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PARAMETERS OF GLUCOSE HOMEOSTASIS AND THEIR RELATIONSHIP WITH XANTHINE OXIDASE ACTIVITY IN PATIENTS WITH TYPE 2 DIABETES

Karachentsev Yurii
Academician of the National Academy of Medical Sciences of Ukraine, Head of the Surgical Department, State Institution "V. Danilevsky Institute for Endocrine Pathology Problems of the National Academy of Medical Sciences of Ukraine", Head of the Department of Endocrinology and Pediatric Endocrinology, Kharkiv National Medical University

Chernyaeva Anna
MD, PhD, Associate Professor, Department of Endocrinology and Pediatric Endocrinology, Kharkiv National Medical University

Mykytyuk Myroslava
MD, PhD, DSc, Professor, Deputy Director for Scientific Work, Head of the Department of Pharmacotherapy of Endocrine Diseases, State Institution "V. Danilevsky Institute for Endocrine Pathology Problems of the National Academy of Medical Sciences of Ukraine"

Worldwide, type 2 diabetes mellitus (T2DM) is a major public health challenge due to its high prevalence and increasing trend, associated morbidity and mortality, as well as huge economic burdens [1, 2]. Hyperuricemia (HU) is increasingly being considered a potential pathogenic factor for T2DM, metabolic syndrome (MetS), arterial hypertension (AG) and chronic kidney disease (CKD), as well as atherosclerosis, and several adverse consequences of vascular disease (stroke, myocardial infarction, and cardiovascular death) [3, 4]. HU is the result of increase in 16% of all mortality causes and 39% of total cardiovascular disease cases (CVD) [5].

Urina acid (UA) significantly affects all types of exchange. HU promotes the development of insulin resistance (IR), accompanied by an increase in blood glucose levels, which stimulates mental activity, ensures the formation of glycogen and lipid reserves in the body. It affects the metabolism of catecholamines, causing an increase in blood pressure, which in conditions of sodium deficiency is an important mechanism for maintaining vital processes. However, the factors that have given rise to evolution pose problems for modern man, leading to the development of AG, atherosclerosis and CKD. Accordingly, HU has been added to the IR a cluster of metabolic abnormalities that are addressed clinically as MetS.

UA metabolism is closely related to glucose and fructose metabolism and obesity [6]. However, not all studies support the association between UA and T2DM.

Xanthine oxidase (XO) is a metalloflavoenzyme that catalyzes oxidation of hypoxanthine to xanthine and then to UA. Apart from its role in UA production, XO

also generates oxidants, which are key players in the T2DM development process [7-9].

However, we still do not know if serum UA is a protective factor for the moderate oxidative stress in these situations or if it is a risk factor. Increased serum UA levels may be an indicator of up-regulated activity of XO, a powerful oxygen radical – generating system in human physiology. Increased reactive oxygen species (ROS) accumulation contributes to endothelium dysfunction, metabolic and functional impairment, inflammatory activation, and other features of cardiovascular pathophysiology [10]. Hydrogen peroxide is a ROS, the excess of which is toxic to individual cells. It also has links to aging and a multitude of conditions such as DM and neurodegenerative disorders such as Alzheimer disease [11, 12].

The study aims to determine the associations between clinical and anthropometric parameters and parameters of glucose homeostasis and serum XO activity in patients with T2DM taking into account gender, glycemic control and serum XO activity.

Material and methods. 125 T2DM patients aged 34 to 81 years, average age (58.9±9.4) years with disease duration from 1 month to 29 years, average (8.9±6.6) years were examined. The age of patients at the time of the disease manifestation (Age manif.) in the general sample was from 29 to 71 years, on average (50.6±9.1) years. According to gender, the subjects were distributed as follows: 55 men aged 34 to 77 years, average age (57.3±9.2) years with disease duration from 1 month to 25 years, on average (8.49±6.55) years, 70 women aged 43 to 81 years, average age (60.1±9.49) years with disease duration from 2 months to 29 years, average (9.25±6.59) years. Subjects received oral hypoglycemic therapy.

