EFFECT OF LEPTIN LEP-2548G > A (rs7799039) AND LEPTIN RECEPTOR LEPR 223Q > R (rs1137101) GENE POLYMORPHIC VARIANTS ON THE DEVELOPMENT OF CARDIOVASCULAR COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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The search for functional single-nucleotide polymorphisms (SNPs) of genes that affect the risk of obesity, type 2 diabetes mellitus, and associated vascular complications development is actively ongoing. The aim of the study: to evaluate the effect of the leptin *LEP-2548G/A* and the leptin receptor *LEPR 223Q/R* gene SNPs on the risk of cardiovascular complications development in patients with type 2 diabetes mellitus in the Eastern Ukrainian population over time.

Materials and methods. Type 2 diabetic (T2D) patients at the initial examination and 10 years later were evaluated. During this time, 5 non-fatal heart attacks and 16 deaths due to cardiovascular disease were registered in the study group (n = 60). At baseline, 60 T2D patients (F/M: 26/34) aged 53.35 ± 1.38 yrs, duration of diabetes 5.33 ± 0.67 yrs, with a HbA1c 7.74 ± 0.19%, body mass index 33.28 ± 0.89 kg/m^2, waist-to-hip ratio 0.99 ± 0.01 were examined. Genotyping was performed by polymerase chain reaction and restriction fragment length polymorphism using appropriate primers (*LEP 2548G/A*: forward: tcccatgagaactattctttttttg; reverse: atatggctccctttgcccgacc; *LEPR 223Q/R*: forward: acctctggttccccaaaag; reverse: tcatcattttagtgcataacttaccc) and endonucleases (HhaI and MspI, respectively). Restriction products were analyzed by electrophoresis in a 2% agarose gel. pUC19 DNA hydrolyzed by MspI endonuclease (MBI Fermentas, Lithuania) was used as a molecular weight marker. Unpaired two-tailed Student's t-test, Mann-Whitney test and χ^2-test were used; probability (P) value of 5% or less was considered statistically significant.

Results. It was determined that SNP *LEP -2548G/A* significantly affects the development of cardiovascular complications in T2D patients in the Eastern Ukrainian population, namely, the *A*-allele is associated with an increased risk of heart failure in women and heart failure and coronary heart disease in men. The presence of a heterozygous genotype for the *LEPR 223Q/R* polymorphism is associated with a lower risk of heart failure development in T2D men in the Eastern Ukrainian population. Minor genotypes, namely, *AA* by the *LEP -2548G/A* polymorphism and *RR* by the *LEPR 223Q/R* polymorphism, significantly increase in the risk of mortality related to cardiovascular events (OR (*AA*) = 21.00; CI 3.75-117.76, P < 0.05; OR (*RR*) = 5.00; CI 1.343–18.62, P < 0.05, respectively).

Conclusions. The functional significance of single-nucleotide polymorphisms *LEP -2548G/A* and *LEPR 223Q/R* in relation to the development of cardiovascular complications in patients with type 2 diabetes mellitus in the Eastern Ukrainian population has been proven. Data on the studied polymorphic variants of the leptin and leptin receptor genes can be used to form risk groups and be taken into account when choosing effective preventive and therapeutic strategies.

Keywords: type 2 diabetes mellitus, cardiovascular complications, leptin, leptin receptor, single nucleotide polymorphisms.

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HYPOURICEMIC EFFECT OF METFORMIN IN GOUT PATIENTS WITH TYPE 2 DIABETES*

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Gout is a common form of inflammatory arthritis, with an age-standardized global prevalence of 0.08 %, and is higher in developed countries [1]. Gout is a crystal-deposition disease resulting from chronic elevation of serum uric acid (SUA) above the saturation point for monosodium urate. SUA is an independent risk factor for insulin resistance (IR), cardiovascular disease, metabolic-associated liver disease, type 2 diabetes mellitus (T2DM), metabolic syndrome (MS), and atherosclerosis [2, 3]. Drug treatment of gout focuses on treating acute gout flares with anti-inflammatory drugs and reducing SUA levels with urate-lowering therapy [4].

