ISSN 2518-1432 (Online); ISSN 2227-4782 (Print) https://doi.org/10.21856/j-PEP.2026.1.02

EFFECT OF SIRT1 GENE POLYMORPHISM *(rs2273773)* ON CARDIOVASCULAR RISK MARKERS IN OVERWEIGHT PATIENTS WITH TYPE 2 DIABETES MELLITUS OF THE EAST UKRAINIAN POPULATION*

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Diabetes mellitus (DM) has long been a public health problem worldwide due to high rates of morbidity, disability, and mortality [1]. Type 2 DM is a complex polygenic metabolic disease associated with many risk factors, the main of which is overweight/obesity [2]. It has been proven that under conditions of obesity, visceral adipose tissue acquires a dysfunctional phenotype and changes the pattern of signaling proteins, which are collectively called adipokines and affect systemic metabolism and inflammation [3]. An important milestone was the emergence of the concept of a state of chronic low-intensity inflammation. The basis for this view is the fact that levels of circulating markers of inflammation, such as pro-inflammatory cytokines and acute phase proteins, are increased in obesity [3, 4]. These markers include leptin, resistin, tumor necrosis factor alpha (TNF-α), retinol-binding protein-4, progranulin, etc. [5]. In addition, adipose tissue is an important inflammatory source in obesity and T2DM not only due to adipokines, but also due to its infiltration by macrophages [6].

On the other hand, the degree of manifestation of the pathogenetic action of these protein molecules may be influenced by polymorphic variants of their genes, genes of their specific receptors and associated regulatory molecules [7–9].

* The work was carried out within the frameworks of the fundamental research of the SI "V. Danilevsky Institute for Endocrine Pathology Problems of the NAMS of Ukraine": "To investigate the role of genetic and pharmacological modulators of energy homeostasis in the development of insulin resistance and associated vascular disorders" (state registration No 0121U111536).

The institution that finances the study is the National Academy of Medical Sciences of Ukraine.

The authors assume responsibility for the published work.

The authors express their gratitude to Eugene H. J. M. Jansen for his participation in joint research, which became the basis for the implementation of this work.

The authors guarantee absence of competing interests and their own financial interest when carrying out the research and writing the article.

The manuscript was received by the editorial staff 18.11.2025.

A separate group of substances that can affect energy homeostasis and have been actively studied recently in connection with metabolic diseases are the so-called energy sensors — sirtuins [10]. Sirtuins are a family of NAD^+-dependent proteins that possess deacetylase or mono-ADP-ribosyltransferase activity. Sirtuins deacetylate lysine residues in histone proteins with the transfer of acetyl to the ADP-ribose fragment from NAD^+, thereby contributing to chromatin condensation and the cessation of expression of genes whose products are currently unnecessary for cells or may even be harmful. In addition to histones, sirtuin targets include transcription factors, coregulators, and metabolic enzymes that adapt gene expression and metabolic activity in response to the energy status of the cell [11].

As part of the study of chronic metabolic diseases, much attention is paid to studying the function of sirtuin-1, a product of the *SIRT1* gene [10, 12]. *SIRT1* consists of 9 exons and 8 introns, is located on chromosome 10p37.5, and *SIRT1* activation has been associated with numerous beneficial metabolic effects. There is also indirect evidence from genetic studies that sirtuin-1 may be involved in the development of obesity in humans, as some of its genetic variants have been found to be associated with weight gain and metabolic shifts [13–15]. Several single nucleotide polymorphisms (SNPs) located in *SIRT1* have been tested for their association with components of obesity, metabolic syndrome, and type 2 DM [13-17].

The *C > T* (*rs2273773*) SNP of the *SIRT1* gene is a so-called «silent» mutation in exon 5 and may be linked to other mutations that affect both the expression of the sirtuin-1 protein and its activity in various tissues.

The **aim** of the study was to assess the association of polymorphic variants *rs2273773* of the sirtuin-1 gene with characteristics of insulin resistance and hormonal activity of adipose tissue in overweight patients with type 2 diabetes from the East Ukrainian population.

