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THE ACTIVITY OF XANTHINE OXIDASE IN PLASMA IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: THE RELATIONSHIP BETWEEN HYPERURICEMIA, INSULIN RESISTANCE, AND LIVER DYSFUNCTION*

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Hyperuricemia (HU) results from overproduction or decreased excretion of uric acid [1]. The prevalence of HU in the general population has been estimated between 19 % and 25 %, with higher in males than females in the majority of reports [2]. HU has been linked to increased risk of cardiovascular events and mortality [3], and chronic kidney disease development and progression [4]. Some previous reports showed that HU is not an independent risk, but just a surrogate marker for them [5]. Collectively, there is still controversy as to whether HU is an independent risk factor for cardiometabolic diseases.

Xanthine oxidase (XO) catalyzes the two terminal reactions of purine catabolism in humans. In particular, XO catalyzes the oxidation from hypoxanthine to xanthine and from xanthine to uric acid, with the simultaneous reduction of nicotinamide adenine dinucleotide (NAD) or O_2. Therefore, XO is the housekeeping and the rate-limiting enzyme in purine catabolism. The serum levels of uric acid (SUA) are kept at a healthy level [6], mainly thanks to the homeostatic regulation involving the renal transport systems.

It was reported that the plasma XO activity in the vasculature is elevated considerably in patients with coronary artery diseases [7]. It showed that the value of plasma XO activity is associated with cardiovascular events and its future risk in patients with chronic heart failure [8]. It has also been suggested that local XO activities in a variety of organs and tissues

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are likely to elevate under a line of stimuli including hypoxia, inflammatory cytokines, and glucocorticoids [9]. Therefore, there is a possibility that local XO activities in a variety of organs or tissues would be elevated in patients with type 2 DM. However, little is known about plasma XO activities in the pathophysiology of insulin resistance (IR) and obesity in humans.

We aimed to investigate the clinical implication of plasma XO activity in patients with type 2 diabetes mellitus (DM).

MATERIALS AND METHODS

127 patients were examined for type 2 DM (72 female and 55 male). The study was conducted by the Helsinki Declaration (196) and revised in 2000), approved by the Ethics Committee of the SI «V. Danilevsky Institute for Endocrine Pathology Problems of the NAMS of Ukraine». Each patient gave informed consent.

The clinical characteristics of patients with type 2 DM (n = 127) in analyses of plasma XO activity about metabolic parameters are summarized in Table 1. The numbers of patients who had used antidiabetic drugs were 21 sulfonylureas, 18 — dipeptidyl peptidase-4 inhibitors, 44 — metformin, and 38 — sodium-glucose cotransporter 2 inhibitors.

Table 1

Clinical characteristics of the patients with type 2 diabetes mellitus

n, male/female	55/72
Age, years	58.7 ± 9.7 (30–81)
Duration of disease, years	9.3 ± 7.7 (0,1–53)
WC male, cm	106.5 ± 14.0 (74.0–139.0)
WC female, cm	104.9 ± 15.9 (56.0–132.0)
BMI, kg/m^2	33.2 ± 5.5 (23.7–54.1)
FPG, mmol/L	8.4 ± 2.6 (3.9–17.4)
PPG, mmol/L	9.3 ± 2.8 (3.7–20.8)
HbA_{1c}, %	7.55 ± 1.86 (4.5–14.3)
IRI, μIU/ml	20.6 ± 12.9 (2.8–55.8)
C-peptide, ng/ml	3.47 ± 1.86 (0.2–9.0)
HOMA_IR	7.49 ± 4.93 (0.58–21.35)
AST, IU/L	0.56 (0.1–4.73)
ALT, IU/L	0.67 (0.1–5.12)
ALT/AST	1.35 ± 0.84 (0.21–5.64)
Cre, μmol/L	89.6 ± 20.3 (14.7–158.0)
eGFR, ml/min/1,73 m^2	65.6 ± 36.6 (40–138)
TC, mmol/L	5.44 ± 1.44 (2.69–9.83)
HDL-C, mmol/L	1.1 ± 0.3 (0.56–2.15)
TG, mmol/L	2.44 ± 1.15 (0.48–9.41)
LDL-C, mmol/L	3.25 ± 1.23 (0.43–7.88)
SUA, male + female, μmol/L	390.6 ± 112.6 (141–724)
SUA, female, μmol/L	378.2 ± 117.0 (141–724)
SUA, male, μmol/L	407.6 ± 105.1 (218–624)
XO activity, male + female, nmol/min/ml	3.34 (1.7–7.95)
XO activity, female, nmol/min/ml	3.41 (1.7–7.67)
XO activity, male, nmol/min/ml	3.27 (1.85–7.95)