Anthropometric data: height (m) was measured using a medical mechanical height meter Harpenden, weight (kg) – on electronic scales Beurer GS 20 Summer Sky with a measurement accuracy of up to 100 g (maximum weight 180 kg), waist circumference (WC) (cm) was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest using a stretch-resistant tape, hip circumference (HC) (cm) was measured with a centimeter tape at the level of a large spit. Calculation of anthropometric indices: determined the ratio of WC to HC (WC/HC); body mass index (BMI) (kg/m^2) was assessed by dividing the person's weight by height squared. According to WHO, BMI of 18.5 to 24.9 kg/m2 defines normal weight, one of 25 to 29.9 kg/m^2 defines overweight and greater than or equal to 30 obesity.

We assessed glucose homeostasis according to the recommendations of the RSSDI-ESI Consensus group 2020. The level of fasting glucose (FBG) in capillary and venous blood and 2-h blood glucose (PBG) in capillary blood (mmol/L) were determined by glucose oxidase method on a Biosen C-line analyzer (EKF, Germany).

Venous blood samples were obtained from the cubital vein after 8 hours of fasting. We determined the level of fasting insulin (μmol/L) by immunochemiluminescence method, using the Insulin Elisa kit ("ELISA" DRG Diagnostics, USA). The degree of IR expression was assessed by the HOMA_IR index, the functional activity of β-cells on an empty stomach by the HOMA_β% index, faster

oral insulin sensitivity – by HOMA_S%, calculated using HOMA Calculator v2.2 for free use. The Caro index was calculated as the ratio of FBG level (mmol/l) to fasting insulin concentration (μmol/L) (normal <0.33). The QUICKI index (normal> 0.45) was calculated using an online calculator for free access.

The level of glycosylated hemoglobin (HbAc1) (%) in the blood was determined by photocolorimetric method using a commercial set of reagents JSC "Reagent" on a photoelectric photometer KFK-3.

Serum UA (μmol/L) was determined by colorimetric method using a set of reagents "Spine Lab, UricasePOD" (Ukraine). The concentration of SC in women ≤360 μmol/L, in men - ≤420μmol/L was considered normal serum UA.

Serum XO activity (nmol/min/ml) was determined by peroxidase method according to the instructions of the Xanthine Oxidase Assay Kit (Sigma-aldrich, USA). The control group consisted of 30 healthy individuals.

The results were statistically processed, using the software package STATISTICA (StatSoft, version 10.1, USA). The normality of variables distribution was determined using the Shapiro-Wilk test. One-way analysis of variance (ANOVA) was used for comparison. We used a regression analysis to determine the relationship between the studied indicators and the normal distribution of variables. Associations between dependent and independent variables were analyzed by multiple regression analysis. The results are presented in a tabular form and include such model characteristics as regression coefficient (B), standardized regression coefficient (β), and determination coefficient (R2). The null hypotheses were tested at the significance level P≤0.05. The obtained results are presented in the tables in the form of±s, where is an arithmetic mean, s – is a standard deviation.

Research results. It has been found that in the total group of examined patients with T2DM serum UA depends on serum XO activity (r =0.34; p=0.007).

This dependence is described by a linear model:

Serum UA (μmol/L) = 324.3+22.7 x serum XO activity (nmol/min/ml), where serum XO activity determines 34% variability of serum UA.

The authors have established nonlinear dependence of serum XO activity on fasting insulin concentration in patients with T2DM in the total sample, described by the multiplicative model (r=0.45; p=0.001) and represented by the equation:

Serum XO activity (nmol/min/ml)=1,5 x Fasting insulin0,27 (μmol/L)

This model shows 20.7% of the variability serum XO activity.

We have determined that serum XO activity in patients with T2DM in the general sample increases with adaptive increase in secretory activity of β-cells on an empty stomach according to the HOMA_β% index. This dependence is nonlinear, described by a reciprocal Y model (r=-0.34; p=0.021) and is represented by the equation:

Serum XO activity (nmol/min/ml) = 1/(0,37-0,001*HOMA_β%).

It has been found that the highest levels of serum XO activity are observed in patients with T2DM with low fasting insulin sensitivity (HOMA_S% <50%). This dependence is nonlinear, described by a multiplicative model (r=-0.52; p=0.00001) and is represented by the equation:

Serum XO activity (nmol/min/ml) = 9,7 x HOMA_S%-0,3.

