

INVESTIGATION OF THE SIRT1 GENE SINGLE NUCLEOTIDE POLYMORPHISM (rs7069102) IN OVERWEIGHT PATIENTS WITH TYPE 2 DIABETES MELLITUS OF THE EAST UKRAINIAN POPULATION*

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The sirtuin-1 gene (*SIRT1*), known as the longevity gene, among other things protects cells from oxidative stress, promotes DNA stability by binding to several substrates and deacetylating these substrates [1].

SIRT1 activation exerts multiple protective effects through various metabolic and stress-reactive pathways. *SIRT1* expression modulates its downstream effects by targeting a number of cellular proteins such as peroxisome proliferator-activated receptor-gamma (PPAR- γ) and its coactivator-1a (PGC-1a), transcription factor FoxO, AMP-activated protein kinase, nuclear factor-kB, protein tyrosine phosphatase (PTP), endothelial NO synthase, p53, etc. [1, 2].

There are some or several or many reports of *SIRT1* suppression in certain types of cells and tissues under conditions of insulin resistance or against the background of impaired glucose tolerance [3]. There is also indirect evidence from genetic studies that sirtuins may be involved in the development of obesity in humans, as some of their genetic variants have been found to be associated with weight gain and metabolic complications. As with *in vitro* and animal studies, most human genetic studies have focused on *SIRT1* [4]. Several single nucleotide polymorphisms (SNPs) located in *SIRT1* have been tested for their association with obesity and metabolic syndrome components [4, 5]. Because *SIRT1* polymorphisms

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have been found to remain in high linkage disequilibrium, most genetic studies have focused on the analysis of SNP-tags that capture information about other linked variants [6].

One of the *SIRT1* polymorphisms that is actively studied in relation to metabolic disorders in various populations is the *C > G rs7069102* polymorphism in intron 4. It was determined that it is linked to several mutations in the promoter region of the gene and to two coding SNPs in exon 1 [4]. It is perhaps due to the different degree of coupling that results regarding its functional role differ significantly between populations. Thus, the association of the *G*-allele with coronary heart disease (CHD) in Turkish patients was determined [5], higher blood pressure and fat mass were noted in Japanese men with the homozygous minor gen-

otype (*GG*) [7], at the same time, an association of the *CC*-genotype with the development of diabetic nephropathy in patients with type 2 diabetes mellitus (T2DM) in Slovenia [8] and the absence of any statistically significant associations with obesity, lifestyle modification and glycemic control in a number of European populations (French, Swedish, German, Dutch) was recorded [4]. Recent studies on the territory of Ukraine have revealed the predominance of the homozygous minor *GG*-genotype among male residents of the Podilsk region with essential hypertension [9].

The aim of the study was to evaluate the association of polymorphic variants of the sirtuin-1 gene *rs7069102* with functional and metabolic characteristics in type 2 diabetes and overweight patients of 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» (No2, 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 T2DM.

A retrospective analysis of clinical and biochemical indicators obtained for patients whose samples are included in the DNA collection of patients with T2DM was performed. 61 patients with T2DM (female/male: 27/34) aged (53.35 ± 1.38) years, duration of diabetes 5.33 ± 0.67 years, HbA_{1c} 7.74 ± 0.19 %, BMI 33.28 ± 0.89 kg/m², 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 [10].

Antidiabetic therapy of patients included the following oral drugs — 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 (hsCRP), 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 (FA) 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 immunoenzymatic methods according to the manufacturer's instructions: resistin, matrix metalloproteinase-9 (MMP-9), osteoprotegerin (OPG) (RayBiotech, USA), retinol-binding protein-4 (RBP-4), fetuin-A (ICL, Newberg, USA), 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 μ g/L); retinol-binding protein-4 (approx. 40 mg/L); adiponectin (5–37 mg/L); progranulin (approx. 41 μ g/L); vaspin (0.2–2.5 μ g/L); osteoprotegerin (approx. 540 ng/L); interleukin-6 (0–3.5 μ g/L); TNF- α (0–8.1 ng/L).

Insulin resistance (IR) was characterized by the HOMA-IR index [11] and the HOMA-IR/adiponectin index [12], the function of pancreatic β -cells was assessed by the HOMA-BCF index. Insulin sensitivity was assessed by the QUICKI [13] and adiponectin/leptin indices [14]. Insulin resistance of adipose tissue was characterized by the index HOMA-IR/leptin and Adipo-IR [15]. The pathological impact of dyslipidemia was assessed by the Castelli risk indices (CRI) I and II according to the following formulas:

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

RESULTS AND THEIR DISCUSSION

Despite the small number of observations in this exploratory study, the frequencies of alleles in men and women of the examined group ($n = 61$) did not differ, and there was a noticeable difference in the distribution of genotype frequencies compared to the theoretical distribution according to the Hardy-Weinberg equilibrium (Table 1). In both men and women from the Eastern Ukrainian population of patients with T2DM, a significant deviation ($\chi^2 = 10.43$,

