and testosterone production. The etiology of these malfunctions is a primary testicular disease (primary hypogonadism) or disease emerging in the hypothalamus/hypophysis (secondary hypogonadism or hypogonadotropic). The consensus of the International Society of Andrology, the International Society for the Study of the Aging, the European Association of Urology, the European Academy of Andrology and the American Society of Andrology recognizes the diagnosis of hypogonadism in men with the recurrent presence of total testosterone levels below 8 nmol/l (2.3 ng/ml). When the total testosterone levels range from 8 to 12 nmol/l (2.3 and 5.21 ng/ml) quantification of free testosterone is useful. Thus, levels of free testosterone below 225 pmol/l (65 pg/ml) are considered diagnostic and support replacement therapy indication.[1] The presence of symptoms of hypogonadism, such as dysthymia, decreased libido, muscle mass and hair is needed to establish the diagnosis.

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Testosterone circulates in plasma bound to: albumin, to the sex hormone-binding globulin (SHBG) and free. Therefore, its overall concentration includes these three forms and is subject to variations in albumin levels and SHBG, being an uncertain index of bioavailable testosterone. The optimal method for quantification of free testosterone is a difficult procedure and not available in most clinical laboratories. Thus, the most accepted method of estimating free testosterone is by Vermeulen formula[2] including SHBG, albumin and total testosterone levels, with excellent correlation with the direct determination.

Hypogonadism in the general population

In the general population the prevalence of hypogonadism is from 5 to 12.3% in men aged from 30 to 79, with an incidence of 12.3 per 1000 inhabitants/year.[3,4] Testosterone levels change with age, decreasing by 3.5 nmol/l (1 ng/ml) from age 20 to 80.[5] In the European Male Aging Study, which included 3220 men aged 40–79, total testosterone levels decreased by 0.4% annually and free testosterone by 1.3%.[6]

We should distinguish the common hypogonadism from late onset caused by a functional suppression of the hypothalamic–pituitary–testicular axis due to age-related comorbidities, especially obesity. The late-onset hypogonadism has been associated with increased all-cause mortality by up to 5 times.[7]

Pathophysiology of hypogonadism in diabetes

Several studies have found an inverse relationship between the testosterone levels, insulin resistance and obesity. This relationship can be explained by several hypotheses. First, testosterone is metabolized to 17-beta-estradiol by aromatase located in adipocytes. Due to excess aromatization lower testosterone levels allow increased lipoprotein lipase activity, resulting in increased uptake of fatty acids and triglycerides in the adipocytes. Consequently, there is increased fatty mass which is correlated with higher insulin resistance and lower testosterone levels.[8] The second hypothesis suggests that the 17-beta-estradiol and adipokines, interleukin-6, tumor necrosis factor alpha and leptin inhibit the response of the hypothalamic–pituitary–testicular axis in response to lower testosterone levels. This impaired homeostatic response explains why some obese men have a hypogonadotropic hypogonadism with normal or low levels of gonadotropins in the presence of low testosterone levels. Furthermore, the insulin resistance is associated with lower testosterone secretion by Leydig cells.[9] Moreover, *in vitro* studies that have evaluated the direct effect of testosterone in adipocytes show that androgen treatment decreases adipogenesis and increases lipolysis by increasing the number of beta adrenergic receptors.[10,11]

Prevalence of hypogonadism in diabetes

Patients with type 2 diabetes mellitus (DM2) have shown prevalence of frank hypogonadism (total testosterone levels below 8 nmol/l) from 4.4% to 17.7% and extreme hypogonadism (total testosterone ranging from 8 to 12 nmol/l) from 25% to 32.1%.[12,13] In type 1 diabetes mellitus (DM1) it has been reported that around 7.2% of patients have total testosterone levels below 2.8 ng/ml (<10 nmol/l), similar to the general population.[14] However, up to 20% of patients with DM1 have free testosterone levels below 225 pmol/l (65 pg/ml), higher levels than those described in healthy men and lower than in patients with DM2. Age is the major predictor of low levels of free testosterone. Therefore, for each decade of life the prevalence of this condition is multiplied by two.[15]

Hypogonadotropic hypogonadism and metabolic syndrome

There is a number of factors in different population groups that can lead to androgen deficiency, increasing the prevalence of hypogonadism. These include the characteristic features of the metabolic syndrome such as obesity, hyperglycemia, hypertension and atherogenic dyslipidemia. A large number of epidemiological studies have related testosterone with metabolic syndrome, and its components, individually, have been associated with lower testosterone levels. A Finnish study with 1896 non-diabetic males found lower total and free testosterone figures in those who had metabolic syndrome. Men with free testosterone levels in the lowest tertile showed an increased risk of metabolic syndrome by 2.7 (95% CI: 2.0–3.7) and 1.7 times (95% CI:1.2–2.4) after age and body mass index (BMI) adjustment, respectively.[16] Conversely, negative associations have been proved between testosterone levels and risk of metabolic syndrome or insulin resistance.[17]

Hypogonadotropic hypogonadism and insulin resistance

Different evidences in healthy men have reported an inverse correlation between total testosterone and insulin, blood sugar and BMI.[9,12,18,19] Lower testosterone levels have also been reported in first-degree male relatives of patients with diabetes compared to healthy controls, in relation to increased insulin resistance, which in turn means higher risk of developing diabetes.[20]

The inverse correlation between total testosterone and insulin is determined by SHBG levels, which are also lower in patients with insulin resistance. Insulin is a key regulator factor on the hepatic production of SHBG. Additionally, it has been reported that men with decreased SHBG levels are at higher risk of developing metabolic syndrome.[21] *In vitro* studies have shown that insulin at physiological levels is a powerful inhibitor of SHBG production. This relationship between testosterone and insulin resistance found in healthy individuals has also been confirmed in those with diabetes. There is a significant association between HOMA-IR index with low levels of total testosterone after age and BMI adjustment. Insulin sensitivity was also associated with free testosterone levels, so that individuals with DM2 and lower levels of free testosterone had higher insulin resistance after age and BMI adjustment.[15]

Patients with DM1 are not exempt from presenting metabolic syndrome or insulin resistance. In Europe, several studies show a 30–40% prevalence of metabolic syndrome in patients with DM1.[22–24] Furthermore, the relationship between insulin resistance in patients with DM1 and chronic complications of diabetes, especially microangiopathy,[22,23,25] has been widely described. Consistent with these results and those obtained in patients with DM2, a direct association has been proved between free and overall testosterone levels and insulin sensitivity in this group of patients.[14,15]

Hypogonadotropic hypogonadism and dyslipidemia

In several studies a positive correlation has been reported between levels of total and free testosterone with HDL cholesterol and ApoA1 ($r = 0.12$; $p < 0.01$),[26] as well as a negative correlation with total cholesterol, LDL and triglycerides.[27] The Massachusetts Male Aging Study, conducted with 1661 men aged from 40 to 70 showed that the relationship between HDL cholesterol and total