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Integrated analysis of gene expression of solute carrier gene *SLC19A3* with proven risk factors of microvascular complications in patients with type 2 diabetes

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INTRODUCTION

Diabetes mellitus (DM) is a chronic progressive disorder which leads to significant disability, morbidity and is likely to progress to become one of the most widespread conditions worldwide and as an additional burden to the healthcare system already reeling under the effects of the COVID-19 pandemic worldwide. According to the International Diabetes Federation Atlas [1] there are approximately 463 million adults (20—79 years) with diabetes mellitus (DM) and it is expected that by 2045 the figure will rise to 700 million. It is noted that the number of patients is increasing in all the countries [2], but around 79 % of the patients live in middle and low income countries.

The pathogenesis of diabetic microvascular complications is complex and marked by metabolic and vascular factors [3, 4]. The presence of diabetic polyneuropathy (DPN) in diabetes patients is estimated to be from 6 % to 51 % and depends on various factors such as duration of disease, glycemic control and age [5]. According to published data 50 % of patients can develop a foot ulcer [6, 7], and DM is the leading cause of amputation of the limbs [8]. The most common form of DPN is distal symmetric polyneuropathy and consists of large and small fiber neuropathies [9]. It accounts for 75 % of all diabetic neuropathies. During the course of various studies and their results show that DPN is caused by nerve dysfunction due to oxidative stress and inflammatory factors [10].

There is ever increasing evidence regarding the risk factors of DPN in diabetes patients, such as age, duration of disease, obesity, smoking, and presence of chronic kidney disease in patients with type 2 DM and the effect of these risk factors in the progression of DPN.

The treatment of diabetic polyneuropathy is generally supportive and targets the prevention of progression of the disease and its complications. Short term tight glycemic control has not been shown to effectively decrease symptoms of DPN in patients with DM. Results of some studies have shown positive results for treatment of painful peripheral neuropathy [11]. Generally, the recommendations for treatment of DPN are targeted for the relief of symptoms of neuropathy, but current treatment patterns and practices are inconsistent and do not addresses the pathways involved in the pathophysiology of diabetic microvascular complications. Taking into consideration the metabolic pathways involved in the complications of DM, antioxidants are a treatment option [12], which

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needs to be further studied. In published data, there is information regarding the effects of benfothiamine, but its effect in the enhancement of the adaptive regulatory response of the expression of THTR-2 have not been elucidated and very little information is available.

Therefore, in-depth study of the frequency and the risk factors for the development of DPN in patients with type 2 DM, development of new diagnostic tool for precise, quick and easy assessment of patients with DPN is a promising area, and the use of novel drugs, addressing the pathogenetic mechanisms involved in the progression of DPN is of great practical importance.

The solute carrier (SLC) group of membrane transport proteins include over 400 members organized into 65 families [13]. Most members of the SLC group are located in the cell membrane, but some are located in the mitochondria. The SLC families include genes that encode passive transporters, ion transporters, and exchangers. The different SLC families are functionally related to each other and generally rely on an ion gradient over the cell membrane as the driving force for transportation, but with a few exceptions [14]. The transport protein *SLC19A3 (THTR2)* is associated with the plasma membrane, mediates the transport of extracellular thiamin into the cytosol. Changes in gene expression by factors such as age has been studied only in animal models [15, 16]. In the body the transporter is widely distributed and is consistent with its involvement in thiamin uptake [17]. Very little data is available regarding the expression of thiamine transporter proteins in diabetic patients with DPN, but data regarding the role of THTR-2 and its expression in the intestine and kidneys is available [18].

Objective — to study the correlative variation in gene expression of *SLC19A3* in type 2 diabetes patients with proven risk factors of diabetes complications.

MATERIALS AND METHODS

In the study, 190 patients with type 2 DM were screened for diabetic peripheral neuropathy (DPN). DPN was confirmed in (n = 105) patients displaying symptoms of diabetic polyneuropathy with the involvement of small nerve fibers and large nerve fibers. Out of the total cohort, 45 patients with type 2 DM were shortlisted and randomized according to the severity of diabetic polyneuropathy, for assessment of the expression of the gene *SLC19A3* in stage 1 of the gene expression study.