Note:
Data are expressed as mean ± standard deviation (range) for normally distributed values and median (range) for non-normally distributed values. WC, waist circumference; BMI, body mass index; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; HbA_{1c}, glycated hemoglobin; IRI, immunoreactive insulin; HOMA-IR, homeostatic model assessment for insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Cre, creatinine; eGFR, estimated glomerular filtration rate; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; serum level of uric acid, SUA; XO, xanthine oxidase.

Table 2

The plasma xanthine oxidase activity (nmol/min/ml) in the control group

Indicator	Average ($\bar{X} \pm s\bar{X}$)	Reference interval	P
The plasma XO activity (male)	2.51 ± 0.29	1.79–3.40	P < 0.001
The plasma XO activity (female)	2.50 ± 0.19	1.69–3.31	P < 0.001

Waist circumference (WC) was measured with an inelastic tape to the nearest 0.1 cm at a midpoint between the bottom of the rib cage and the top of the iliac crest, following exhalation. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m).

Glucose homeostasis was assessed according to the recommendations of RSSDI-ESI Consensus group 2020 [10].

Following an overnight fast, blood was collected by venipuncture and tested immediately for fasting plasma glucose (FPG) and glycohemoglobin A_{1c} (HbA_{1c}). Serum biochemical variables including postprandial plasma glucose (PPG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine (Cre) and SAU were measured with a conventional automated analyzer. In the present study, males with SUA≥420 μmol/l and females with SUA≥360 μmol/l were defined as HU [11]. The level of fasting insulin (IRI) was determined by the immuno-chemiluminescent method («ELISA» DRG Diagnostics, USA). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the formula: HOMA-IR = IRI, μmol/L × FPG, mmol/L/22.5.

The plasma XO activity was determined by a photometric method based on the principle of «sandwich» immunoassay by the instructions of the «Xanthine Oxidase Assay Kit» test system (Sigma-Aldrich, USA).

The control group was 30 practically healthy people. The obtained results are presented in nmol/min/ml. There were no statistically significant differences between the main and control groups by demographic characteristics (Table 2).

According to the recommendations of Kidney Disease Improving Global Outcomes (KDIGO) experts on the diagnosis and treatment of chronic kidney disease, the rate of glomerular filtration (eGFR) was calculated according to CKD-EPI formulas [12].

Statistical analysis. All statistical analyses were performed using STATISTICA software version 10.0. Continuous variables in the present study were presented as $\bar{X} \pm$ SD (Min-Max), and Me (Min-Max). Statistical calculations for significant differences were carried out using Spearman's rank correlation coefficient. To explore possible independent factors for directly influencing the plasma XO activity in patients with type 2 DM, we carried out multiple regression analyses. As serum values of AST, ALT, and plasma XO activity did not show a normal distribution, they were converted logarithmically (lnAST, lnALT, and lnXO activity in plasma). Significance was accepted at P< 0,05.

RESULTS AND THEIR DISCUSSION

The presence of a correlation between plasma lnXO activity and SUA (r_s = – 0.28; P = 0.03).

The plasma lnXO activity was correlated with fasting IRI (r_s = 0.52; P < 0.001) and HOMA-IR (r_s = 0.51; P < 0.002). In addition, the plasma lnXO activity was correlated with BMI (r_s = 0.40; P < 0.001). In contrast, lnXO activity was not correlated with age (r_s = – 0.07; P = 0.61), duration of disease (r_s = 0.09; P = 0.53), HbA_{1c} (r_s = – 0.11; P = 0.41), FPG (r_s = – 0.4; P = 0.74) and PPG (r_s = – 0.09; P = 0.57).