MATERIALS AND METHODS

The studies were conducted in compliance with the principles of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine, and the current legislation of Ukraine. The study protocol was approved by the institutional review board (IRB) of SI «V. Danilevsky Institute for Endocrine Pathology Problems of the NAMS of Ukraine» (No 2, 27/01/2022). Patients provided written informed consent to participate in the study.

All examined patients underwent inpatient treatment in the clinic of the SI «V. Danilevsky Institute for Endocrine Pathology Problems of the NAMS of Ukraine». They were clinically and biochemically confirmed as type 2 DM.

A retrospective analysis of clinical and biochemical indicators obtained for patients whose samples are included in the DNA collection of patients with type 2 DM was performed. 61 patients with type 2 DM (female/male: 27/34) aged (53.35 ± 1.38) years, duration of diabetes 5.33 ± 0.67 years, glycated haemoglobin (HbA_{1C}) 7.74 ± 0.19%, body mass index (BMI) 33.28 ± 0.89 kg/m^2, were selected for analysis. All patients were interviewed regarding a full medical history that included age, gender, occupation, duration of diabetes, mode and duration of treatment, presence of any associated diseases, surgical history, personal history of smoking/alcohol/drug abuse, dietary habit and family history of diabetes.

The presence and stage of diabetic microangiopathies (retinopathy and nephropathy), diabetic neuropathy, macroangiopathies (primarily coronary artery disease) and arterial hypertension were diagnosed according to the guidelines [18].

Antidiabetic therapy of patients included sulfonamides, biguanides, or their combination. The patients underwent a general clinical examination, including vascular pathology characteristic of diabetes and comorbid pathology. Biochemical and immunoenzymatic measurements were carried out on the basis of the National Institute of Public Health and the Environment (Bilthoven, the Netherlands) within the scope of scientific cooperation. The following indicators were measured in samples of biological material (blood plasma, serum, erythrocytes), which were stored and transported frozen: glucose, HbA_{1C}, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), high-sensitivity C-reactive protein, creatinine, bilirubin, uric acid levels. The above indicators were determined on a Hitachi 912 clinical autoanalyzer using Roche Diagnostics (Switzerland) kits, as well as on an X20-Pro, Beckman-Coulter (Netherlands) autoanalyzer using the appropriate Beckman-Coulter kits. The low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald formula. Free fatty acids (FFA) were measured using a kit from Wako Diagnostics (USA). All samples before measuring the above parameters were checked for hemolysis, lipemia and icteric coloration.

The following parameters were determined using ELISA methods according to the manufacturer's instructions: resistin, osteoprotegerin (RayBiotech, USA), retinol-binding protein-4 (RBP-4), TNF-α, interleukin (IL)-6, IL-1b (R&D Systems, UK), leptin, progranulin, vaspin, omentin-1, lipocalin-2 (Biovendor, Czech Republic), total adiponectin (Biovendor, Czech Republic; ALPCO Diagnostics, USA), high molecular weight adiponectin (ALPCO Diagnostics, USA), insulin (DRG, Germany).

The normal (reference) values for some of hormones/adipokines were:

Insulin (30-78 pmol/L); leptin (2-11 μg/L); retinol-binding protein-4 (approx. 40 mg/L); adiponectin (5-37 mg/L); progranulin (approx. 41 μg/L); vaspin (0.2-2.5 μg/L); osteoprotegerin (approx. 540 ng/L); interleukin-6 (0-43.5 μg/L); TNF-α (0-8.1 ng/L).

Insulin resistance (IR) was characterized by the HOMA-IR index [19], the HOMA-IR/adiponectin index [20], and the estimated glucose disposal rate (eGDR) [21], the function of pancreatic β-cells was assessed by the HOMA-BCF index. Insulin sensitivity was assessed by the QUICKI [22] and adiponectin/leptin indices [23]. Insulin resistance of adipose tissue was characterized by the index HOMA-IR/leptin and Adipo-IR [24]. The pathological impact of dyslipidemia was assessed by the Castelli risk indices (CRI) I and II according to the following formulas:

$$\text{CRI-I} = \text{TC} / \text{HDL-C}$$
$$\text{CRI-II} = \text{LDL-C} / \text{HDL-C}.$$