The patients were divided into three categories depending upon the severity of DPN. Patients in group 1 (n = 15) had a positive DNS score, positive 5.07—10.00 g monofilament test for testing protective sensory loss and a VPT of 16—25 Vindicating stage 1 DPN. Patients in group 2 (n = 15) had a positive DNS score, positive 5.07—10.00 g monofilament test and a VPT of 26—35 V indicating stage 2 DPN. Patients in group 3 (control) (n = 15) had a positive DNS score but with negative 5.07—10.00 g monofilament test and a normal VPT value of 01—15 V. The patients enlisted for gene expression analysis in different categories of patients did not have any significant difference and statistical variations in the blood tests and the anthropometric data (Table 1).

All the patients included in the gene expression analysis were of white European ancestry (Caucasian), which in theory corresponds to the Hardy—Weinberg principle of allele and genotype frequencies in a population.

Gene expression analysis of *SLC19A3* was examined by RT-qPCR, the material for gene expression testing was the mRNA. The mRNA was extracted from the leucocytes in the peripheral blood of the patients. Extraction and reverse transcription was done with the commercially available SuperScript VILO cDNA Synthesis Kit. It allows to generate the first strand of cDNA for two step RT-qPCR application. The procedure was done according to the procedure recommendations provided by the manufacturer. The next step involved the amplification of DNA in qPCR. In the process TaqMan Fast Advanced Master Mix was used, it contains AmpliTaq Fast DNA Polymerase, uracil-N-glycosylase (UNG), dNTPs with dUTP, ROX dye (passive reference), and optimized buffer components . The primers used for *SLC19A3* gene expression were: Forward, 5'-*TTCTCC ATGATGAGACCCTC* and Reverse, 5'-*ATGATGACTGGCTTG TAGCG*. The *SLC19A3* TaqMan Gene Expression Assay was used to evaluate the gene expression in the samples for the target gene. The expression levels of *SLC19A3* mRNA were normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Fold change of

Table 1

DNS and VPT values of patients in different groups

DPN assessment	**Group 1 (Grade 1 VPT loss), n = 15**	**Group 2 (Grade 2 VPT loss), n = 15**	**Group 3 n = 15**
DNS	1—3	2—4	1—2
VPT	17—25 V	26—34 V	6—11 V

SLC19A3 expression was calculated by the equation $2^{-\Delta\Delta Ct}$. ΔCt was calculated by subtracting the Ct values of GAPDH from the Ct values of *SLC19A3*. The expression of the gene *SLC19A3* was done initially before therapy and after benfothiamine therapy in the patients in stage 2 of the study.

RESULTS AND DISCUSSION

Analysis of *SLC19A3* gene expression in patients with type 2 diabetes. In the initial phase (stage 1) of our investigation samples were collected from 45 patients to check the gene expression of the target gene (*SLC19A3*). The expression levels of *SLC19A3* mRNA were normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (Table 2).

Table 2

Gene expression C_T values of Target gene

Gene	Group 1 (Grade 1 VPT loss), n = 15	Group 2 (Grade 2 VPT loss), n = 15	Group 3, n = 15
SLC19A3 Stage 1	26.2667 ± 0.6520	26.7333 ± 0.5380	26.6667 ± 0.7080
GAPDH Stage 1	20.0714 ± 0.6990	20.9333 ± 0.5380	19.8667 ± 0.8640

It is evident that the C_T value of the target gene (*SLC19A3*) in all the three groups in comparison to each other did not have significant difference in the initial phase of the investigation, the difference in expression of *SLC19A3* in the groups was ± 2.65 %. In group 1 (C_T —26.2667 ± 0.6520) and group 3 (C_T — 26.6667 ± 0.7080) the C_T values for *SLC19A3* were quite similar and the expression was more abundant as compared to group 2 (C_T — 26.7333 ± 0.5380) where the C_T value was higher. The scenario for GAPDH was also quite similar to the trend as in the target gene, in group 1 (C_T — 20.0714 ± 0.6990) and group 3 (C_T — 19.8667 ± ± 0.8640) the C_T value for GAPDH was lower, whereas the C_T value in group 2 (C_T — 20.9333 ± 0.5380) was higher, meaning that the expression was less abundant as compared to the other two groups in the study. The ΔC_T μ (mean) for group 1 (with grade 1 VPT loss) was 6,1333 ($p < 0.05$). The ΔC_T μ (mean) for group 2 (with grade 2 VPT loss) was 5.80 ($p < 0.05$). The ΔC_T μ (mean) for group 3 was 6.8 ($p < 0.05$) (Figure).

