**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...
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.

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:

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

(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 m²).

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.
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

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Metformin group (n = 107)</th>
<th>Control group (n = 101)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>60 (58.7 ± 9.7)</td>
<td>61 (60.9 ± 9.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33.2 ± 6.8</td>
<td>33.7 ± 6.2</td>
<td>0.10</td>
</tr>
<tr>
<td>WC, cm</td>
<td>105.8 ± 16.3</td>
<td>105.4 ± 15.7</td>
<td>0.89</td>
</tr>
<tr>
<td>FPG, mmol/L</td>
<td>7.9 ± 1.9</td>
<td>7.2 ± 1.8</td>
<td>0.54</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>7.7 ± 1.7</td>
<td>7.7 ± 1.9</td>
<td>0.79</td>
</tr>
<tr>
<td>IRI, μmol/L</td>
<td>28.1 ± 11.3</td>
<td>26.3 ± 14.2</td>
<td>0.81</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>3.5 ± 1.5</td>
<td>3.4 ± 1.8</td>
<td>0.86</td>
</tr>
<tr>
<td>SUA, μmol/L</td>
<td>468.9 ± 61.9</td>
<td>480.9 ± 71.8</td>
<td>0.68</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>Me 60 [50–70]</td>
<td>Me 50 [44–66]</td>
<td>0.005</td>
</tr>
<tr>
<td>CKD, %</td>
<td>26.2</td>
<td>47.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Monoarticular disease (1 joint), %</td>
<td>20.6</td>
<td>16.8</td>
<td>0.72</td>
</tr>
<tr>
<td>Oligoarticular disease (2-4 joints), %</td>
<td>47.6</td>
<td>49.5</td>
<td>0.78</td>
</tr>
<tr>
<td>Polyarticular disease (&gt; 4 joints), %</td>
<td>31.8</td>
<td>33.7</td>
<td>0.76</td>
</tr>
<tr>
<td>Alcohol use, %</td>
<td>44.9</td>
<td>47.7</td>
<td>0.67</td>
</tr>
<tr>
<td>Arterial hypertension, %</td>
<td>65.4</td>
<td>62.6</td>
<td>0.77</td>
</tr>
<tr>
<td>Kidney stones, %</td>
<td>3.7</td>
<td>4.7</td>
<td>0.73</td>
</tr>
</tbody>
</table>

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.
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 A1C 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].

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.

REFERENCES

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.
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 — нормалізації глюкемії. Часто 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. Досліджувалося було поділено на дві групи: група Мет (n = 107) — хворі на подагру, які отримували 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 (Мет 60 [50–70] та 50 [44–66], відповідно) (P < 0,005) порівняно з групою контролю. Вихідні середні сироваткові рівні СК у досліджуваних групах становили (468,9 ± 61,9) і (480,9 ± 71,8) мкмоль/л, відповідно (P < 0,68). У перекритої частині пацієнтів у групах були уражені більше двох суглобів (79,4 і 83,2 %, відповідно). Препаратом вибору для старту уратознижуючої терапії в більшості випадків був алопуринол (98,1 і 98,0 %, відповідно). Через рік спостереження у хворих в групі Мет спостерігалося значне 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 значного зниження рівні інсулинорезистентності (ІРІ) з 28,1 [12,8; 49,2] до 19,1 [11,5; 45,8] мкмоль/л (P < 0,01) та індексу ГОМА-ІР (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 (P < 0,01). Середньодобові доzi 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 інсулинорезистентності і частоти нападів подагри.

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