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Effects of Metformin on Ceramide Production in Local Fat Depots in Patients with Coronary Artery Disease

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ABSTRACT

Aim. To evaluate the effects of metformin on the expression level of ceramide synthesis enzyme genes, and on the total content and spectrum of ceramides in local fat depots in patients with coronary heart disease (CHD).

Materials and methods. The study included 41 patients with CHD, who were scheduled to undergo coronary artery bypass grafting. Samples of subcutaneous, epicardial, and perivascular adipose tissue (SAT, EAT, and PVAT) were obtained during surgery, adipose tissue adipocytes were isolated and cultured for 24 hours with the addition of metformin (Sigma-Aldrich, USA) at concentrations of 1 and 10 mmol/l. The expression characteristics of *de novo* ceramide synthesis enzymes were assessed by quantitative polymerase chain reaction on a ViiA 7 amplifier (Applied Biosystems, USA). The total content and spectrum of ceramides (Cer) were determined by high-performance liquid chromatography with mass spectrometry (HPLC-MS/MS). Statistical processing of the results was performed using the STATISTICA 12 software package.

Results. Metformin at a concentration of 1 mmol/l statistically significantly decreased the gene expression of the enzymes serine palmitoyltransferase-1 (SPTLC1) in SAT, EAT and PVAT, ceramide synthase-2 (CERS2) in EAT and SAT, ceramide synthase-4 (CERS4) in EAT and PVAT, and increased dihydroceramide desaturase (DEGS1) in EAT and SAT. Metformin at a concentration of 10 mmol/l decreased the level of SPTLC1 and CERS2 mRNA in EAT, CERS4 in EAT and PVAT. A significant decrease in the content of Cer d18:1/16:0 in EAT at a metformin concentration of 1 mmol/l, and Cer d18:1/18:0 in EAT and PVAT, Cer d18:1/20:0 in SAT and EAT at concentrations of 1 and 10 mmol/l was revealed.

Conclusion. Thus, the potential ability of metformin to inhibit *de novo* ceramide synthesis in isolated SAT, EAT and PVAT adipocytes and to reduce the content of ceramides associated with adverse cardiovascular events in fat cells was demonstrated in *in vitro* experiments.

Keywords: ceramides, metformin, adipose tissue, coronary heart disease

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this manuscript.

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Conformity with the principles of ethics. All individuals signed an informed consent to participate in the study. The study was approved by the Ethics Committee of the Research Institute for Complex Issues of Cardiovascular Diseases (Minutes No. 12 dated March 20, 2023).

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Эффекты метформина на продукцию церамидов в локальных жировых депо у пациентов с ишемической болезнью сердца

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РЕЗЮМЕ

Цель: оценить эффекты метформина на уровень экспрессии генов ферментов синтеза церамидов и общее содержание и спектр церамидов в локальных жировых депо у пациентов с ишемической болезнью сердца (ИБС).

Материалы и методы. В исследование включен 41 пациент с ИБС, которому планировалось проведение аортокоронарного шунтирования. Образцы подкожной, эпикардиальной и периваскулярной жировой ткани (ПЖТ, ЭЖТ и ПВЖТ) были получены во время оперативного вмешательства, адипоциты ЖТ изолировали и культивировали в течение суток с добавлением метформина (Sigma-Aldrich, США) в концентрациях 1 и 10 ммоль/л. Оценку экспрессии ферментов синтеза церамидов *de novo* проводили методом количественной полимеразной цепной реакции на амплификаторе ViiA 7 (Applied Biosystems, США). Общее содержание и спектр церамидов (Cer) устанавливали методом высокоэффективной жидкостной хроматографии с масс-спектрометрическим детектированием (ВЭЖХ-МС/МС). Статистическую обработку результатов осуществляли с использованием программного пакета Statistica 12.

Результаты. Метформин в концентрации 1 ммоль/л статистически значимо снижал генную экспрессию ферментов серинпальмитоилтрансферазы-1 (SPTLC1) в ПЖТ, ЭЖТ и ПВЖТ, церамидсинтазы-2 (CERS2) в ЭЖТ и ПЖТ, церамидсинтазы-4 (CERS4) в ЭЖТ и ПВЖТ и повышал экспрессию ферментов дигидроцерамиддесатуразы (DEGS1) в ЭЖТ и ПЖТ. Метформин в концентрации 10 ммоль/л снижал уровень мРНК SPTLC1 и CERS2 в ЭЖТ, CERS4 в ЭЖТ и ПВЖТ. Выявлено снижение содержания Cer d18:1/16:0 в ЭЖТ при концентрации метформина 1 ммоль/л и Cer d18:1/18:0 в ЭЖТ и ПВЖТ, Cer d18:1/20:0 в ПЖТ и ЭЖТ при концентрациях 1 и 10 ммоль/л.