Plasma lnXO activity and indices of liver dysfunction and parameters closely related to SUA level in patients with type 2 DM: plasma lnXO activity was correlated with lnALT (r_s = 0.73; P < 0.001), lnAST (r_s = 0.69; P < 0.001), ALT/AST (r_s = 0.85; P < 0.001), Cre (r_s = – 0.15; P = 0.46) and eGFR (r_s = 0.13;

Table 3

Multiple regression analysis with the plasma lnXO activity as a dependent variable and metabolic parameters as explanatory variables

Variable		B	β	t	P
dependent	**independent**				
lnXO activity (plasma)	Model 1				
	BMI, kg/m^2	0.001	0.0008	2.36	0.04
	ALT, IU/L	0.02	0.006	3.65	0.004
	Model 2				
	BMI, kg/m^2	– 0.04	0.011	– 3.66	0.006
	ALT, IU/L	0.002	0.0007	3.35	0.01
	Model 3				
	BMI, kg/m^2	– 0.41	0.011	– 3.66	0.006
	HOMA-IR	0.002	0.001	3.35	0.01

$P = 0.34$), both of which are known to be associated with SUA in patients with chronic kidney diseases.

In a series of multiple regression analyses, plasma lnXO activity was used as a dependent variable, and age, BMI, HbA_{1c}, SUA, eGFR, lnAST, lnALT, IRI, and HOMA-IR as explanatory variables were carried out. In all the models developed, plasma lnXO activity was included as a dependent variable, and age, BMI, HbA_{1c}, SUA, and eGFR as common explanatory variables. We then carried out analyses by using lnAST, lnALT, and IRI as independent variables (Model 1) and lnAST, lnALT, and HOMA-IR as independent variables (Model 2), as well as HOMA-IR as an independent variable (Model 3) (Table 3).

When used as explanatory variables, the value of lnALT (Model 1) was an independent strong factor for determining plasma XO activity ($R^2 = 95.3$ %; $P < 0.00001$). When used as explanatory variables, the value of lnALT (Model 2) was also an independent strong factor for determining the plasma XO activty ($R^2 = 97.2$ %; $P < 0.00001$).

When used as explanatory variables without AST and ALT, the value of HOMA-IR was an independent factor for determining the plasma XO activity (Model 3) ($R^2 = 97.3$ %; $P < 0.00001$). These data suggest that the values of ALT and HOMA-IR, a clinical marker for hepatic IR, might be independent factors for directly influencing the plasma XO activity in patients with type 2 DM.

The major finding of the present study was that the value of the plasma XO activity was significantly correlated with indices of IR and liver dysfunction in a small number of Japanese patients with type 2 DM [13]. At the same time, some authors point to the lack of an association between HU and indices of IR.

Several epidemiological studies have demonstrated that patients with non-alcoholic fatty liver disease (NAFLD) have significantly higher SUA levels relative to controls, and elevated SUA levels are an independent risk factor for NAFLD [14, 15]. Notably, SUA itself has been reported to promote *de novo* lipogenesis and induce IR [16, 17]. These observations indicate that HU plays a causative role in the development of NAFLD; it is not merely a consequence of this liver disease.

It is widely accepted that hyperinsulinemia followed by systemic IR causes elevation of SUA levels through enhancement of renal proximal tubular sodium reabsorption [18]. Furthermore, IR in the liver, commonly seen in type 2 DM alternatively activates the pentose phosphate pathway, resulting in the activation of a *de novo* synthesis pathway of SUA [19]. Importantly, the level of SUA is influenced by a variety of factors, including dehydration, purine' or fructose-rich foods, alcohol, and urinary sugar-associated excretion of urate [21]. In this context, it might be critical to identify patients showing normal levels of SUA with higher activity of XO, thereby uncovering hidden risks for type 2 DM.