In addition, the triglyceride-glucose index was calculated:

$$\text{TGGI} = \ln[\text{TG (mg/dL)} \times \text{fasting glucose (mg/dL)} / 2].$$

Determination of the single-nucleotide substitution of cytosine for thymine in exon 5 of the *SIRT1* gene *rs2273773* (*C>T*) was carried out by polymerase chain reaction with two pairs of opposite primers [17, 25]:

forward 1 (F1): *5'-GTGTGTCGCATCCATCTAGATAC-3';*
forward 2 (F2): *5'-CTCTCTGTCACAAATTCATAGCCT-3';*
reverse 1 (R1): *5'-GTAGTTTTCCTTCCT TATCTGACAG-3';*
reverse 2 (R2): *5'-CTGAAGTTTACTAA CCATGACACTG-3'.*

In this case, all four primers were simultaneously in the reaction amplification mixture, and three DNA fragments of different lengths (314, 228, and 135 bp) were synthesized in PCR between primers F1 and R1, F2 and R2, and between F1 and R2. Further electrophoretic fractionation of the synthesized DNA fragments allowed us to determine the following genotypes for the *SIRT1 rs2273773* (*C > T*) gene: *CC* — 314/228 bp; *CT* — 314/228/135 bp; *TT* — 314/135 bp.

Allele frequencies for the studied genotype were calculated. The normality of the distribution of variables was determined using the Kolmogorov-Smirnov test. To compare the indices with normal distribution Student's t-test was used and for comparison variables with abnormal distribution Mann-Whitney's U-test was used. The χ^2 was used to statistically evaluate the differences observed between empirical and theoretical frequencies of the variation series. The data are presented as mean ± SEM, some of data are presented as median and 25th and 75th percentiles. All statistical tests were two tailed and a probability (p) value of 5% or less was considered statistically significant.

RESULTS AND THEIR DISCUSSION

The results of genotyping according to the above-mentioned SNP indicate that in the examined group of patients with type 2 DM, the actual (Table 1) and theoretically expected (according to the Hardy-Weinberg equilibrium) frequency distributions coincide. Thus, there is no accumulation of certain genotypes under the conditions of the studied pathology.

A preliminary analysis of the polymorphism functional significance was performed using a recessive inheritance model, i.e. *CC* carriers (n=24) versus *CT+TT* (n=37).

Analysis of clinical parameters of the examined group revealed that this SNP did not have a statistically significant effect on the age of manifestation of type 2 DM, the degree of diabetes compensation, insulin resistance parameters, atherogenicity indices, blood pressure, and degree of obesity (Table 2). However, there was a trend (0.05 < P < 0.1) towards worse indicators characterizing adipose tissue insulin resistance (HOMA-IR/adiponectin, HOMA-IR/leptin, adiponectin/leptin) in carriers of the mutant *T*-allele. The above was accompanied by a shift in the dyslipidemia parameters (triglycerides, high-density lipoprotein cholesterol).

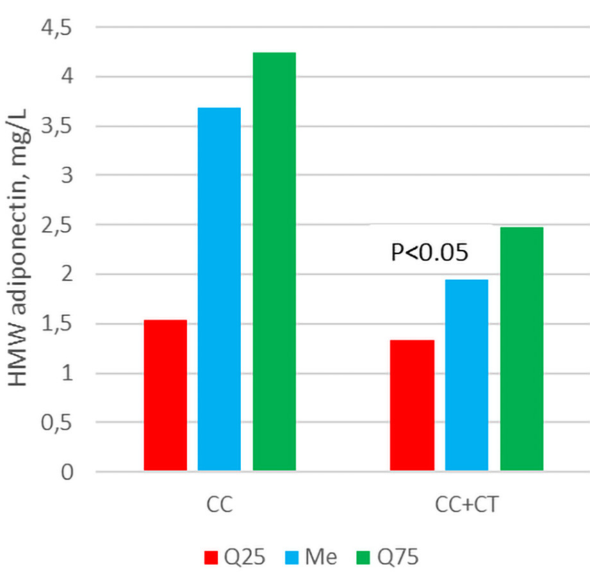
It should also be added that the mutant *T*-allele has a proatherogenic effect on indicators related to inflammation in adipose tissue. Thus, a statistically significant decrease in the levels of the most active form of the anti-inflammatory adipocytokine — high molecular weight adiponectin [26] — was found in *T*-allele carriers relative to the indicator for the *CC* genotype (Fig. 1). A decrease in vaspin, an adipokine that increases insulin sensitivity, inhibits the synthesis of pro-inflammatory cytokines, and is involved in the regulation of food intake [27, 28], was also identified in *T*-allele carriers. There were trends toward higher levels of other markers of chronic inflammation (TNF-α, IL-6, IL-1b, data not shown), consistent with evidence on greater inflammatory joint damage in rheumatoid arthritis patients with the *T*-allele [29].

