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The effect of metformin treatment on the level of GLP-1, NT-proBNP and endothelin-1 in patients with type 2 diabetes mellitus

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Abstract. Background. Type 2 diabetes mellitus (T2DM) is closely associated with an increased risk of cardiovascular diseases. It was shown that endothelial dysfunction is one of the key pathological events in the development of chronic vascular diabetic complications. An important effect of endothelial dysfunction is that it increases the production and biological activity of the potent vasoconstrictor and the pro-inflammatory peptide — endothelin (ET). Metformin is used in the treatment of T2DM as a first-line medication. It has been shown that the mechanism of action of metformin may be associated with biochemical processes in the gastrointestinal tract. Brain natriuretic peptide (BNP) is used as a marker in the diagnosis of heart failure. The purpose of this work was to determine and compare ET-1, NT-proBNP and glucagon-like peptide-1 (GLP-1) blood levels in diabetic patients treated with metformin. **Materials and methods.** NT-proBNP, GLP-1, endothelin-1 and glycated hemoglobin were determined using enzyme-linked immunosorbent assay. To compare the data groups, Student's t-test and one-way ANOVA were used. **Results.** The content of ET-1 in the blood of patients with T2DM significantly exceeds its concentration in the control samples. Monotherapy with metformin leads to a decrease in ET-1 levels by more than 65 %. The combination therapy of metformin with insulin causes even greater decrease in ET-1. The blood level of GLP-1 in patients with T2DM is significantly, more than 2 times, reduced compared to healthy people. After metformin treatment, the content of GLP-1 is increased to the control level. The concentration of NT-proBNP in the blood of diabetic patients more than 2 times exceeds the control values. Treatment with metformin leads to a decrease in the content of natriuretic peptide by more than 40 %. **Conclusions.** Thus, treatment with metformin causes a decrease in ET-1 and NT-proBNP concentrations, and an increase in blood GLP-1 of patients with type 2 diabetes. These events together may indicate a positive protective effect of metformin on the cardiovascular system.

Keywords: type 2 diabetes; NT-proBNP; glucagon-like peptide-1; endothelin-1

Introduction

Diabetes mellitus is a metabolic disorder with high blood glucose levels for an extended period. Most studies show that type 2 diabetes mellitus (T2DM) is closely associated with an increased risk of cardiovascular diseases. Although the exact mechanisms responsible for accelerated atherosclerosis are not fully understood, it has been shown that endothelial dysfunction is one of the earliest

and key pathological events in the development of chronic vascular diabetic complications [1, 2]. It is a systemic pathological condition of the endothelium, which is defined as an imbalance between the vasodilator and vasoconstrictor substances produced by the endothelium. An important effect of endothelial dysfunction is that it increases the production and biological activity of the potent vasoconstrictor and the pro-inflammatory peptide — en-

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dothelin (ET). Diabetes is one of the diseases associated with pathologically elevated ET levels [3]. ET-1 is the main cardiovascular isoform of the endothelin system. Vascular ET-1 is produced primarily in the endothelium, although it can also be produced in vascular smooth muscle cells, macrophages, leukocytes, cardiomyocytes, and fibroblasts [4]. Two subtypes of receptors, endothelin A and B, mediate the effects of ET-1. On smooth muscle cells, A receptors mediate vasoconstriction and mitogenesis, while the B receptors have a dual function and have been shown to induce both vasoconstriction and vasodilation [5]. Changing the ET-1 endothelial balance is a key event in the initiation of arteriosclerosis [6].

Metformin is used in the treatment of T2DM as a first-line medication. Despite widespread use, precise mechanisms of its action are still insufficiently studied [7]. It is known to reduce liver gluconeogenesis and improve peripheral insulin sensitivity by activating adenosine monophosphate-activated protein kinase in metabolically active organs such as the liver, in skeletal muscles, and in adipose tissue. It has been shown that the mechanism of action of metformin may be associated with biochemical processes in the gastrointestinal tract [7, 8]. There is growing evidence that the direct or indirect effects of metformin in the gastrointestinal tract explain most, if not all, its glucose-lowering effects [9].