Treatment of gout and T2DM is strategically similar: with gout, the goal is to achieve a normal SUA level, with T2DM — normalization of glycemia, a frequent combination of these metabolic diseases requires taking into account the effect of drug therapy on concomitant diseases. For example, allopurinol and febuxostat protected rats from fructose-induced hyperinsulinemia and other manifestations of MS [5, 6]. It is important to study the pleiotropic effects that cause the possibility of the effect of hypoglycemic drugs on urate metabolism and crystal-induced inflammation. Among such substances, metformin (Met) stands out, various not related to the direct impact on the level of glycemia which predetermines wider possibilities of using the drug, including a number in gout patients.

Met, a first-line therapeutic agent for the treatment of T2DM, is a biguanide synthetically derived from glucose-lowering herbal medicines. Although its efficacy and safety in T2DM have been known for decades, the molecular mechanisms of Met remain under investigation. Studies have found that multiple modes

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of action are involved in the glucose-lowering effect of Met [7]. As Met regulates cell metabolism, proliferation, growth, and autophagy, it might have disease-modifying effects in various other conditions. Met has shown therapeutic benefits in obesity, aging, cardiovascular diseases, liver diseases, renal diseases, and cancers [8]. Based on these findings, Met may represent a suitable treatment for gout, even considering that biguanide seems to lower SUA levels via a not proven interference with the purine pathway [9].

As compared to the current drugs used in gout treatment, Met has the potential advantage of targeting multiple aspects of the disease. That is, it inhibits inflammation, reduces hyperuricemia, and decreases the high cardiovascular and metabolic risk characteristic of gout patients [10].

The aim of the study is to investigate the effect of metformin on serum urine acid levels in gout patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

A retrospective analysis of medical records was carried out on 208 patients ≥ 18 years with a diagnosis of gout and at least one year of follow-up treatment in the rheumatology department of the city hospital No. 28 (Kharkiv). All patients included in the study had T2DM. The survey was divided into 2 groups: Met group (n = 107) — gout patients who received Met and control group 2 (n = 101) — gout patients who received other peroral hypoglycemic therapy. The age of patients in the Met group — Me was 60 (58.72 ± 9.73); in the control group – Me 61 (60.9 ± 9.4), respectively. Patients received Met at a daily dose of 1000–2500 mg.

Demographic information and lifestyle risk factors were gathered from standard questionnaires. Drinking and smoking status was divided into never drinking/smoking and past or current drinking/smoking.

Waist circumference (WC) was measured at the level of 1 cm above the umbilicus. Weight and height were measured with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (meters).

Systolic and diastolic blood pressure was measured three times with a sphygmomanometer. The mean of the three records was used in the analysis.

Following an overnight fast, blood was collected by venipuncture and tested immediately for glucose and glycohemoglobin A_{1c} (HbA_{1c}). Fasting plasma levels of glucose (FPG), serum creatinine, and SUA levels were measured by a biochemical autoanalyzer. The level of 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:

$$\text{HOMA-IR} = \text{fasting insulin (μmol/L)} \times \times \text{FPG (mmol/L)} / 22.5$$

(*Matthews et al. 1985*).

Kidney function was assessed by serum creatinine measurement. Glomerular filtration rate (eGFR) was estimated for each patient using a standardized serum creatinine assay and the Chronic Kidney Disease Epidemiology Collaboration formula estimation by using serum creatinine value [11]. Chronic kidney disease (CKD) was defined as low eGFR (i.e. < 60 ml/min / 1.73 m^2).

To evaluate the SUA lowering effect of Met, we assessed SUA levels at baseline, SUA change over one year, the proportion of patients who reached the SUA target within one year, and the dose of allopurinol at the SUA target. The incidence of gout flares during the one year of starting urate-lowering therapy was calculated by attributing the number of flares reported during a consultation to the time since the last consultation.

Data analyses were performed using STATISTICA software version 10.0. $P < 0.05$ was considered statistically significant. Continuous variables in the present study were presented as mean ± standard deviation and medians (Me) [interquartile range]. Categorical variables were expressed as a percentage (%). Comparisons were conducted using one-way analysis of variance (ANOVA) tests for continuous variables, and chi-square tests for categorical variables.