CONCLUSIONS

1. The value of plasma xanthine oxidase activity was significantly correlated with indices of insulin resistance and liver dysfunction in patients with type 2 diabetes mellitus.
2. The values of alanine aminotransferase and homeostatic model assessment for insulin resistance (HOMA-IR) index, a clinical marker for hepatic insulin resistance, might be independent factors for directly influencing the plasma xanthine oxidase activity in patients with type 2 diabetes mellitus.

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THE ACTIVITY OF XANTHINE OXIDASE IN PLASMA IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: THE RELATIONSHIP BETWEEN HYPERURICEMIA, INSULIN RESISTANCE, AND LIVER DYSFUNCTION

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We aimed to investigate the clinical implication of plasma xanthine oxidase (XO) activity in patients with type 2 diabetes mellitus (DM).

Materials and methods. 127 patients were examined for type 2 DM (72 female and 55 male). Serum biochemical variables include aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting (FPG) and postprandial (PPG) plasma glucose, glycohemoglobin A_{1c} (HbA_{1c}), total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine (Cre) and serum urine acid (SUA) was measured with a conventional automated analyzer. The level of fasting insulin (IRI) was determined by the immuno-chemiluminescent method. Homeostasis model assessment of insulin resistance (IR) (HOMA-IR) index was calculated by the formula: HOMA-IR = fasting insulin (μmol/L) × FPG(mmol/L) / 22.5. The plasma XO activity was determined by a photometric method. The rate of glomerular filtration (eGFR) was calculated according to CKD-EPI formulas. All statistical analyses were performed using STATISTICA software version 10.0.

Results and their discussion. The plasma lnXO activity was correlated with IRI ($r_s = 0.52$; $P < 0.001$) and HOMA-IR ($r_s = 0.51$; $P < 0.002$). In addition, the plasma lnXO activity was correlated with BMI ($r_s = 0.40$;

$P < 0.001$). In contrast, plasma lnXO activity was not correlated with age ($r_s = -0.07$; $P = 0.61$), HbA_{1c} ($r_s = -0.11$; $P = 0.41$), FPG ($r_s = -0,4$; $P = 0.74$) and PPG ($r_s = -0.09$; P = 0.57). lnXO activity and indices of liver dysfunction or parameters closely related to SUA level in patients with type 2 DM: lnALT ($r_s = 0.73$; $P < 0.001$), lnAST ($r_s = 0.69$; $P < 0.001$), ALT/AST ($r_s = 0.85$; $P < 0.001$). The plasma lnXO activity was correlated with Cre ($r_s = -0.15$; $P = 0.46$) and eGFR ($r_s = 0.13$; $P = 0.34$). In a series of multiple regression analyses, plasma lnXO activity was used as a dependent variable, and age, BMI, HbA_{1c}, SUA, eGFR, lnAST, lnALT, IRI, and HOMA-IR as explanatory variables were carried out. When used as explanatory variables, the value of lnALT (Model 1) was an independent strong factor for determining plasma XO activity ($R^2 = 95.3$ %; $P < 0.00001$). When used as explanatory variables, the value of lnALT (Model 2) was also an independent strong factor for determining the plasma XO activity ($R^2 = 97.2$ %; $P < 0.00001$). When used as explanatory variables without parameters for liver functions, the value of HOMA-IR was an independent factor for determining the plasma XO activity (Model 3) ($R^2 = 97.3$ %; $P < 0.00001$). These data suggest that the values of ALT and HOMA-IR, a clinical marker for hepatic IR, might be independent factors for directly influencing the plasma XO activity in patients with type 2 DM.

Conclusions. The value of plasma xanthine oxidase activity was significantly correlated with indices of insulin resistance and liver dysfunction in patients with type 2 diabetes mellitus. The values of alanine aminotransferase and homeostatic model assessment for insulin resistance (HOMA-IR), a clinical marker for hepatic insulin resistance, might be independent factors for directly influencing the plasma xanthine oxidase activity in patients with type 2 diabetes mellitus.

Keywords: xanthine oxidase activity, type 2 diabetes mellitus, insulin resistance, liver dysfunction.