Заключение. Показана потенциальная способность метформина в экспериментах *in vitro* ингибировать синтез церамидов *de novo* в изолированных адипоцитах ПЖТ, ЭЖТ и ПВЖТ и снижать содержание в жировых клетках церамидов, ассоциированных с неблагоприятными сердечно-сосудистыми событиями.

Ключевые слова: церамиды, метформин, жировая ткань, ишемическая болезнь сердца

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Соответствие принципам этики. Все лица подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом НИИ КПССЗ (протокол № 12 от 20.03.2023).

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INTRODUCTION

Metformin is the oldest first-line oral hypoglycemic agent for patients with type 2 diabetes mellitus (T2DM). Over the past two decades, metformin has demonstrated a number of beneficial effects beyond its efficacy in the context of hypoglycemic therapy, both in experimental models and in clinical trials.

Among the drug's most significant pleiotropic effects are its cardioprotective properties [1] and its impact on modifiable cardiovascular risk factors, such as dyslipidemia, obesity, and insulin resistance [2–4], suppression of oxidative stress in vascular cells, and reduction of inflammatory responses [5–7]. Furthermore, there is growing evidence demonstrating the efficacy of metformin in secondary cardiovascular prevention [8]. Pleiotropic effects are likely mediated, as demonstrated in studies, through the drug's ability to suppress adipocyte differentiation and modulate their functional activity, reducing adipose tissue inflammation, thereby potentially reducing the risk of cardiac fibrosis, which leads to structural changes and systolic and diastolic myocardial dysfunction.

Using untargeted and targeted lipidomics methods, a comprehensive and advanced analytical approach to studying lipidome changes, the effect of metformin on the serum lipidome in obesity and diabetes mellitus was assessed. The drug demonstrated positive effects by significantly reducing certain lipid classes, the role of which has been demonstrated in the development of obesity, diabetes mellitus, and cardiovascular disease [9–12]. Furthermore, adipose tissue (AT) of the heart and blood vessels can also act as a potential source of complex lipids, as its epicardial and perivascular compartments are located in close proximity to atherosclerotic lesions.

In this regard, the class of sphingolipids, especially ceramides, is of particular interest, as experimental and clinical studies have shown their association with the development and progression of atherosclerosis [13, 14]. Currently, the question remains open as to whether metformin is capable of modulating the functional activity of local cardiac fat depots and regulating the synthesis of ceramides associated with coronary diseases.

This study aimed to evaluate the effect of metformin on the level of expression of enzyme-encoding genes responsible for *de novo* synthesis of ceramides and the total content and spectrum of ceramides in local fat depots in patients with coronary heart disease (CHD).

MATERIALS AND METHODS

The inclusion criteria for the study were the presence of stable CHD and indications for coronary artery bypass grafting (CABG). Exclusion criteria were as follows: age over 75 years, myocardial infarction, carbohydrate metabolism disorders (T1DM and T2DM), and the presence of clinically significant comorbidities (renal failure, liver failure, anemia, acute oncological and infectious and inflammatory diseases, and autoimmune diseases).

Thus, the study included 41 patients meeting the inclusion and exclusion criteria. The study was approved by the local Ethics Committee of the Research Institute for Complex Issues of Cardiovascular Diseases (Minutes No. 12 dated March 20, 2023) and complied with the principles of good clinical practice and the principles of the World Medical Association's Declaration of Helsinki, taking into account the amendments adopted in 2013, as well as the "Rules of Clinical Practice in the Russian Federation" (Order of the Ministry of Health of the Russian Federation No. 266 dated June 19, 2003).

All patients had their medical history taken upon admission to the hospital, their height (m) and weight (kg) were measured, and their body mass index (BMI, kg/m^2) was calculated. The clinical characteristics of the patients are presented in Table 1.