Brain natriuretic peptide (BNP) is used as a marker in the diagnosis of heart failure. ProBNP is released in response to stimulation of ventricular cardiomyocytes

and is cleaved into two fragments: the active hormone BNP (32 amino acids) and the inactive N-terminal peptide NT-proBNP (76 amino acids). The plasma content of BNP and NT-proBNP significantly correlates with the functional classes of chronic heart failure [10]. Determination of the BNP level in the blood allows one to assess the severity of chronic heart failure, predict the further development of the disease and evaluate the effect of therapy [11, 12].

The purpose of this work was to determine and compare ET-1, NT-proBNP and glucagon-like peptide-1 (GLP-1) levels in the blood of patients with type 2 diabetes mellitus treated with metformin.

Materials and methods

The study was conducted in the diabetology department of the State Institution “V.P. Komisarenko Institute of Endocrinology and Metabolism of the NAMS of Ukraine”. The study protocol (No 8, 09.03.2020) was approved by the Institute’s ethics committee. All patients signed informed consent to conduct further diagnostic and research study.

Blood was obtained by standard venipuncture and stored in EDTA vacutainer tubes. Plasma was separated by centrifugation within 10 min after blood sampling. The samples were stored at –80 °C until use. NT-proBNP (n = 78) was determined using enzyme-linked immunosorbent assay (ELISA) kit E-EL-H0902 (Elabsience, USA), GLP-1 (n = 78) — using ELISA kit BMS2194

Figure 1. The calibration curves for the NT-proBNP (left) and GLP-1 (right) concentration determination in the blood

(eBioscience, Austria). The calibration curves for the NT-proBNP and GLP-1 indicate acceptable data dispersion (Fig. 1). The level of ET-1 was evaluated with ELISA in 103 individuals: 17 healthy volunteers and 86 patients with T2DM. To determine the concentration of ET-1, the endothelin (1-21) EIA kit (Biomedica, Austria) was used. The measurement was carried out at an optical density of 450 nm. Glycated hemoglobin was determined using one HbA1c FS kit (DiaSys Diagnostic Systems GmbH, Germany). The measurement was carried out at an optical density of 660 nm. The protein concentration in the blood plasma was determined using Novagen BCA protein assay kit (USA).

Statistical calculations and data presentation were performed using Origin 7.0 software. The results of the study are presented as $M \pm SD$. To compare the data groups, Student's t-test and one-way ANOVA were used. Values of $P \leq 0.05$ were considered significant.

Results

ET-1 concentration was determined in 86 patients (+ 17 control samples). The average body mass index was $29.98 \pm 0.67 \text{ kg/m}^2$; average HbA1c level — $8.64 \pm 0.19 \%$; the average duration of the disease — 17.25 ± 1.42 years. NT-proBNP and GLP-1 concentrations were determined in 78 patients (+ 8 controls). The average body mass index was $29.13 \pm 0.83 \text{ kg/m}^2$; the average level of HbA1c — $8.65 \pm 0.23 \%$; the average duration of the disease — 16.01 ± 1.29 years.

As can be seen from Table 1, the blood content of ET-1 in patients with T2DM significantly exceeds its concentration in the control samples (lines 1 and 2). Monotherapy with metformin leads to a decrease in ET-1 levels by more than 65 %. The combination therapy of metformin with insulin causes even greater decrease (although not to the control value).

The level of GLP-1 in patients with T2DM is significantly, more than 2 times, reduced, compared to healthy people. After metformin treatment, the content of GLP-1 is increased to the control level.

The content of NT-proBNP in the blood of diabetic patients exceeds the control values more than 2 times. Treatment with metformin leads to a decrease in the content of natriuretic peptide by more than 40 %.