It is noteworthy that carriers of the *T*-allele had significantly higher superoxide dismutase activity (24.77 ± 0.92 vs 20.46 ± 0.68 kU/mmol

Table 1

Results of genotyping by polymorphism *C > T rs2273773* of the *SIRT1* gene in patients with type 2 diabetes mellitus

Group	n	Genotype frequency, n (%)			Allele frequencies	
		CC	CT	TT	pC	pT
Males	34	14 (41)	16 (47)	4 (12)	0,65	0,35
Females	27	10 (37)	13 (48)	4 (15)	0,61	0,39
Total	61	24 (39)	29 (48)	8 (13)	0,63	0,37



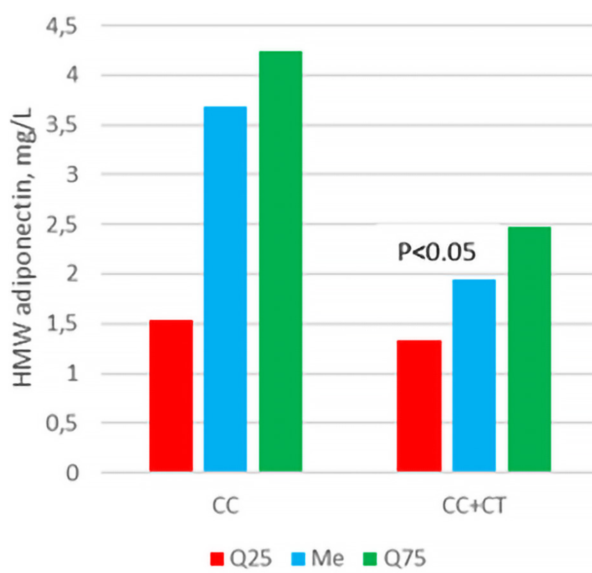


Fig. 1. Serum levels of antiatherogenic adipocytokines in the carriers of different genotypes by polymorphism *C > T rs2273773* of the *SIRT1* gene, Me [Q_{25}; Q_{75}]; HMW — high molecular weight

Table 2

Characteristics of type 2 diabetes patients with different genotypes by polymorphism *C > T rs2273773* of the *SIRT1* gene, ($\bar{X} \pm S_{\bar{X}}$), Me [Q_{25}; Q_{75}]