Table 1

Clinical Characteristics of Patients with Coronary Heart Disease

Parameter	CHD patients, $n = 41$
Male gender, *n* (%)	27 (66)
Age, years, *Me* (Q_{25}; Q_{75})	66.2 (48.5;70.3)
Body mass index, kg/m^2, *Me* (Q_{25}; Q_{75})	26.9 (22.1;29.7)
History of myocardial infarction, *n* (%)	30 (73)
History of CHD, *n* (%)	21 (56)
Arterial hypertension, *n* (%)	25 (61)
Dyslipidemia, *n* (%)	20 (49)
Smoking, *n* (%)	21 (56)
Acute cerebrovascular accident, *n* (%)	3 (7)
Atherosclerosis of one coronary artery, *n* (%)	6 (15)
Atherosclerosis of two coronary arteries, *n* (%)	7 (17)
Atherosclerosis of three or more coronary arteries, *n* (%)	28 (68)
Atherosclerosis of other vascular basins, *n* (%)	8 (20)
Class I heart failure, *n* (%)	28 (68)

End of table 1

Parameter	CHD patients, $n = 41$
Class II heart failure, *n* (%)	13 (32)
Class III heart failure, *n* (%)	0
Class IV heart failure, *n* (%)	0
No angina pectoris, *n* (%)	3 (7)
Class I angina pectoris, *n* (%)	0
Class II angina pectoris, *n* (%)	14 (34)
Class III angina pectoris, *n* (%)	24 (57)
Class IV angina pectoris, *n* (%)	0
Ejection fraction, %, *Me* (Q_{25}; Q_{75})	53.6 (46.3;58.9)
Aspirin, *n* (%)	38 (93)
Clopidogrel, *n* (%)	6 (15)
β-blockers, *n* (%)	37 (90)
Angiotensin-converting enzyme inhibitors, *n* (%)	31 (76)
Statins, *n* (%)	41 (100)
Ca-channel blockers, *n* (%)	31 (76)
Nitrates, *n* (%)	1 (2)
Diuretics, *n* (%)	33 (81)

Note. Class is functional class according to NYHA.

Patients' medical histories often included cardiovascular risk factors, such as hypertension, dyslipidemia, and smoking. Left ventricular ejection fraction calculated according to the Teicholz formula was preserved. During their hospital stay, patients received standard medications in accordance with the guidelines of the Ministry of Health of the Russian Federation (2020) and the European Society of Cardiology (2020) (Table 1).

Obtaining cardiac adipose tissue samples and isolating adipocytes were performed according to a previously described method [15]. To assess the effect of the drug on the functional activity of adipocytes in subcutaneous, epicardial, and perivascular adipose tissue (SAT, EAT, and PVAT, respectively), the cells were cultured for 24 hours with the addition of metformin (Sigma-Aldrich, USA) at concentrations of 1 and 10 mmol/l. To obtain the required concentrations, metformin was diluted with complete culture medium M199 containing a glucose solution at a concentration of 5.3 mmol/l and dexamethasone 10^{-9}M. These substances are necessary to create a state of adipocytes in the body that is as close as possible to the physiological state.

Next, 2 x 106 adipocytes were added to the wells of a sterile 24-well plate (Greiner, Germany) and brought to a volume of 1 ml with complete M199 culture medium containing glucose at a final concentration of 5.3 mmol/l, dexamethasone 10^{-9}M, and metformin at the specified concentration. The cells were cultured for 24 hours in a CO_2 incubator (CB-53, BINDER, Germany) at 37°C and 5% CO_2. After the incubation period, the cultured cells were carefully removed for subsequent gene expression determination.

The expression of ceramide synthesis enzymes in isolated adipocytes was assessed by quantitative polymerase chain reaction on a ViiA 7 amplifier (Applied Biosystems, USA) using primers (Eurogen, Russia) indicated in Table 2.

Table 2

Nucleotide Sequences in the Primers of Enzymes Involved in *de novo* Ceramide Synthesis

Gene	Sequence Direction	Sequence (5'->3')	Primer Length
Serine palmitoyltransferase long chain base subunit 1 *(SPTLC1)*	Forward primer	aggaagcggctaactatggc	20
	Reverse primer	ccagaggatcagaatcccttcc	22
Ceramide synthase 2 *(CERS2)*	Forward primer	ggacgtgtctacgccaaagc	20
	Reverse primer	atgttcaagagggcagccagt	21
Ceramide synthase 4 *(CERS4)*	Forward primer	caggacttgttggcagccct	20
	Reverse primer	cgttgggcttcacttgcctc	20
Delta 4-desaturase, sphingolipid 1 *(DEGS1)*	Forward primer	ccactgagctggagtttcct	20
	Reverse primer	caggaattgtagtgagggaggt	22