Clinical trials have shown the beneficial effects of metformin on the cardiovascular system. Moreover, drug can directly protect endothelial cells from damage [2]. Metformin positively affects the viability and functions of the endothe-

lium, it also markedly improves endothelium-dependent vasodilation, and simultaneously reduce the expression of dysfunctional biomarkers such as ET-1, plasminogen activator inhibitor-1, and C-reactive protein in endothelial cells, perhaps through activation of 5'adenosine monophosphate-activated protein kinase (AMPK) [13].

It is known that transforming growth factor (TGF) β , an important regulator of ET-1 production in endothelial cells [14, 15], is a target of metformin. The direct binding of metformin to TGF- β 1 was identified, and it was found that metformin inhibits [^{125}I]-TGF- β 1 binding to its receptor [16], so probably can reduce ET-1 synthesis.

In combination therapy of insulin and metformin (Table 1, line 4), and other hypoglycemic drugs [17], the ET-1 level in patients with T2DM was significantly reduced. This is difficult to explain given the complex relationships of both agents. Metformin therapy improves insulin secretion and protects against pancreatic β -cell apoptosis [18]. Metformin-mediated activation of AMPK inhibits the NF- κ B cascade, resulting in improved insulin signaling [1, 19]. However, insulin suppresses AMPK activity in leucocytes, liver, muscles, and possibly in other tissues and organs [20, 21].

The normal action of insulin is associated with vasodilation and redistribution of blood flow. However, in type 2 diabetes and insulin resistance, insulin stimulates the secretion of ET-1 [22, 23]. It is possible that a decrease in insulin resistance after treatment with metformin normalizes the action of insulin, which leads to a synergistic effect of both agents in reducing the concentration of ET-1.

In addition to stimulation of glucose-dependent insulin secretion by β -cells in the pancreas, GLP-1 has extra-pancreatic effects. A recent study shows that treatment with the GLP-1 analogue liraglutide reduces the incidence of cardiovascular events and mortality in patients with T2DM [2]. New data indicate that GLP-1 and its analogues have a direct protective effect on the vascular endothelium [24].

Discussion

Glucagon like peptide-1, an incretin hormone, regulates glucose metabolism by inducing insulin secretion and suppressing glucagon secretion. In diabetes, the secretion of GLP-1 decreases [25]. According to the data obtained, the action of metformin in the intestine includes an increased secretion of the hormones of enteroendocrine L-cells — GLP-1 and peptide YY, possibly through a pathway dependent on intestinal AMPK, influence on the

Table 1. ET-1, GLP-1 and NT-proBNP concentration in the blood

N	Therapy	ET-1, fmol/ml	SD	GLP-1, pg/ml	SD	NT-proBNP, ng/ml	SD
1	Control	1.18	0.17	6.15	1.45	1.06	0.29
2	Average indices	7.78 _(1, 3, 4)	1.53	2.78 _(1, 3)	0.1	2.12 _(1, 3)	0.23
3	Metformin	4.7 _(1, 2, 4)	0.47	5.59	1.19	1.49 _(1, 2)	0.35
4	Metformin + insulin	3.03 _(1, 2, 3)	0.41	—	—	—	—

Notes: group 2 — average blood concentrations of ET-1, GLP-1 and NT-proBNP in patients with T2DM. Indexes show significant differences between corresponding groups.

metabolism of bile acids and on the microbiome [7, 26, 27]. The increased GLP-1 secretion may arise partially due to reduced glucose absorption in the gut during metformin treatment, as well as direct action of the drug in the distal intestine (unrelated to effects on glucose). Thus, more glucose influences distal intestinal L-cells that secrete GLP-1. The fact that the action of metformin is realized through the intestine is evidenced by the observation that intravenous metformin has a weakened glucose-lowering effect compared to oral administration, and has no acute effect on glucose utilization or glucose production in the liver in humans [9]. A synergistic or additive effect of metformin coadministered with a dipeptidyl peptidase-4 inhibitor on increasing GLP-1 levels has also been shown in people with T2DM [27].