АКТИВНІСТЬ КСАНТИНОКСИДАЗИ В ПЛАЗМІ КРОВІ У ПАЦІЄНТІВ З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ: ЗВ'ЯЗОК МІЖ ГІПЕРУРИКЕМІЄЮ, ІНСУЛІНОРЕЗИСТЕНТНІСТЮ ТА ДИСФУНКЦІЄЮ ПЕЧІНКИ

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Мета дослідження — з'ясувати клінічне значення активності ксантиноксидази (ХО) у плазмі крові у пацієнтів з цукровим діабетом (ЦД) 2 типу.

Матеріали та методи. Обстежено 127 пацієнтів з ЦД 2 типу (72 жінки та 55 чоловіків). Досліджували біохімічні параметри крові: рівень аспартатамінотрансферази (АСТ), аланінамінотрансферази (АЛТ), глюкози плазми натщесерце (ГН) і постпрандіальний рівень глюкази (ППГ), глікогемоглобін A_{1c} (HbA_{1c}), загальний холестерин, тригліцериди, холестерин ліпопротеїнів високої щільності, холестерин ліпопротеїнів низької щільності, креатинін (Кр) і сечову кислоту (СК). Рівень інсуліну (IPI) натще визначали імуно-хемілюмінесцентним методом. Індекс інсулінорезистентності (IP) (HOMA-IR) розраховували за формулою: HOMA-IR = (IPI, мкмоль/л × ГН, ммоль/л) / 22.5. Активність ХО плазми визначали фотометричним методом. Швидкість клубочкової фільтрації (рШКФ) розраховувалася за формулами CKD-EPI. Статистичний аналіз проводили за допомогою пакету програм STATISTICA версії 10.0.

Результати та їх обговорення. Встановлено, що рівень активності lnXO в плазмі корелює з IPI ($r_s = 0.52$; $P < 0.001$), індексом HOMA-IR ($r_s = 0.51$; $P < 0.002$) та ІМТ ($r_s = 0.40$; $P < 0.001$). Доведено відсутність кореляції активності lnXO в плазмі з віком ($r_s = -0.07$; $P = 0.61$), HbA_{1c} ($r_s = -0.11$; $P = 0.41$), ГН ($r_s = -0.4$; $P = 0.74$) и ППГ ($r_s = -0.09$; $P = 0.57$). Встановлено наявність кореляції між активністю lnXO плазми з маркерами дисфункції печінки (АСТ, АЛТ) та параметрами, тісно пов'язаними з метаболізмом СК у пацієнтів з ЦД 2 типу: lnАЛТ ($r_s = 0.73$; $P < 0.001$), lnАСТ ($r_s = 0.69$; $P < 0.001$), АЛТ/АСТ ($r_s = 0.85$; $P < 0.001$). Активність lnXO в плазмі корелювала з Кр ($r_s = -0.15$; $P = 0.46$) та рШКФ ($r_s = 0.13$; $P = 0.34$).

Для оцінки зв'язку між активністю ХО в плазмі з досліджуваними метаболічними показниками використовували багатофакторний регресійний аналіз, де активність ХО в плазмі визначали як залежну змінну, а вік, ІМТ, HbA_{1c}, СК, рШКФ, lnАСТ, lnАЛТ, IPI та HOMA-IR як незалежні змінні. Визначено, що рівень АЛТ є фактором, що визначає активність ХО плазми ($R^2 = 95.3$ %; $P < 0.00001$). При виключенні з аналізу АСТ і АЛТ активність ХО в плазмі визначає індекс HOMA-IR ($R^2 = 97.3$ %; $P < 0.00001$). Отримані дані визначають значення АЛТ та HOMA-IR як клінічних маркерів, що впливають на активність ХО в плазмі у хворих на ЦД 2 типу.

Висновки. У хворих на цукровий діабет 2 типу активність ксантиноксидази в плазми крові корелює з показниками інсулінорезистентності та дисфункції печінки. Рівень аланінамінотрансферази та значення індексу HOMA-IR є клінічними маркерами, що визначають активність ксантиноксидази в плазмі крові у хворих на цукровий діабет 2 типу.

Ключові слова: активність ксантиноксидази в плазмі, цукровий діабет 2 типу, інсулінорезистентність, дисфункція печінки.