The total content and spectrum of ceramides (Cer) in adipocytes were assessed by high-performance liquid chromatography with mass spectrometry to identify precursor ions of the fragment with m/z 264 in the mass/charge ratio range from 500 to 700 (HPLC-MS). First, liquid–liquid extraction was performed using chloroform, methanol, and water. Calculation of ceramide concentrations was performed using calibration standards (ng/ml). The HPLC-MS/MS system consisted of a Sciex QTRAP 5500 tandem triple quadrupole mass spectrometric detector (ab Sciex, USA) and an Agilent 1260

Infinity liquid chromatograph (Agilent Technologies, USA). For chromatographic determination of ceramides in adipose tissue adipocytes, a ZORBAX Eclipse XDB-C18 column, 2.1 × 100 mm, 1.8 μm (Agilent Technologies, USA) with a Security Guard precolumn (Phenomenex, USA) was used. Ceramide identification was performed using LipidMatch scripts and the LipidMaps lipid nomenclature.

Statistical processing was performed using the Statistica 12 software package. Quantitative data were presented as the median and the interquartile range *Me* (Q_{25}; Q_{75}), while qualitative data were presented as frequency indices in absolute and relative units *n* (%). Intergroup differences were determined using nonparametric tests. Three dependent groups were compared using the Friedman test, and pairwise comparisons were performed using the Wilcoxon test. Using the Bonferroni correction, the critical level of significance was taken to be $p \leq 0.017$ when comparing three study groups; when comparing two groups, differences were considered as statistically significant at $p < 0.05$.

RESULTS

Metformin was found to modulate the functional activity of cardiac adipose tissue adipocytes. Concentrations of 1 and 10 mmol/l metformin had consistent effects on the gene expression of *de novo* ceramide synthesis enzymes in cultured subcutaneous, epicardial, and perivascular adipocytes from individuals with CHD. However, the effect of the drug at a concentration of 1 mmol/l was more pronounced than at 10 mmol/l. Among patients with coronary heart disease, decreased gene expression of the enzyme encoding the first step in *de novo* ceramide synthesis, serine palmitoyltransferase-1 *(SPTLC1)*, was observed in SAT, EAT, and PVAT (Figure).