Table 1

Baseline clinical and biochemistry parameters of the studied groups

Parameter	Metformin group (n = 107)	Control group (n = 101)	P value
Age, years	60 (58.7 ± 9.7)	61 (60.9 ± 9.4)	0.02
BMI, kg/m^2	33.2 ± 6.8	33.7 ± 6.2	0.10
WC, cm	105.8 ± 16.3	105.4 ± 15.7	0.89
FPG, mmol/L	7.9 ± 1.9	7.2 ± 1.8	0,54
HbA_{1c}, %	7.7 ± 1.7	7.7 ± 1.9	0,79
IRI, µmol/L	28.1 ± 11.3	26.3 ± 14.2	0.81
HOMA-IR	3.5 ± 1.5	3.4 ± 1.8	0.86
SUA, µmol/L	468.9 ± 61.9	480.9 ± 71.8	0.68
eGFR, ml/min/1.73 m^2	Me 60 [50–70]	Me 50 [44–66]	0.005
CKD, %	26.2	47.1	0.003
Monoarticular disease (1 joint), %	20.6	16.8	0.72
Oligoarticular disease (2-4 joints), %	47.6	49.5	0.78
Polyarticular disease (> 4 joints), %	31.8	33.7	0.76
Alcohol use, %	44.9	47.7	0.67
Arterial hypertension, %	65.4	62.6	0.77
Kidney stones, %	3.7	4.7	0.73

Notes:
BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; HbA1c, glycohemoglobinA1c; IRI, insulin; HOMA-IR, homeostatic model assessment of insulin resistance; SUA, serum uric acid; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

RESULTS AND THEIR DISCUSSION

Analysis of the baseline parameters in the groups of gout patients showed that Met users were somewhat younger and had better renal function compared to non-Met users (Table 1). Mean SUA levels at baseline in the groups were (468.9 ± 61.9) and (480.9 ± 71.8) µmol/L, respectively. The vast majority of patients in both groups had more than two joints affected (79.4 and 83.2%, respectively). The drug of the choice to start urate-lowering therapy in most cases was allopurinol (98.1 and 98.0%, respectively). Febuxostat was used in 1.9 and 2.0%, respectively).

After one year, gout patients in the Met group showed a significant decrease in SUA levels from (468.9 ± 61.9) to (318.7 ± 44.9) µmol/L ($P < 0.0001$). Within one year, 63.6 % of the Met group had reached target SUA levels (< 360.0 µmol/L) compared to 47.5 % in the control group ($P < 0.023$).

The achievement of a significant decrease in IRI fasting blood (from 28.1 [12.8; 49.2] to 19.1 [11.5; 45.8] µmol/L ($P < 0.01$), the HOMA-IR (from 3.5 [1.7; 9.1] to 2.8 [1.4; 9.2] ($P < 0.01$) in patients Met group. At the same time, the hypouricemic effect of Met is not associated with a decrease in blood pressure and weight loss.

Retrospective analysis of gout patients using Met compared to patients in the control group, showed that the use of a combination of Met + allopurinol was significantly associated with a lower incidence of gout attacks ($P < 0.01$). The mean incidence of gout attacks was 2.02 per year (95% CI (1.28–2.36)) in the Met group and 4.00 per year (95 % CI (2.56–5.42)) in the control group.

The mean daily dosages of allopurinol at target for the Met group and control group

did not differ significantly and amounted to (258 ± 120) and (246 ± 110) mg, respectively.

In a large retrospective case-control study in T2DM patients, increased A_{1C} levels but not the use of antidiabetic drugs, lowered the risk of incident gout [12]. However, concerning insulin and sulfonylureas, Met appeared to lower the adjusted odd ratio, even despite the lack of a consistent association with the duration of therapy. The small prospective study (n = 30) was to evaluate the results of Met therapy during 1 year of SUA metabolism and the clinical course of gout with IR. The study showed that Met therapy resulted in a decrease in SUA, insulin, and the degree of IR. The hypouricemic effect of Met was unrelated to renal SUA excretion, and body weight. The authors hypothesize that Met reduces the production of SUA in patients' tissue due to that inhibits the synthesis of free fatty acids [9].