Parameter	*C > T rs2273773 SIRT1* genotype	
	***CC* (n = 24)**	***CT + TT* (n = 37)**
Age, years	52.59 ± 2.03	54.77 ± 1.49
Age of diabetes manifestation, years	45.82 ± 1.96	49.86 ± 1.40
BMI, kg/m^2	33.07 ± 1.16	32.41 ± 1.04
Waist-to-hip ratio	0.99 ± 0.02	0.97 ± 0.01
Systolic blood pressure, mm Hg	137.33 ± 8.19	143.57 ± 2.31
Diastolic blood pressure, mm Hg	84.33 ± 2.96	91.43 ± 2.59
Glucose, mmol/L	8.67 ± 0.59	9.16 ± 0.48
HbA_{1c}, %	7.49 ± 0.26	8.00 ± 0.25
Triglycerides, mmol/L	2.22 ± 0.29	2.68 ± 0.20
Total cholesterol, mmol/L	6.75 ± 0.46	5.78 ± 0.27
HDL-C, mmol/L	1.03 ± 0.08	0.95 ± 0.03
FFA, mmol/L	0.86 ± 0.13	0.91 ± 0.05
Insulin, pmol/L	146.60 ± 21.22 117.62 (78.52; 168.90)	121.52 ± 12.99 110.25 (76.28; 143.90)
HOMA-IR, units	8.22 ± 1.05 6.96 (4.14; 10.16)	7.91 ± 1.09 6.23 (4.32; 8.88)
eGDR, mg/kg/min	4.65 ± 0.41 4.48 (4.43; 5.72)	5.55 ± 0.39 5.27 (4.20; 7.36)
HOMA-BCF, units	107.47 ± 21.44 81.33 (49.00; 116.61)	94.27 ± 18.29 60.34 (38.10; 93.84)
QUICKI, units	0.46 (0.42; 0.51)	0.47 (0.43; 0.50)
HOMA-IR/adiponectin, units	1.66 ± 0.28 1.57 (0.81; 2.18)	2.83 ± 0.98 1.67 (0.89; 2.65)
HOMA-IR/leptin, units	0.17 ± 0.04 0.13 (0.11; 0.17)	0.25 ± 0.06 0.21 (0.09; 0.31)
Adiponectin/leptin, units	0.14 ± 0.03 0.12 (0.06; 0.15)	0.19 ± 0.05 0.12 (0.04; 0.21)
Adipo-IR, units	111.48 ± 16.41 86.42 (58.11; 128.54)	109.84 ± 12.07 90.57 (55.50; 147.05)
Atherogenicity coefficient, units	4.39 (3.67; 7.25)	5.07 (4.34; 5.87)
Castelli index I, units	8.99 ± 1.88 5.39 (4.67; 8.25)	6.10 ± 0.22 6.07 (5.34; 6.87)
Castelli index II, units	3.93 ± 0.55 2.91 (2.35; 3.91)	3.39 ± 0.16 3.24 (2.63; 4.05)
Triglyceride-glucose index, units	8.59 ± 0.16 8.64 (8.00; 9.24)	8.90 ± 0.10 8.94 (8.47; 9.34)

Note:
BMI — body mass index;
eGDR — estimated Glucose Disposal Rate;
FFA — free fatty acids;
HDL-C — high-density lipoprotein cholesterol;
HOMA-IR — Homeostatic Model Assessment for Insulin Resistance;
QUICKI — Quantitative Insulin sensitivity Check Index.

Hb in *CC*-carriers, P < 0.01) and levels of total (44.24 ± 3.45 vs 31.39 ± 2.96 μmol/mmol Hb in *CC*-carriers, P < 0.01) and reduced glutathione (35.10 ± 2.96 vs 21.86 ± 2.24 μmol/mmol Hb in *CC*-carriers, P < 0.01) in erythrocytes. The above is most likely compensatory in nature and indicates active lipoperoxidation processes. This coincides with the available literature data on the influence of the *C > T rs2273773* SNP variants of the *SIRT1* gene on the antioxidant system functioning in pregnant women of the Middle Eastern population [30].

The results obtained demonstrate a negative (pro-inflammatory and pro-atherogenic) effect of the minor allele of the *C > T rs2273773* polymorphism of the sirtuin-1 gene on the hormonal activity of adipose tissue in patients with type 2 DM of the East Ukrainian population.

CONCLUSIONS

Analysis of functional and metabolic indicators in carriers of different genotypes for sirtuin-1 gene variants *C>T* (*rs2273773*) proves a higher cardiovascular risk in carriers of minor allele for this polymorphism among overweight patients with type 2 diabetes in the East Ukrainian population. Thus, the results obtained can be used to optimize prevention and treatment regimens for overweight individuals and patients with type 2 diabetes, which will help preserve performance capability and increase the duration and quality of life.

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There is evidence that sirtuins as energy sensors contribute to the pathogenesis of obesity and related metabolic and cardiovascular diseases in humans. The single nucleotide polymorphism (SNP) *C > T (rs2273773)* of the *SIRT1* gene is a so-called «silent» mutation in exon 5 and may be linked to other mutations that affect both sirtuin-1 protein levels and its activity. The **aim** of the study was to assess the association of polymorphic variants *rs2273773* of the sirtuin-1 gene with characteristics of insulin resistance and hormonal activity of adipose tissue in overweight patients with type 2 diabetes from the East Ukrainian population.

