www.wordlyknowledge.uz Volume: 2, Issue: 1, 2023

CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF HYPOGONADISM IN MEN WITH TYPE 2 DIABETES MELLITUS

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Annotation: Men hypogonadism is a common complication of type 2 diabetes mellitus (T2DM); therefore, it is of interest to study its clinical and epidemiological characteristics. There is no doubt that diabetes mellitus (DM) is a serious medical, socio-economic problem, which is due to its high prevalence, continuing trend towards an increase in the number of patients, chronic course, high disability and frequency of complications [1,3].

Keywords: hypogonadism, type 2 diabetes mellitus, insulin resistance, hyperinsulinemia, 3b-hydroxysteroid dehydrogenase.

Relevance. According to WHO experts, in 1989 there were 98.9 million patients worldwide with type 2 diabetes mellitus, in 2000 – 157.3 million patients. Currently, there are about 180 million people with diabetes on our planet[2,6,7]. In 2010, according to forecasts, about 215 million people with type 2 diabetes will live on our planet. Type 2 diabetes is a heterogeneous disease that develops as a result of a combination of congenital and acquired factors, in the mechanism of its development characterized by a combination of two fundamental pathophysiological defects: insulin resistance and dysfunction of pancreatic b-cells [4,5]. Type 2 diabetes usually develops in old age, after 40 years. It is also known that in men, with age, there is a gradual decrease in testosterone levels, leading to a condition such as age-related hypogonadism, defined as a biochemical syndrome that occurs in adulthood and is characterized by androgen deficiency in the blood serum, accompanied or not accompanied by a decrease in the body's sensitivity to androgens, which can lead to a significant deterioration in the quality of life and adversely affect the functions of many body systems [8,9,10]. The simultaneous occurrence of diabetes mellitus and age-related hypogonadism, accompanied by a decrease in the secretion of both total and free testosterone, has been noted in numerous studies. At the same time, many researchers have found a connection between the level of total testosterone in plasma and the development of type 2 diabetes [11,12]. Research aimed at finding possible mechanisms of the relationship between the development of carbohydrate metabolism disorders and androgen deficiency was carried out earlier, more than 10 years ago. Thus, already in the 90s of the twentieth century, works appeared indicating the possible participation of insulin in the multifactorial system of regulation of androgen secretion, on the one hand, and the influence of androgens on the action of insulin, on the other. Using a model of experimental diabetes in rats, it was found that the development of diabetes is accompanied by a decrease in the concentration of testosterone in the peripheral blood, a decrease in the number of LH receptors in Leydig cells, as well as a decrease in the functional activity of Leydig cells [13,15]. When exogenous insulin was administered to these animals, activation of 3b-hydroxysteroid dehydrogenase in Leydig cells was observed and, as a consequence, an increase in testosterone secretion. At the same time, the number of LH receptors also reached normal levels. A number of studies have found that in hypogonadism in men there is insulin resistance and hyperinsulinemia [16,17]. The TELECOM study, which examined 1292 patients, revealed a clear negative relationship between testosterone and insulin levels, which did