A small retrospective study found that T2DM gout patients who used Met and allopurinol had a significantly lower number of gout attacks, compared to diabetic gout patients who used allopurinol alone [13].

At the same time, F. Veenstra, L.M. Verhoef, M. Opdam et al. did note observing a relevant anti-inflammatory or SUA lowering effect of Met during the first six months after starting urate-lowering therapy in a real-world setting [14]. The authors note that although these effects of Met are supported by pharmacological and empirical evidence, several contextual factors can lead to a null effect when treating gout patients in a real-world setting.

Met may be notably beneficial for long-term treatment regimens as it is an old and widely used drug, with two precious qualities: low cost and excellent safety profile. Met is not likely to cause hypoglycemia when used as a monotherapy, and common adverse effects are relatively mild and mainly represented by gastrointestinal intolerance. A more serious but very rare adverse effect is lactic acidosis, usually determined by drug misuse [15]. At any rate, a large proportion of rheumatologic patients can currently benefit from the drug, e.g., those with concomitant obesity and T2DM, two conditions strongly associated with gout.

CONCLUSIONS

The use of a combination of metformin + urate-lowering therapy (allopurinol) in gout patients with type 2 diabetes mellitus allows to achieve the target level of serum uric acid (< 360 μmol/L) in 64 % of patients; helps to reduce the severity of insulin resistance and significantly associated with a lower incidence of gout attacks.

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HYPOURICEMIC EFFECT OF METFORMIN IN GOUT PATIENTS WITH TYPE 2 DIABETES

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Treatment of gout and type 2 diabetes mellitus (T2DM) is strategically similar: with gout, the goal is to achieve a normal serum urine acid (SUA) level (< 360 µmol/L), with T2DM — normalization of glycemia, a frequent combination of these metabolic diseases requires taking into account the effect of drug therapy on concomitant diseases. As compared to the current drugs used in gout treatment, metformin (Met) has the potential advantage of targeting multiple aspects of the disease. The study **aims** to investigate the effect of Met on SUA levels in gout patients with T2DM.

Materials and methods. A retrospective analysis of medical records was carried out on 208 gout patients with T2DM ≥ 18 years with at least one year of follow-up treatment in the rheumatology department. The survey was divided into 2 groups: Met group (n = 107) — gout patients received Met (1000–2500 mg/daily) and control group (n = 101) — gout patients received other peroral hypoglycemic therapy.

Results. Analysis of the baseline parameters in the groups of gout patients showed that Met users were somewhat younger (60 (58.72 ± 9.73) and 61 (60.9 ± 9.4), respectively) (P < 0.02) and had better renal function ((Me 60 [50–70] and 50 [44–66], respectively) (P < 0,005) compared to non-Met users. The vast majority of patients in both groups had more than two joints affected (79.4 and 83.2 %, respectively). The drug of the choice to start urate-lowering therapy in most cases was allopurinol (98.1 and 98.0 %, respectively). After one year, gout patients in the Met group showed a significant decrease in SUA levels from (468.9 ± 61.9) to (318.7 ± 44.9) µmol/L (P < 0.0001). Within one year, 63.6 % of the Met group had reached target SUA levels compared to 47.5 % in the control group (P < 0.023). The achievement of a significant decrease in fasting blood IRI (from 28.1 [12.8; 49.2] to 19.1 [11.5; 45.8] µmol/L (P < 0.01), the HOMA-IR (from 3.5 [1.7; 9.1] to 2.8 [1.4; 9.2] (P < 0.01) in patients Met group. The mean incidence of gout attacks was 2.02 per year (95 % CI (1.28–2.36)) in the Met group and 4.00 per year (95% CI (2.56–5.42)) in the control group (P < 0.01). The mean daily dosages of allopurinol at target for the Met group and control group did not differ significantly and amounted to (258 ± 120) and (246 ± 110) mg, respectively.