In addition, the triglyceride-glucose index was calculated:

$$\text{TGGI} = \text{TG} \times \text{fasting glucose} / 2.$$

Determination of the substitution of cytosine for guanine in intron 4 of the *SIRT1* gene *rs7069102* ($C > G$) was carried out by the method of polymerase chain reaction with two pairs of opposite primers:

- forward 1 (F1):
5'-GTAGCAGGAAGACTACAGGCCTG-3';
- forward 2 (F2):
5'-GAGAAGAAAGAAAGGCATAATCTCTGC-3';
- reverse 1 (R1):
5'-CTATCTGCAGAAATAATGGCTTTTCTC-3';
- reverse 2 (R2):
5'-GATCGAGACCATCCTGGCTAAG-3'

Electrophoretic fractionation made it possible to determine the following genotypes for the *SIRT1 rs7069102* ($C > G$): *CC* — 391/277 b.p.; *CG* — 391/277/167 b.p.; *GG* — 391/167 b.p. 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 \pm 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.

$P = 0.005$; $\chi^2 = 11.76$, $P = 0.003$, respectively) of the actual series from the expected frequencies in the direction of the accumulation of heterozygotes was observed, which requires further research.

Due to the small number of carriers of the minor homozygous genotype (*GG*), the minor allele carriers, i.e., *CG* and *GG*, were pooled for analysis of metabolic differences, and the analysis was performed under a recessive in-

Table 1

**Results of genotyping by polymorphism C > G rs7069102
of the SIRT1 gene in patients with type 2 diabetes mellitus**

Group	n	Genotype frequency, n (%)			Allele frequencies	
		CC	CG	GG	P _C	P _G
Males	34	6 (18)	26 (76)	2 (6)	0,56	0,44
Females	27	4 (15)	22 (81)	1 (4)	0,56	0,44
Total	61	10 (16)	48 (79)	3 (5)	0,56	0,44

Table 2

**Characteristics of type 2 diabetes patients
with different genotypes by polymorphism C > G rs7069102
of the SIRT1 gene, ($\bar{X} \pm S_{\bar{X}}$), Me [Q₂₅; Q₇₅]**

Parameter	C > G rs7069102 SIRT1 genotype	
	CC (n = 10)	CG + GG (n = 51)
Age, years	53.40 ± 2.63	54.04 ± 1.36
Age of diabetes manifestation, years	48.90 ± 2.47	48.17 ± 1.32
BMI, kg/m ²	36.80 ± 2.59	31.74 ± 0.68
Waist-to-hip ratio	0.98 ± 0.03	0.98 ± 0.01
Systolic blood pressure, mm Hg	139.40 ± 4.73	143.75 ± 2.69
Diastolic blood pressure, mm Hg	89.60 ± 1.91	90.42 ± 3.17
Glucose, mmol/L	8.96 ± 0.69	8.97 ± 0.42
Triglycerides, mmol/L	4.21 ± 1.47	2.89 ± 0.46
Total cholesterol, mmol/L	7.07 ± 0.87	5.99 ± 0.24
HbA _{1c} , %	8.45 ± 0.47	7.66 ± 0.20
Insulin, pmol/L	106.76 ± 16.19 107.69 (64.74; 130.12)	136.21 ± 13.29 113.14 (79.64; 162.01)
HOMA-IR, units	6.44 ± 0.78	8.32 ± 0.90
HOMA-BCF, units	78.60 ± 23.41 48.00 (40.00; 69.38)	132.48 ± 33.00 69.33 (44.77; 113.81)
QUICKI, units	0.48 (0.44; 0.50)	0.46 (0.43; 0.50)
HOMA-IR/adiponectin, units	0.84 ± 0.31 0.96 (0.54; 1.25)	2.35 ± 0.60 1.57 (0.78; 2.41) P < 0.05
HOMA-IR/leptin, units	0.09 ± 0.04 0.05 (0.05; 0.11)	0.22 ± 0.04 0.14 (0.11; 0.24) P < 0.02
Adiponectin/leptin, units	0.06 ± 0.02 0.05 (0.04; 0.07)	0.18 ± 0.04 0.12 (0.05; 0.22) P < 0.01
Adipo-IR, units	91.31 ± 16.19 84.55 (57.18; 101.75)	114.05 ± 11.09 96.60 (58.42; 143.81)
Castelli index I	10.38 ± 2.70	6.63 ± 0.74
Castelli index II	4.93 ± 0.96	3.34 ± 0.20
Triglyceride-glucose index	19.51 ± 7.43	12.97 ± 1.86

Note.

P is the significance of changes relative to the CC-group.