Materials and methods. The study was conducted in accordance with international and domestic ethical and legal requirements and was approved by the Medical Ethics Committee at the IEPP. All examined patients underwent inpatient treatment at the institute's clinic. A retrospective analysis of clinical and biochemical parameters obtained for patients whose samples are included in the DNA collection of patients with type 2 diabetes mellitus (DM) was conducted. 61 patients with type 2 DM (male/female: 27/34) aged 53.35 ± 1.38 years, with diabetes duration of 5.33 ± 0.67 years, glycosylated hemoglobin level of 7.74 ± 0.19%, with body mass index of 33.28 ± 0.89 kg/m^2, and with waist-to-hip ratio of 0.99 ± 0.01 were selected. Antidiabetic therapy included sulfonamides, biguanides, or their combinations. Clinical, biochemical, and enzyme-linked immunosorbent assay measurements were performed at the National Institute for Public Health and the Environment (Bilthoven, the Netherlands) within the framework of scientific cooperation. Insulin resistance was characterized by the HOMA-IR index, HOMA-IR/adiponectin, adiponectin/leptin, HOMA-IR/leptin, Adipo-IR and a number of other surrogate indices. The pathological impact of dyslipidemia was assessed by Castelli risk indices I and II and triglyceride-glucose index.

Determination of the single-nucleotide substitution of cytosine for thymine in exon 5 of the *SIRT1* gene *rs2273773* (*C > T*) was carried out by polymerase chain reaction with two pairs of opposite primers. Electrophoretic fractionation determined the following genotypes for the *rs2273773* (*C > T*) *SIRT1* gene: *CC* — 314/228 bp; *CT* — 314/228/135 bp; *TT* — 314/135 bp. Allele frequencies for the studied genotype were calculated. The normality of the distribution of variables was determined using the Kolmogorov-Smirnov criterion. To compare the indicators characterized by normal distribution, the unpaired two-tailed Student's t-test was used, to compare the parameters with non-normal distribution, the Mann-Whitney test. To statistically assess the differences observed between the empirical and theoretical frequencies of the variation series, the χ2 (chi-square) test was used.

Results. Genotyping according to the above-mentioned SNP indicates that there is no accumulation of certain genotypes under the conditions of the studied pathology. A preliminary analysis of the polymorphism functional significance was performed using a recessive inheritance model, i.e. *CC*-carriers (n = 24) versus *CT + TT* (n = 37).

Analysis of clinical parameters revealed that this SNP did not have a statistically significant effect on the age of manifestation of type 2 DM, the degree of diabetes compensation, HOMA-IR, atherogenicity indices, blood pressure, and degree of obesity. However, there was a trend (0.05 < P < 0.1) towards worse indicators characterizing insulin resistance of adipose tissue (HOMA-IR/adiponectin, HOMA-IR/leptin, adiponectin/leptin) in carriers of the mutant *T*-allele. The above was accompanied by a shift in the triglyceride-glucose index (*CC*-carriers: 8.15 (4.29; 14.81) units vs 10.91 (6.88; 16.39) units in the *CC + CT* group, 0.05 < P < 0.1) and dyslipidemia parameters (triglycerides, high-density lipoprotein cholesterol). The mutant T-allele has been found to have a negative effect on indicators related to the hormonal function of adipose tissue. Thus, there is a statistically significant decrease in the levels of the most active form of anti-inflammatory adipocytokine — high molecular weight adiponectin — in *T*-allele carriers relative to the indicator for the *CC* genotype (1.96 ± 0.19 vs 3.09 ± 0.50 mg/L, respectively, P < 0.05). This was accompanied by a decrease in the levels of vaspin, an adipokine that increases insulin sensitivity, inhibits the synthesis of pro-inflammatory cytokines, and is involved in the regulation of food intake (*CC*-carriers: 0.33 (0.20; 0.64) vs 0.19 (0.08; 0.49) μg/L in the *CC + CT* group, P < 0.05). There are trends toward higher levels of chronic inflammation markers (TNF-α, IL-6, and IL-1b), which, however, do not reach statistical significance. In addition, carriers of the *T*-allele had significantly higher superoxide dismutase

activity (24.77 ± 0.92 vs 20.46 ± 0.68 kU/mmol Hb in *CC*-carriers, P < 0.01) and levels of total (44.24 ± 3.45 vs 31.39 ± 2.96 µmol/mmol Hb in *CC*-carriers, P < 0.01) and reduced glutathione (35.10 ± 2.96 vs 21.86 ± 2.24 µmol/mmol Hb in *CC*-carriers, P < 0.01) in erythrocytes. The above is most likely compensatory in nature and indicates active lipoperoxidation processes.