The variability of C_T values SLC19A3 and GAPDH in correlation to HbA1c in patients with type 2 diabetes in study groups

Group 1. The C_T values for *SLC19A3* in the patients with HbA1c < 7.5 % (25.800 ± 0.656 (± 2.54 %)) and patients with HbA1c 7.6—8—9 % (C_T — 25.800 ± 1.022 (± 3.96 %)) the C_T values were quite similar and the expression was more abundant as compared to patients with HbA1c > 9.0 % (C_T — 27.200 ± 1.163 (± 4.28 %)) where the C_T value was higher. The scenario for GAPDH was also quite similar to the trend as in the target gene patients with HbA1c < 7.5 % (C_T — 19.600 ± 1.052 (± 5.37 %)) and patients with HbA1c 7.6—8—9 % (C_T — 19.600 ± 1.052 (± 5.37 %)) the C_T value for GAPDH was lower, whereas the C_T value in patients with HbA1c > 9.0 % (C_T — 21.200 ± 0.656 (± 3.09 %)) was higher, meaning that the expression was less abundant as compared to the patients with HbA1c < 8.9 %. The ΔC_T μ (mean) for patients with HbA1c < 7.5 % was 6.2. The ΔC_T μ (mean) for patients with HbA1c 7.6—8.9 % was 6.2. The ΔC_T μ (mean) for patients with HbA1c > 9.0 % was 6.0.

Group 2. The C_T values for *SLC19A3* in the patients with HbA1c < 7.5 % (26.400 ± 0.894 (± 3.39 %)) and patients with HbA1c 7.6—8—9 % (C_T — 26.200 ± 0.656 (± 2.50 %)) the C_T values were quite similar and the expression was more abundant as compared to patients with HbA1c > 9.0 % (C_T — 27.600 ± 0.701 (± 2.54 %)) where the C_T value was slightly higher. In the case of GAPDH the trend was also quite similar to the target gene in patients with HbA1c < 7.5 % (C_T — 20.800 ± ± 0.656 (± 3.15 %)) and patients with HbA1c 7.6—8—9 % (CT — 20.600 ± 0.701 (± 3.40 %)) the C_T value for GAPDH was lower, whereas the C_T value in patients with HbA1c > 9.0 % (C_T — 21.400 ± 1.189 (± 5.56 %)) was higher, meaning that the expression was slightly less profound as compared to the patients with HbA1c

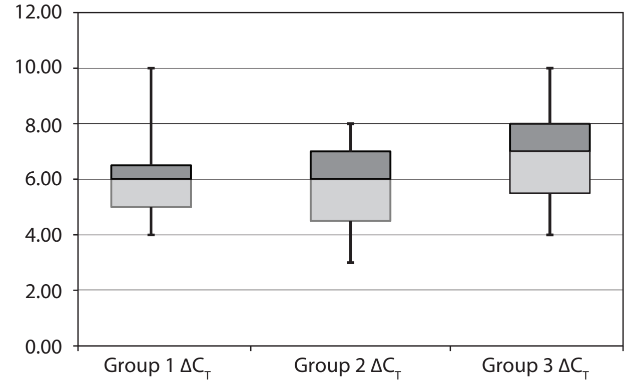

Figure. *Box Plot — Comparative analysis of changes in ΔC_T in patients before treatment with benfothiamine. The boxes mark the interval between the 25th and 75th percentiles. The whiskers denote the interval between the 10th and 90th percentiles* of < 7.5 % and HbA1c of 7.6—8,9 %. The ΔC_T μ (mean) for patients with HbA1c < 7.5 % was 5.6. The ΔC_T μ (mean) for patients with HbA1c 7.6—8.9 % was 5.6. The ΔC_T μ (mean) for patients with HbA1c > 9.0 % was 6.2.