Fasting insulin sensitivity in this model determines 22.4% variability in serum XO activity in T2DM patients.

In addition, it has been determined that the serum XO activity in the subjects is nonlinearly associated with the indices QUICKI (r=-0.35; p=0.016) and Caro (r=-0.40; p=0.007).

There were no significant gender differences in serum UA and XO activity in groups of patients with glycemic control. Indicators characterizing the state of glucose homeostasis differed significantly between the study groups and were characteristic of the state of glycemic control.

We have found a nonlinear dependence of serum XO activity on fasting insulin (r=0.50; p=0.08) and HOMA_β% index values (r=-0.53; p=0.06), HOMA_S% (r=-0.48; p=0.09), HOMA_IR (r=-0.48; p=0.09) in men with optimal glycemic control (HbAc1<7.5%) at the trend level and Caro (r=-0,64; p=0.02). In women of this group, there was a nonlinear dependence of serum XO activity on fasting insulin (r=0.56; p=0.004), values of HOMA_β% indices (r=0.56; p=0.003), HOMA_S% (r=-0,54; p=0.005), HOMA_IR (r=0.54; p=0.005), QUICKI (r=-0.50; p=0.01) and Caro (r=-0.61; p=0.003).

The authors have found a nonlinear dependence of serum XO activity on fasting insulin (r=-0.86; p=0.007), HOMA_S% index values (r=0.87); p=0.005), HOMA_IR (r=0.87; p=0.005), QUICKI (r=0.70; p<0.05) and Caro (r=0.76; p=0.03) in men with suboptimal glycemic control and high risk (HbAc1≥7.5%). In women of this group, there was a nonlinear dependence of serum XO activity on fasting insulin (r=-0.69; p=0.004), values of HOMA_β% indices (r=-0.62; p=0.039), HOMA_S% (r=0,57; p=0.005), HOMA_IR (r=-0.59; p=0.005), QUICKI (r=0.58; p=0.02) and Caro (r=0.54; p=0.03).

Analysis of the studied clinical, anthropometric parameters and indicators of glucose homeostasis in patients with T2DM in groups taking into account the level of serum XO activity showed that patients with high serum XO activity had significantly higher concentrations of fasting insulin, fasting β-cell secretory activity, low sensitivity fasting insulin and more pronounced manifestations of IR (HOMA_IR, Caro, QUICKI indices).

Thus, in the general sample of patients with T2DM serum XO activity is associated with serum UA and WC/HC (p=0.001). In patients with T2DM with optimal glycemic control, serum XO activity is determined by fasting insulin concentration (p=0.015). We determine the patient's age and HOMA_IR index (p=0.003) in patients with suboptimal glycemic control and a high risk of 52.7% variability in serum XO activity. The high serum XO activity in patients with T2DM determines the level of PBG in the blood and serum UA (p=0.001). This model determines 67.6 % variability of serum XO activity.

Conclusions:

1. In patients with T2DM, the serum UA is linearly associated with the level of serum XO activity, which determines 34% of its variability.

2. In patients with T2DM, regardless of the state of glycemic control, serum XO activity is nonlinearly associated with parameters characterizing the state of glucose homeostasis (fasting insulin, HOMA_% S, HOMA_% β, indexes QUICKI and Caro).

3. Patients with T2DM with high serum XO activity have significantly higher fasting insulin, fasting β-cell secretory activity, low fasting insulin sensitivity, and more pronounced manifestations of IR compared with patients with normal serum XO activity.

4. The level of serum XO activity in patients with T2DM, regardless of the state of glycemic control is determined by serum UA (t=2.52; p=0.02) and WC/HC (t=-2.87; p=0.007).

5. In patients with T2DM with optimal glycemic control serum XO activity determines the fasting insulin (t=2.68; p=0.015), with suboptimal glycemic control and high risk - the patient's age (t=-2.74; p=0.015) and the HOMA_IR index (t=2.62; p=0.02).

6. Predictors of high serum XO activity in patients with T2DM are the level of PBG (t=-3.53; p=0.004) and serum UA (t=4.73; p=0.0005).

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