Conclusions. Analysis of the hormonal activity of adipose tissue suggests a higher cardiovascular risk in carriers of the minor allele of the *C > T rs2273773* polymorphism of the sirtuin-1 gene among overweight patients with type 2 diabetes in the East Ukrainian population. The results obtained can be used to optimize prevention and treatment regimens for overweight individuals and patients with type 2 diabetes, which will help maintain working capacity and increase the duration and quality of life.

Keywords: type 2 diabetes mellitus, sirtuin-1, single nucleotide polymorphism, insulin resistance, obesity, adipocytokines, cardiovascular risk.

ВПЛИВ ПОЛІМОРФІЗМУ ГЕНА SIRT1 *(rs2273773)* НА МАРКЕРИ СЕРЦЕВО-СУДИННОГО РИЗИКУ У ПАЦІЄНТІВ З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ ТА НАДЛИШКОВОЮ ВАГОЮ ЗІ СХІДНОУКРАЇНСЬКОЇ ПОПУЛЯЦІЇ

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Наявні свідчення того, що сиртуїни як енергетичні сенсори мають внесок до патогенезу ожиріння та пов'язаних метаболічних і серцево-судинних захворювань у людини. Однонуклеотидний поліморфізм (ОНП) *C > T (rs2273773)* гена *SIRT1* являє собою так звану «мовчазну» мутацію в екзоні 5 і може бути зчепленим з іншими мутаціями, що впливають як на рівні білка сиртуїну-1, так і на його активність. **Метою** дослідження була оцінка зв'язку поліморфних варіантів *rs2273773* гена сіртуїну-1 з характеристиками інсулінорезистентності та гормональної активності жирової тканини у пацієнтів з надлишковою вагою та цукровим діабетом 2 типу зі східноукраїнської популяції.

Матеріали та методи. Дослідження проведено відповідно до міжнародних та вітчизняних етичних та морально-правових вимог та ухвалено Комітетом з медичної етики при ДУ ІПЕП. Всі обстежені пацієнти проходили стаціонарне лікування в клініці інституту. Проведено ретроспективний аналіз клініко-біохімічних показників, отриманих для пацієнтів, зразки яких входять до колекції ДНК хворих на цукровий діабет (ЦД) 2 типу. Відібрано 61 хворого на ЦД 2 типу (ж/ч: 27/34) віком 53,35 ± 1,38 років, з тривалістю діабету 5,33 ± 0,67 років, рівнем глікозильованого гемоглобіну 7,74 ± 0,19 %, з індексом маси тіла 33,28 ± 0,89 кг/м^2, зі співвідношенням обсягу талії до обсягу стегон 0,99 ± 0,01. Антидіабетична терапія включала сульфаніламіди, бігуаніди або їх поєднання. Клініко-біохімічні та імуноферментні вимірювання проведено на базі Національного Інституту громадського здоров'я та навколишнього середовища (м. Білтховен, Нідерланди) в межах наукового співробітництва. Інсулінорезистентність характеризували за індексом HOMA-IR, HOMA-IR/адипонектин, адипонектин/лептин, HOMA-IR/лептин, Adipo-IR та рядом інших сурогатних індексів. Патологічний вплив дисліпідемії оцінювали за індексами ризику Кастеллі I та II і тригліцерид-глюкозним індексом.