A decrease in BNP levels in the treatment of diabetic patients using metformin is another piece of evidence confirming the positive effect of the drug on the cardiovascular system. This is also confirmed by other data. Treatment with metformin alleviated the histological abnormalities in the heart, decreased the elevation of creatine kinase-myocardial band and BNP, probably through the phosphorylation and activation of AMPK α [28]. Additionally, cardiac expression of brain-like natriuretic peptide was significantly reduced in metformin-treated mice after 14 days of cardiac ischemia-reperfusion. Metformin represses cardiac apoptosis at least in part through inhibition of forkhead box protein O1 pathway [29]. It is interesting that metformin reduced all-cause mortality in myocardial infarction and heart failure, the incidence of cardiovascular events in T2DM but had no significant effect on non-T2DM patients [30].

Studies of cardiovascular protection with metformin in newly diagnosed and insulin-treated T2DM patients suggest that cotreatment with metformin may enhance the impact of newer incretin-based therapies on cardiovascular outcomes, an important observation as metformin can be combined with any other antidiabetic agent. Multiple potential mechanisms support the concept of cardiovascular protection with metformin beyond those provided by reduced blood glucose, including weight loss, improvements in haemostatic function, reduced inflammation and oxidative stress, and inhibition of key steps of atherosclerosis. Several studies have demonstrated increased secretion of GLP-1 following administration of metformin to people with or without T2DM [27].

The binding of monocytes to the activated endothelium and their differentiation into macrophages is an early event in the development of atherosclerosis. Recent experimental data have shown that metformin inhibited the conversion of monocytes to macrophages and angiotensin II-induced atherosclerotic plaque formation. Reduced infiltration of macrophages into the vascular wall, with reduced secretion of inflammatory cytokines, was also observed in a rabbit model of atherogenesis [31]. The effect of metformin on angiogenesis was associated with stimulation of the AMPK and inhibition of mechanistic target of rapamycin. Other potentially vascular protective mechanisms described for metformin in experimental studies include reduced cholesterol uptake or enhanced cholesterol efflux from macro-

phages, inhibition of fission of mitochondria in endothelial cells, protection of mitochondrial function during and after myocardial ischaemia, and reduced formation of foam cells or neointima in the developing plaque [27].

Conclusions

Thus, treatment with metformin leads to a decrease in ET-1 and NT-proBNP concentrations, and to an increase in GLP-1. These events together indicate a positive protective effect of metformin on the cardiovascular system of patients with type 2 diabetes mellitus.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Вплив лікування метформіном на рівень GLP-1, NT-proBNP та ендотеліну-1 у крові хворих на цукровий діабет 2-го типу

Резюме. Актуальність. Цукровий діабет 2-го типу (ЦД2) тісно пов'язаний з підвищеним ризиком серцево-судинних захворювань. Було показано, що ендотеліальна дисфункція є однією з ключових патологічних подій у розвитку хронічних судинних ускладнень діабету. Важливим ефектом ендотеліальної дисфункції є те, що вона збільшує продукцію і біологічну активність сильнодіючого вазоконстриктора і прозапального пептиду — ендотеліну (ЕТ). Метформін використовується при лікуванні ЦД2 як препарат першої лінії. Встановлено, що механізм дії метформіну може бути пов'язаний з біохімічними процесами в шлунково-кишковому тракті. Мозковий натрійуретичний пептид (BNP) використовується як маркер при діагностиці серцевої недостатності. **Метою** цієї роботи було визначення і зіставлення рівнів ЕТ-1, NT-proBNP і глюкагоноподібного пептиду-1 (GLP-1) у крові пацієнтів із ЦД2, які отримували метформін. **Матеріали та методи.** Концентрації NT-proBNP, GLP-1, ЕТ-1 і глікованого гемоглобіну визначали за допомогою імуноферментного аналізу. Для порівняння груп даних використовували t-критерій Стюдента