Group 3. The C_T values for *SLC19A3* in the patients with HbA1c < 7.5 % (26.000 ± 1.240 (± 4.77 %)) and patients with HbA1c 7.6—8—9 % (C_T — 26.400 ± 0.894 (± 3.39 %)) the C_T values were quite similar and the expression was more abundant as compared to patients with HbA1c > 9.0 % (C_T — 27.600 ± 1.052 (± 3.81 %)) where the C_T value was slightly higher. This trend was seen in all the groups, that C_T value had a tendency to increase in patients with high levels of HbA1c. In the case of GAPDH the trend was also quite similar to the target gene in patients with HbA1c < 7.5 % (C_T — 19.000 ± 1.839 (± 9.68 %)) and patients with HbA1c 7.6—8—9 % (C_T — 19.6 ± 0.894 (± 4.56 %)) the C_T value for GAPDH was lower, whereas the C_T value in patients with HbA1c > 9.0 % (C_T — 21.000 ± 0.96 (± 4.57 %)) was higher, meaning that the expression was slightly less profound as compared to the patients with HBA1c of < 7.5 % and HbA1c of 7.6—8.9 %. The ΔC_T μ (mean) for patients with HbA1c < 7.5 % was 7.0. The ΔC_T μ (mean) for patients with HbA1c 7.6—8.9 % was 6.8. The ΔC_T μ (mean) for patients with HbA1c > 9.0 % was 6.6.

The variability of C_T values SLC19A3 and GAPDH in correlation to duration of disease in patients with type 2 diabetes

Group 1. The C_T values for *SLC19A3* in the patients with duration of disease < 7 years (C_T — 25.8571 ± ± 0.8330 (± 3.22 %)) was slightly less as compared to patients with duration of disease 7—10 years (C_T — 26.625 ± 0.913 (± 3.43 %)). The difference in C_T values was not significant. For GAPDH there was no significant difference between the two categories. In patients with duration of disease < 7 years (C_T — 20.1429 ± 1.004 (± 4.98 %)) was almost identical to the C_T value of patients with duration of disease 7—10 years (C_T — 20.125 ± 0.879 (± 4.37 %)). The ΔC_T μ (mean) for patients with duration of disease < 7 years was 5.71. The ΔC_T μ (mean) for patients duration of disease 7—10 years was 6.5.

Group 2. The C_T values for *SLC19A3* in the patients with duration of disease < 7 years (C_T — 26.200 ± 0.656 (± 2.50 %)) and in patients with duration of disease >10 years (C_T — 26.600 ± 0.894 (± 3.36 %)) was less as compared to patients with duration of disease 7—10 years (C_T — 27.400 ± 0.894 (± 3.26 %)). The difference in C_T values between the categories representing duration of disease did not show any statistical valid trend. For GAPDH in patients with duration of disease < 7 years (C_T 20.600 ± 1.052 (± 5.11 %)) and in patients with duration of disease > 10 years (C_T — 20.800 ± ± 0.656 (± 3.15 %)) was less as compared to the $C_T$value in patients with duration of disease 7—10 years (C_T— 21.400 ± 0.894 (± 4.18 %)). The difference in C_T values in the categories of duration of disease indicated that gene expression of the target gene and the normalizing gene in group 2 was independent of the duration of disease. The ΔC_T μ (mean) for patients with duration of disease < 7 years was 5.6. The ΔC_T μ (mean) for patients duration of disease 7—10 years was 6.0. The ΔC_T μ (mean) for patients duration of disease > 10 years was 5.8.

Group 3 (control). The C_T values for *SLC19A3* in the patients with duration of disease < 7 years (C_T — 26.00 ± ± 0.97 (± 3.73 %)) and inpatients with duration of disease >10 years (C_T — 27.000 ± 1.386 (± 5.13 %)) was less as compared to patients with duration of disease 7—10 years (C_T — 27.3333 ± 0.9980 (± 3.65 %)). The difference in C_T values between the categories representing duration of disease did not show any statistical valid trend. For GAPDH in patients with duration of disease < 7 years (C_T — 19.1429 ± 1.3390 (± 6.99 %)) the C_T value was less as compared to the patients with duration of disease > 10 years (C_T — 20.500 ± 0.693 (± 3.38 %)) and duration of disease 7—10 (C_T — 20.5 ± 1.2 (± 5.85 %)). The difference in C_T values in the categories of duration of disease indicated that gene expression of the target gene and the normalizing gene in group 3 was independent of the duration of disease. The ΔC_T μ (mean) for patients with duration of disease < 7 years was 6.8. The ΔC_T μ (mean) for patients duration of disease 7—10 years was 6.8. The ΔC_T μ (mean) for patients duration of disease > 10 years was 6.5.