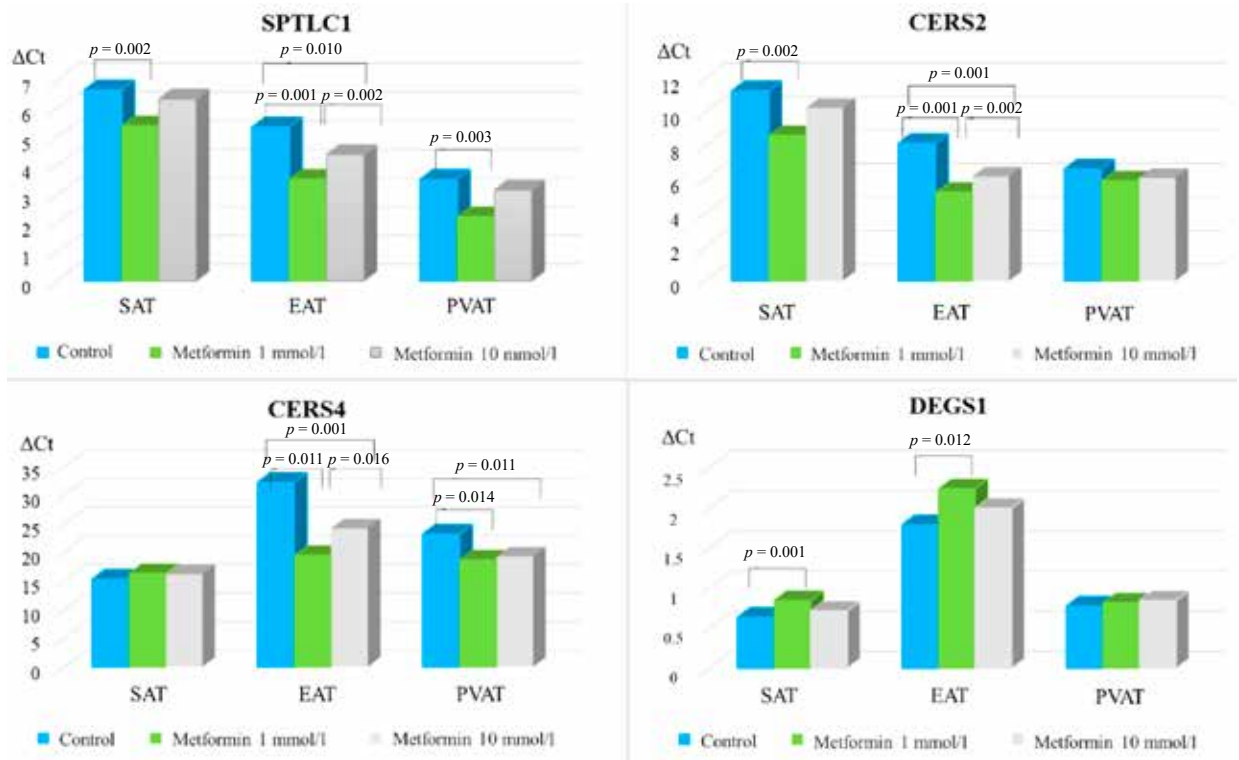

Figure. Evaluation of the effect of metformin on the expression levels of serine palmitoyltransferase-1 *(SPTLC1),* ceramide synthase 2 *(CERS2),* ceramide synthase 4 *(CERS4),* and delta 4-desaturase, sphingolipid 1 *(DEGS1)* in adipocytes of various locations in patients with coronary heart disease. ΔCt (delta Ct) is the difference between the threshold cycles (Ct) for the gene under study and the reference gene in the same sample

In patients with CHD, metformin at a concentration of 1 mmol/l suppressed the expression of genes encoding enzymes responsible for ceramide species diversity: ceramide synthase-4 *(CERS4*) in EAT and PVAT, and ceramide synthase-2 *(CERS2*) in EAT and SAT, which synthesize ceramides with a long hydrocarbon chain of C16-C24. Furthermore, metformin at a concentration of 1 mmol/l increased

the expression level of the delta 4-desaturase, sphingolipid 1 *(DEGS1)* gene, an enzyme involved in the final stage of *de novo* ceramide synthesis in EAT and SAT.

Ceramides containing saturated fatty acid residues were detected in patients with CHD: Cer d18:1/16:0, Cer d18:1/18:0, Cer d18:1/20:0, and Cer d18:1/24:0. Metformin at concentrations of 1 and 10 mmol/l was shown to modulate ceramide levels in adipocytes. The effects of metformin were consistent with the identified patterns of changes in gene expression of enzymes involved in *de novo* ceramide synthesis. Metformin had a unidirectional effect regardless of concentration. However, the effect of the drug at a concentration of 1 mmol/l on the levels of some ceramides was more pronounced.

Adipocytes in the epicardial region were most susceptible to the effects of metformin. A significant decrease in the content of Cer d18:1/16:0, Cer d18:1/18:0, and Cer d18:1/20:0 in EAT was observed. In perivascular adipocytes, only the level of Cer d18:1/18:0 decreased, while in subcutaneous adipocytes, Cer d18:1/20:0 decreased. Metformin had no statistically significant effect on the production of Cer d18:1/24:0 (Table 3).

Table 3

Evaluation of Ceramide Concentration in Adipocytes of Local Fat Depots of Patients with Coronary Heart Disease with the Addition of Metformin, *Me* (Q_{25}; Q_{75})

Ceramides, ng/ml	SAT			EAT			PVAT		
	C	1 mmol/l	10 mmol/l	C	1 mmol/l	10 mmol/l	C	1 mmol/l	10 mmol/l
	1	2	3	4	5	6	7	8	9
Cer d18:1/16:0	42.18 (21.07; 49.28)	44.20 (22.03; 50.32)	45.16 (22.21; 51.2)	75.33 (53.07; 87.25)	60.07 (47.82; 79.45)	71.21 (51.17; 86.02)	37.67 (32.13; 51.04)	35.61 (29.53; 49.81)	36.35 (28.44; 45.22)
	$p_{Ft} \geq 0.05$			$p_{Ft} = 0.012$ $p_{Wt4,5} = 0.021$			$p_{Ft} \geq 0.05$		
Cer d18:1/18:0	12.04 (9.22; 15.91)	13.00 (9.27; 16.42)	13.03 (9.32; 16.63)	25.27 (17.15; 30.37)	15.32 (10.22; 19.54)	19.63 (11.53; 21.64)	18.75 (11.03; 23.68)	15.13 (10.30; 20.63)	15.60 (10.61; 23.21)
	$p_{Ft} \geq 0.05$			$p_{Ft} = 0.015$ $p_{Wt4,5} = 0.003$ $p_{Wt4,6} = 0.018$			$p_{Ft} = 0.001$ $p_{Wt7,8} = 0.014$ $p_{Wt7,9} = 0.027$		
Cer d18:1/20:0	22.01 (18.11; 30.11)	16.93 (11.31; 22.49)	19.83 (12.98; 23.83)	15.95 (9.35; 21.80)	10.30 (8.38; 13.11)	12.26 (8.57; 18.95)	13.04 (9.11; 19.50)	10.13 (8.01; 12.53)	12.15 (8.38; 17.44)
	$p_{Ft} = 0.001$ $p_{Wt1,2} = 0.003$			$p_{Ft} = 0.001$ $p_{Wt4,5} = 0.002$ $p_{Wt4,6} = 0.009$ $p_{Wt5,6} = 0.011$			$p_{Ft} \geq 0.05$		
Cer d18:1/24:0	60.54 (33.78; 71.24)	59.55 (34.19; 67.51)	60.05 (32.55; 69.33)	45.85 (24.51; 53.22)	45.97 (24.88; 58.04)	45.92 (24.61; 58.31)	42.03 (21.32; 52.12)	41.29 (23.08; 50.76)	43.53 (22.14; 53.35)
	$p_{ft} \geq 0.05$			$p_{Ft} \geq 0.05$			$p_{Ft} \geq 0.05$		