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not lose its significance after adjusting for weight, age, obesity, glycemic levels, alcohol consumption and smoking [16,17,18]. The 1994 long-term Massachusetts Men Aging Study (MMAS) found that low levels of free testosterone increased the risk of developing insulin resistance and type 2 diabetes, and that testosterone supplementation led to a decrease in insulin resistance [19,20]. Men with prostate cancer who underwent pharmacological castration with gonadotropin-releasing hormone agonists also experienced increased insulin levels and decreased insulin sensitivity [16,18]. The CALDIA study found that in men, type 2 diabetes was associated with lower testosterone levels, which were also negatively associated with BMI and fasting insulin concentrations. In a study of a cohort of 985 men aged 40 to 79 years, 110 of them with type 2 diabetes had significantly lower levels of total testosterone and SHBG than patients without this disease. Moreover, the statistical difference did not disappear after adjustment for age and BMI [15,19]. At the same time, the levels of estrogen and androstenedione did not have such a correlation. A major contribution came from the Massachusetts Men Aging Study, a prospective study that assessed, among other parameters, testosterone levels and the subsequent development of diabetes mellitus in men 40–70 years of age[28]. Initially, the level of total testosterone, free testosterone and SHBG was determined in 1987–1989, and after 10 years, the incidence of type 2 diabetes mellitus was assessed in patients of the study group, and risk factors for its occurrence were determined [17,23]. This study showed that low testosterone levels and low SHBG levels are predictors of the development of insulin resistance and, consequently, type 2 diabetes. The risk of developing type 2 diabetes was 1.58 for a 1 standard deviation decrease in free testosterone (4 ng/dL) and 1.89 for a 1 standard deviation decrease in SHBG (16 nmol/L) [28,30]. These data are confirmed by a study of risk factors for the development of type 2 diabetes (MRFIT study) [18,22,25]. In men with type 1 diabetes mellitus, hypogonadism is sometimes detected, the cause of which is tissue wasting that occurs against the background of decompensation of diabetes, but our experience shows that androgen secretion in this case is completely restored after compensation of diabetes [23,26]. In rare cases, hypogonadism is observed in patients in whom diabetes mellitus developed before the onset of puberty and the period of puberty occurred against the background of decompensation of diabetes mellitus. Consequently, in patients with type 1 diabetes mellitus with good metabolic control, which is only possible in the absence of a deficiency of administered insulin, there is no decrease in testosterone secretion. In type 2 diabetes mellitus, patients on oral hypoglycemic therapy always have insulin resistance or insulin deficiency, therefore, the metabolism of androgens is fundamentally different from their metabolism in patients with type 1 diabetes mellitus on insulin therapy. We believe that androgen secretion and metabolism differ depending not only on the type of diabetes, but also on the nature of the therapy received. According to our data, obtained as a result of a study of testosterone levels in men suffering from type 2 diabetes mellitus and on insulin therapy, as in patients with type 1 diabetes mellitus, there is no pronounced decrease in testosterone secretion, which is most likely due to the stimulating effect of insulin on testosterone production in Leydig cells. At the same time, all patients with type 2 diabetes mellitus receiving oral hypoglycemic therapy experienced a decrease in testosterone secretion.

Purpose of the study. Assessment of clinical and epidemiological characteristics of hypogonadism syndrome in men with T2DM.

Research methods. A continuous one-stage screening multicenter non-interventional study included men with T2DM. The study period was from November 2022 to August 2023. An anamnesis study, sexological questionnaires, determination of luteinizing hormone (LH), sex hormone binding globulin, total testosterone and glycated hemoglobin (HbA1c) in the blood were carried out. The level of free testosterone was determined by the calculation method according to Vermeullen. Group comparisons were made using the χ method with Yates'

correction, Mann–Whitney U test, and Spearman's rank correlation method. Differences were considered statistically significant at $p<0.05$.

Research results. The age of the 554 men included in the study was 55 [50; 58] years, total testosterone concentration – 12.5 [9.1; 16.4] nmol/l, free testosterone – 0.266 [0.205; 0.333] nmol/l, HbA1c – 7.2 [6.2; 8.9]%. Hypogonadism syndrome was identified in 181 men (32.7%). The concentration of total testosterone in these patients was 7.8 [6.5; 9.4] nmol/l, free – 0.182 [0.152; 0.217] nmol/l. In patients without hypogonadism, these indicators were 14.7 [12.4; 18.0] nmol/l and 0.308 [0.265; 0.362] nmol/l, respectively. For patients with hypogonadism, in most cases the LH concentration is normal, but lower - 3.3 [2.2; 4.9] U/l, compared with patients without hypogonadism – 3.8 [2.7; 4.9], $p=0.022$. Normogonadotropic hypogonadism was most often detected (89.5%). Statistically significant inverse correlations were found between the concentration of total testosterone and body mass index ($r=-0.24$; $p<0.001$), as well as waist circumference ($r=-0.21$; $p<0.001$). The prevalence of decreased libido in patients with hypogonadism (66.8%) was statistically significantly higher than that in men without hypogonadism – 56.3%, $p=0.022$.

Conclusion. The prevalence of hypogonadism syndrome in men with T2DM is 32.7%. This type of hypogonadism is characterized by normal LH levels.

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