CONCLUSIONS

In the first stage of the study in patients with type 2 diabetes with diabetic polyneuropathy with the involvement of small nerve fibers and large nerve fibers we found that the difference in expression of the solute carrier gene *SLC19A3* in patients with variable levels of neuropathy was not significant. As evident from the C_T values and the value of ΔC_T there was no statistically valid difference between the groups. The C_T value of the target gene (*SLC19A3*) in all the three groups, in comparison to each other did not have significant difference in the initial phase of the investigation, the difference in expression of *SLC19A3* in the groups was ± 2.65 %. In correlation to duration of disease the trend was similar, showing that duration of disease does not play an altering role in the expression of the target gene. In correlation to risk factor glycemic control (level of HbA1c) the expression of the target gene was slightly more profound in patients with an HbA1c of < 8.9 % as compared to the patients with HbA1c value 9.0 %. Taking into consideration the results of the study it can be stated the expression of *SLC19A3* is independent of the severity of diabetic polyneuropathy, duration of diabetes and the glycemic compensation in patients with type 2 diabetes.

Authors' contributions. *K. Singh and Yuzvenko T. participated in the conception and design of the study. All authors took part in the collection and analyses of the data. K Singh drafted the initial manuscript and Yuzvenko T revised the manuscript. All authors read and approved the final manuscript.*

Competing interests. *The authors declare that they have no competing interests.*

Ethics approval and consent to participate. This study conformed to the guidelines of the Declaration of Helsinki, and the study procedures were reviewed and approved by the medical research ethics committee Each patient agreed to participate and signed the informed consent form.

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ABSTRACT

Integrated analysis of gene expression of solute carrier gene *SLC19A3* with proven risk factors of microvascular complications in patients with type 2 diabetes

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Diabetes mellitus (DM) is a chronic progressive disorder which leads to significant disability, morbidity and is likely to progress to become one of the most widespread conditions worldwide and as an additional burden to the healthcare system already reeling under the effects of the COVID-19 pandemic worldwide.

Aim — to study the correlative variation in gene expression of *SLC19A3* in type 2 diabetes patients with proven risk factors of diabetes complications.

Materials and methods. In the study, 190 patients with type 2 DM were screened for diabetic peripheral neuropathy (DPN). DPN was confirmed in (n = 105) patients displaying symptoms of diabetic polyneuropathy with the involvement of small nerve fibers and large nerve fibers. Out of the total cohort, 45 patients with type 2 DM were shortlisted and randomized according to the severity of diabetic polyneuropathy, for assessment of the expression of the gene *SLC19A3* in stage 1 of the gene expression study.

Results. In the first stage of the study in patients with type 2 diabetes with diabetic polyneuropathy with the involvement of small nerve fibers and large nerve fibers we found that the difference in expression of the solute carrier gene *SLC19A3* in patients with variable levels of neuropathy was not significant. As evident from the C_T values and the value of ΔC_T there was no statistically valid difference between the groups. The C_T value of the target gene (*SLC19A3*) in all the three groups, in comparison to each other did not have significant difference in the initial phase of the investigation. In correlation to duration of disease the trend was similar, showing that duration of disease does not play an altering role in the expression of the target gene. In correlation to risk factor glycemic control (level of HbA1c) the expression of the target gene was slightly more profound in patients with an HbA1c of < 8.9 % as compared to the patients with HbA1c value > 9.0 %.

Conclusions. Taking into consideration the results of the study it can be stated the expression of *SLC19A3* is independent of the severity of diabetic polyneuropathy, duration of diabetes and the glycemic compensation in patients with type 2 diabetes.

Keywords: type 2 diabetesmellitus, microvascular complications, expression of solute carrier gene *SLC19A3*.

РЕЗЮМЕ

Комплексний аналіз експресії гена *SLC19A3* у хворих на цукровий діабет 2-го типу з факторами ризику мікросудинних ускладнень

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Цукровий діабет (ЦД) — це хронічна патологія, котра прогресує і призводить до значної втрати працездатності, росту захворюваності та додаткового навантаження на систему охорони здоров’я.