Note. C – control, SAT – subcutaneous adipose tissue, PVAT – perivascular adipose tissue, EAT – epicardial adipose tissue. The levels of statistical significance: *p*Ft – the level when comparing three groups using the Friedman method, *p*Wt – the level when comparing two groups using the Wilcoxon method, and 1 mmol/l and 10 mmol/l – metformin concentration.

DISCUSSION

Metformin is a widely used biguanide with antihyperglycemic properties. However, its potential uses have long extended beyond the treatment of T2DM. The beneficial effects of metformin on cardiovascular health are being increasingly discussed.

The mechanisms of this phenomenon are not fully understood and are related to metformin's ability to modulate lipid homeostasis, but the molecular and genetic aspects require further clarification [16]. Ceramides are key molecules in sphingolipid metabolism and are considered to be important modulators of various cells and tissues, including cardiac and vascular adipose tissue [17]. According to experimental data, metformin inhibits the synthesis of ceramides and other complex lipids in animal skeletal muscle [18, 19], significantly reduces the

levels of certain lipid classes in the myocardium, as well as the expression of genes encoding enzymes that synthesize them, and regulates fatty acid composition [20].

The obtained results indicate the ability of metformin to regulate ceramide metabolism *in vitro* in epicardial and perivascular adipocytes to a greater extent than in subcutaneous ones, among patients with CHD. The pleiotropic effect of metformin was expressed in the ability to regulate the pathways of ceramide synthesis in cardiac adipocytes. Thus, at a low concentration (1 mmol/l), metformin more effectively suppressed the *de novo* ceramide synthesis from palmitoyl-CoA and serine at the stage of the first enzymatic reaction, as evidenced by a reduced expression of *SPTLC1*. Metformin suppressed the expression of genes of some ceramide synthases *CERS2* and *CERS4* in epicardial and perivascular adipocytes responsible for the synthesis of ceramides containing C-16, C-18, C-20, and C-24 residues of fatty acids associated with cardiovascular diseases [21]. At the same time, the drug increased the expression of the gene encoding the enzyme for the final reaction of *de novo* ceramide synthesis (*DEGS1*).

Based on the obtained results, it was established that the use of metformin *in vitro* promotes changes in ceramide concentrations in adipocytes, primarily in EAT and PVAT, in patients with CHD. Moreover, the drug effect was more pronounced at a concentration of 1 mmol/l compared to 10 mmol/l. Thus, ceramide levels, which are closely linked to the development and progression of cardiovascular disease, decreased in EAT and PVAT.

The pronounced effect of metformin in patients with CHD is likely due to the fact that one of the drug pleiotropic effects is the ability to suppress adipocyte differentiation and hypertrophy and reduce AT inflammation [22]. Therefore, metformin has the potential to reduce the ceramide-producing capacity of adipocytes. The reduction in ceramide production is achieved through the regulation of gene expression of enzymes synthesizing ceramides *de novo*, thereby inhibiting the accumulation of Cer in the ventricular tract of the heart and coronary vessels, which have adverse cardiovascular effects.

CONCLUSION

The potential ability of metformin to inhibit *de novo* ceramide synthesis in isolated adipocytes (SAT, EAT, and PVAT) and to reduce the content of ceramides associated with adverse cardiovascular events in fat cells was demonstrated in *in vitro* experiments.

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