Conclusions: The use of a combination of metformin plus urate-lowering therapy (allopurinol) in gout patients with type 2 diabetes mellitus allows to achieve the target of serum urine acid level in 64 % of patients; helps to reduce the severity of insulin resistance and significantly associated with a lower incidence of gout attacks.

Keywords: gout, type 2 diabetes mellitus, urate-lowering therapy, metformin.

ГІПОУРИКЕМІЧНИЙ ЕФЕКТ МЕТФОРМІНА У ХВОРИХ НА ПОДАГРУ І ЦУКРОВИЙ ДІАБЕТ 2 ТИПУ

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Лікування подагри і цукрового діабету (ЦД) 2 типу стратегічно схоже: при подагрі метою лікування є досягнення цільового сироваткового рівня сечової кислоти (СК) (< 360 мкмоль/л), при ЦД 2 типу — нормалізація глікемії. Часте поєднання цих метаболічних захворювань вимагає врахування впливу медикаментозної терапії на супутні захворювання. Серед сучасних препаратів, що використовуються для лікування подагри, метформін (Мет) має потенційну перевагу. Мета дослідження — з'ясувати вплив метформіну на сироватковий рівень сечової кислоти у хворих на подагру з цукровим діабетом 2 типу.

Матеріали та методи. Проведено ретроспективний аналіз медичної документації 208 хворих на подагру з ЦД 2 типу старше 18 років зі строком спостереження у ревматологічному відділенні не менше одного року. Досліджуваних було поділено на дві групи: група Мет (n = 107) — хворі на подагру, які отримували лікування Мет (1000–2500 мг/добу) та контрольну групу (n = 101) — хворі на подагру, які отримували іншу пероральну цукрознижуючу терапію.

Результати. Аналіз досліджуваних вихідних параметрів у групах показав, що хворі групи Мет були дещо молодшими (60 (58,72 ± 9,73) та 61 (60,9 ± 9,4), відповідно) (P < 0,02) та мали кращу ниркову функцію (Me 60 [50–70] та 50 [44–66], відповідно) (P < 0,005) порівняно з групою контролю. Вихідні середні сироваткові рівні СК в досліджуваних групах становили (468,9 ± 61,9) і (480,9 ± 71,8) мкмоль/л, відповідно (P < 0,68). У переважної більшості пацієнтів в обох групах були уражені більше двох суглобів (79,4 і 83,2 %, відповідно). Препаратом вибору для старту уратзнижуючої терапії в більшості випадків був алопуринол (98,1 і 98,0 %, відповідно). Через рік спостереження у хворих в групі Мет спостерігалося значуще зниження сироваткового рівня СК з (468,9 ± 61,9) до (318,7 ± 44,9) мкмоль/л (P < 0,0001). Протягом року 63,6 % хворих цієї групи досягли цільового сироваткового рівня СК (< 360,0 мкмоль/л) порівняно з 47,5 % у контрольній групі (P < 0,023). У хворих групи Мет було досягнуто значущого зниження рівня IPI (з 28,1 [12,8; 49,2] до 19,1 [11,5; 45,8] мкмоль/л (P < 0,01) та індексу HOMA-IR (з 3,5 [1,7; 9,1] до 2,8 [1,4; 9,2] (P < 0,01). Середня частота нападів подагри становила 2,02 на рік (95 % ДІ (1,28–2,36)) в групі Мет і 4,00 на рік (95 % ДІ (2,56-5,42)) в контрольній групі, відповідно (P < 0,01). Середньодобові дози алопуринолу в досліджуваних групах істотно не відрізнялися і становили (258 ± 120) і (246 ± 110) мг, відповідно.

Висновки: Застосування комбінації алопуринолу і метформіну у хворих на подагру з цукровим діабетом 2 типу дозволяє досягти цільового сироваткового рівня сечової кислоти у 64 % пацієнтів, сприяє зниженню виразності інсулінорезистентності та частоти нападів подагри.

Ключові слова: подагра, цукровий діабет 2 типу, уратзнижуюча терапія, метформін.