Мета — вивчити кореляційні варіації експресії гена *SLC19A3* у хворих на ЦД 2 типу з чинниками ризику діабетичних ускладнень.

Матеріали та методи. Проведено обстеження 190 пацієнтів із ЦД 2 типу на наявність діабетичної периферичної нейропатії (ДПН). У 105 пацієнтів, які мали симптоми діабетичної полінейропатії із залученням дрібних та великих нервових волокон, наявність ДПН підтверджено. Із загальної когорти 45 пацієнтів із ЦД 2 типу були рандомізовані відповідно до тяжкості діабетичної полінейропатії для оцінки експресії гена *SLC19A3*.

Результати. На першому етапі дослідження у пацієнтів з цукровим діабетом 2 типу з діабетичною полінейропатією з залученням дрібних і великих нервових волокон ми виявили, що різниця в експресії гена *SLC19A3* була несуттєвою. Очевидно, що в значеннях C_T і значеннях ΔC_T статистично достовірної різниці між групами не було. Значення C_T цільового гена (*SLC19A3*) в усіх трьох групах один з одним не мали істотної різниці в початковій фазі дослідження. В кореляції фактора ризику, такого як тривалість захворювання, тенденція була аналогічною, показуючи, що тривалість хвороби не відіграє ролі в зміні експресії гена. В кореляції фактора ризику за рівнем глікованого гемоглобіну — експресія гена була трохи більшою у пацієнтів з HbA1c < 8,9 % порівняно із пацієнтами з значенням HbA1c > 9,0 %.

Висновки. Беручи до уваги результати дослідження можна констатувати, що експресія гена *SLC19A3* не залежить від ступеня тяжкості діабетичної полінейропатії, тривалості цукрового діабету і компенсації глікемії у пацієнтів з цукровим діабетом 2 типу.

Ключові слова: цукровий діабет 2 типу, мікросудинні ускладнення, експресія гена розчинного носія SLC19A3 .

РЕЗЮМЕ

Комплексный анализ экспрессии гена *SLC19A3* у больных с сахарным диабетом 2 типа с факторами риска микрососудистых осложнений

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Сахарный диабет (СД) — это хроническая патология, которая прогрессирует и приводит к значительной потере трудоспособности, росту заболеваемости и дополнительной нагрузке на систему здравоохранения.

Цель — изучить корреляционные вариации экспрессии гена *SLC19A3* у больных с сахарным диабетом 2 типа с факторами риска диабетических осложнений.

Материалы и методы. Проведено обследование 190 пациентов с СД 2 типа на наличие диабетической периферической нейропатии (ДПН). У 105 пациентов, имевших симптомы диабетической полинейропатии с вовлечением мелких и крупных нервных волокон, наличие ДПН подтверждено. Из общей когорты 45 пациентов с СД 2 типа были рандомизированы в соответствии с тяжестью диабетической полинейропатии для оценки экспрессии гена *SLC19A3*.

Результаты. На первом этапе исследования у пациентов с сахарным диабетом 2 типа с диабетической полинейропатией с вовлечением мелких и крупных нервных волокон мы обнаружили, что разница в экспрессии гена-носителя *SLC19A3* была незначительна. Очевидно, что в значениях C_T значениях ΔC_T статистически достоверной разницы между группами не было. Значение C_T целевого гена (*SLC19A3*) во всех трех группах по сравнению друг с другом не имели существенной разницы в начальной фазе исследования. В корреляции фактора риска, такой как продолжительность заболевания, тенденция была аналогичной, показывая, что продолжительность болезни не играет изменяющей роли в выражении экспрессии гена. В корреляции фактора риска по результатам гликированного гемоглобина — экспрессия гена была незначительно больше у пациентов с HbA1c < 8,9 % по сравнению с пациентами со значением HbA1c > 9,0 %.

Выводы. Принимая во внимание результаты исследования можно констатировать, что экспрессия гена *SLC19A3* не зависит от степени тяжести диабетической полинейропатии, продолжительности сахарного диабета и компенсации гликемии у пациентов с сахарным диабетом 2 типа.

Ключевые слова: сахарный диабет 2 типа, микрососудистые осложнения, экспрессия гена раастворимого носителя SLC19A3.

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