і однофакторний дисперсійний аналіз. **Результати.** Кількість ЕТ-1 у крові хворих на ЦД2 значно перевищує його концентрацію в контрольних зразках. Монотерапія метформіном приводить до зниження рівня ЕТ-1 більше ніж на 65 %. Комбінована терапія метформіном з інсуліном викликає ще більше зменшення кількості ЕТ-1. Рівень GLP-1 у крові хворих на ЦД2 значно, більше ніж удвічі, знижений порівняно зі здоровими людьми. Після лікування метформіном уміст GLP-1 збільшується до контрольного рівня. Кількість NT-proBNP у крові хворих на цукровий діабет перевищує контрольні значення більше ніж удвічі. Лікування метформіном приводить до зниження рівня натрійуретичного пептиду більше ніж на 40 %. **Висновки.** Таким чином, лікування метформіном обумовлює зниження концентрацій ЕТ-1 і NT-proBNP, а також підвищення рівня GLP-1 у крові пацієнтів із ЦД2. Разом ці події можуть указувати на позитивний захисний ефект метформіну на серцево-судинну систему.

Ключові слова: цукровий діабет 2-го типу; NT-proBNP; глюкагоноподібний пептид-1; ендотелін-1

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Влияние лечения метформином на уровень GLP-1, NT-proBNP и эндотелина-1 в крови больных сахарным диабетом 2-го типа

Резюме. Актуальность. Сахарный диабет 2-го типа (СД2) тесно связан с повышенным риском сердечно-сосудистых заболеваний. Было показано, что эндотелиальная дисфункция является одним из ключевых патологических событий в развитии хронических сосудистых осложнений диабета. Важным эффектом эндотелиальной дисфункции является то, что она увеличивает продукцию и биологическую активность сильнодействующего вазоконстриктора и провоспалительного пептида — эндотелина (ЭТ). Метформин используется при лечении СД2 в качестве препарата первой линии. Установлено, что механизм действия метформина может быть связан с биохимическими процессами в желудочно-кишечном тракте. Мозговой натрийуретический пептид (BNP) используется в качестве маркера при диагностике сердечной недостаточности. **Целью** данной работы было определение и сопоставление уровней ЭТ-1, NT-proBNP и глюкагоноподобного пептида-1 (GLP-1) в крови пациентов с СД2, получавших метформин. **Материалы и методы.** Концентрации NT-proBNP, GLP-1, ЭТ-1 и гликированного гемоглобина определяли с помощью иммуноферментного анализа. Для сравнения групп данных использовались

t-критерий Стюдента и однофакторный дисперсионный анализ. **Результаты.** Количество ЭТ-1 в крови больных СД2 значительно превышает его концентрацию в контрольных образцах. Монотерапия метформином приводит к снижению уровня ЭТ-1 более чем на 65 %. Комбинированная терапия метформином и инсулином вызывает еще большее уменьшение количества ЭТ-1. Уровень GLP-1 в крови больных СД2 значительно, более чем в 2 раза, снижен по сравнению со здоровыми людьми. После лечения метформином содержание GLP-1 увеличивается до контрольного уровня. Количество NT-proBNP в крови больных сахарным диабетом превышает контрольные значения более чем в 2 раза. Лечение метформином приводит к снижению уровня натрийуретического пептида более чем на 40 %. **Выводы.** Таким образом, лечение метформином обуславливает снижение концентраций ЭТ-1 и NT-proBNP, а также повышение уровня GLP-1 в крови пациентов с СД2. Вместе эти события могут указывать на положительный защитный эффект метформина на сердечно-сосудистую систему.

Ключевые слова: сахарный диабет 2-го типа; NT-proBNP; глюкагоноподобный пептид-1; эндотелин-1