Визначення однонуклеотидної заміни цитозину на тимін у екзоні 5 гена *SIRT1 rs2273773 (C > T)* здійснювали методом полімеразної ланцюгової реакції з двома парами протиставлених праймерів. Електрофоретичне фракціонування визначало наступні генотипи за геном *SIRT1 rs2273773 (C > T)*: *CC* — 314/228 п.н.; *CT* — 314/228/135 п.н.; *TT* — 314/135 п.н. Розраховували частоти алелей для дослідженого генотипу. Нормальність розподілу змінних визначали за допомогою критерію Колмогорова-Смірнова. Для порівняння показників, які характеризуються нормальним розподілом, застосовували непарний двобічний *t*-критерій Стьюдента, для порівняння параметрів із ненормальним розподілом — критерій Манна-Уітні. Для статистичної оцінки розбіжностей, спостережуваних між емпіричними і теоретичними частотами варіаційного ряду, застосовувався критерій χ^2 (хі-квадрат).

Результати. Генотипування за вищевказаним ОНП свідчить про те, що немає накопичення певних генотипів за умов дослідженої патології. Попередній аналіз функціональної значущості поліморфізму було проведено за рецесивною моделлю успадкування, тобто носіїв *CC* (n = 24) проти *CT* + *TT* (n = 37).

Аналіз клінічних параметрів виявив, що даний ОНП не впливав зі статистичною значущістю на вік маніфестації ЦД 2 типу, ступінь компенсації діабету, HOMA-IR, індекси атерогенності, артеріальний тиск та ступінь ожиріння. Однак спостерігалася тенденція (0,05 < P < 0,1) стосовно гірших показників, які характеризують інсулінорезистентність жирової тканини (HOMA-IR/адипонектин, HOMA-IR/лептин, адипонектин/лептин), у носіїв мутантного *T*-алеля. Вищевказане супроводжувалося зсувом тригліцерид-глюкозного індексу (*CC*-носії: 8,15 (4,29; 14,81) од. проти 10,91 (6,88; 16,39) од. у групі *CC* + *CT*, 0,05 < P < 0,1) та параметрів дисліпідемії (тригліцериди, холестерин ліпопротеїнів

високої щільності). Виявлено негативний вплив мутантного *T*-алеля на показники, які пов'язані з гормональною функцією жирової тканини. Так, має місце статистично значуще зниження рівнів найбільш активної форми протизапального адипоцитокіну — адипонектину з високою молекулярною масою — у носіїв *T*-алеля відносно показника за *CC*-генотипу (1,96 ± 0,19 проти 3,09 ± 0,50 мг/л, відповідно, P < 0,05). Це супроводжувалося зниженням рівнів васпіну — адипокіну, який підвищує чутливість до інсуліну, гальмує синтез прозапальних цитокінів та бере участь у регуляції прийому їжі (*CC*-носії: 0,33 (0,20; 0,64) проти 0,19 (0,08; 0,49) мкг/л у групі *CC* + *CT*, P < 0,05). Наявні тенденції щодо більших рівнів показників хронічного запалення (ФНП-α, ІЛ-6 та ІЛ-1b), які, однак, не сягають статистичної значущості. Також у носіїв *T*-алеля спостерігалася суттєво вища активність супероксиддисмутази (24,77 ± 0,92 проти 20,46 ± 0,68 кОд/ммоль Hb, P < 0,01) та рівні загального (44,24 ± 3,45 проти 31,39 ± 2,96 мкмоль/ммоль Hb, P < 0,01) і відновленого глутатіону (35,10 ± 2,96 проти 21,86 ± 2,24 мкмоль/ммоль Hb, P < 0,01) в еритроцитах. Вищезазначене, скоріше за все, має компенсаторний характер та свідчить про активні процеси ліпопероксидації.

Висновок. Аналіз гормональної активності жирової тканини дозволяє припустити більший серцево-судинний ризик у носіїв мінорного алеля за поліморфізмом *C* > *T* rs2273773 гена сиртуїну-1 серед хворих на цукровий діабет 2 типу з надлишковою вагою у східноукраїнській популяції. Отримані результати можуть бути використані для оптимізації режимів профілактики та лікування осіб з надмірною вагою та пацієнтів з діабетом 2 типу, що сприятиме збереженню працездатності та підвищенню тривалості та якості життя.

Ключові слова: цукровий діабет 2 типу, сиртуїн-1, однонуклеотидний поліморфізм, інсулінорезистентність, ожиріння, адипоцитокіни, серцево-судинний ризик.