**Adipokine levels in diabetic patients
with different genotypes by polymorphism C > G rs7069102
of the SIRT1 gene, ($\bar{X} \pm S_{\bar{X}}$), Me [Q₂₅; Q₇₅]**

Parameter	C > G rs7069102 SIRT1 genotype	
	CC (n = 10)	CG + GG (n = 51)
Total adiponectin, mg/L	6.32 ± 0.71 6.74 (6.03; 7.03)	5.10 ± 0.37 5.03 (3.83; 6.68)
High molecular adiponectin, mg/L	2.35 ± 0.60 2.17 (1.87; 2.66)	2.44 ± 0.28 1.98 (1.43; 3.21)
Leptin, µg/L	122.05 ± 25.00 131.25 (99.73; 153.58)	56.84 ± 7.31* 47.15 (23.55; 81.98)
Vaspin, µg/L	0.28 (0.13; 0.43)	0.23 (0.14; 0.58)
Omentin-1, µg/L	563.25 ± 52.14	505.22 ± 24.46
Progranulin, µg/L	32.68 ± 2.85	29.66 ± 1.21
Retinol-binding protein-4, mg/L	32.03 ± 2.14	36.58 ± 2.53
Osteoprotegerin, ng/L	609.50 (489.00; 770.50)	424.00 (312.50; 628.50)
Interleukin-6, µg/L	7.83 ± 2.03 7.56 (4.67; 10.72)	10.34 ± 1.53 6.99 (5.22; 14.46)
TNF-α, ng/L	1.62 ± 0.23 1.44 (1.32; 1.74)	3.50 ± 0.79* 1.41 (0.90; 5.06)

Note.

* P < 0.05 relative to the CC-group.

heritance model. The analysis of the clinical parameters of the examined group revealed that the evaluated SNP did not affect the age of T2DM manifestation, the degree of diabetes compensation, blood pressure, and the degree of obesity (Table 2). At the same time, there were significant changes in the indicators characterizing insulin resistance, which is specifically related to the adipose tissue (HOMA-IR/ adiponectin, HOMA-IR/leptin, adiponectin/leptin). It is interesting that, despite some trend of higher levels of TG and TC in carriers of the CC-genotype, the above indices of insulin resistance were statistically increased in carriers of the minor allele G (see Table 2).

It is worth noting that, under the specified conditions, carriers of the dominant CC-genotype are characterized by significantly increased levels of leptin in the bloodstream compared to carriers of the recessive allele (Table 3), which remained even after comparison in groups divided by gender. At the same time, among patients with type 2 diabetes with a minor allele, a clear gender difference was found in the manifestations of adipose tissue resistance to insulin, which was accompanied by

statistically higher levels of such an inflammatory parameter as TNF-α. Namely, men had much worse than women, indexes Adipo-IR (139.59 ± 17.44 vs 85.18 ± 10.48, respectively, P < 0.05) and adiponectin/leptin (0.23 ± 0.06 vs 0.12 ± 0.0, respectively, P < 0.05) against the background of statistically constant parameters of carbohydrate and lipid metabolism, as well as the same degree of obesity, while the high TNF-α levels in the group of G-allele carriers were associated with male gender (4.73 ± 1.30 vs 1.92 ± 0.46 ng/L in women, respectively, 0.05 < P < 0.1).

Thus, the obtained results allow us to assume that the C > G rs7069102 polymorphism of the SIRT1 gene chosen for research is functional in the East Ukrainian population, since there is a shift in genotype frequencies towards the accumulation of heterozygotes, and the alleles themselves are associated with metabolic differences in the examined patients with T2DM and obesity. Accumulation of heterozygous genotypes among the diabetic population of both genders may be associated with a number of factors, for example, homozygotes for the studied minor allele may be linked to another

functional genotype that is able to influence survival at different stages of ontogenesis [4]. Recently data has been accumulating that this SNP may also be associated in the Ukrainian population with the risk of developing cardiovascular diseases (in men) [9]. The obtained results emphasize the presence of unique ge-

netic traits inherent in the examined total of patients with T2DM of the East Ukrainian population, and justify the need for further research involving a larger number of participants to assess the role of this polymorphism in different samples.

CONCLUSIONS

1. The C > G *rs7069102* polymorphism of the *SIRT1* gene is functional for the East Ukrainian population, as there is a statistically significant shift in the distribution of genotype frequencies towards heterozygotes, and alleles are associated with significant metabolic differences in overweight type 2 diabetes patients.
2. Against the background of a comparable degree of obesity and compensation of carbo-

hydrate metabolism, carriers of the minor G-allele of both genders are characterized by a greater degree of insulin resistance of adipose tissue.

3. A significantly higher intensity of the chronic inflammatory process was found in men with type 2 diabetes carrying the G-allele, which requires further research.

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Introduction. Sirtuin-1, *SIRT1*, known as the gene of longevity, among other things, protects cells from oxidative stress and promotes DNA stability. Genetic studies show that sirtuins can be involved in the development of obesity in humans, as it has been found that some of their genetic variants are associated with weight gain and metabolic complications. One of the *SIRT1* single-nucleotide polymorphisms (SNP), which is actively studied in relation to metabolic disorders in different populations, is the *C > G* polymorphism in intron 4 (*rs7069102*). It is determined that it is linked to several mutations in the promoter of the gene and with two coding SNPs in exon 1. It is the different degree of linkage which explains that the results relative to its functional role are significantly different between populations.

The aim of the study was to evaluate the association of polymorphic variants of the sirtuin-1 gene *rs7069102* with functional and metabolic characteristics in type 2 diabetes and overweight patients of the East Ukrainian population.

Materials and methods. The study was conducted in accordance with international and domestic ethical and moral and legal requirements and approved by the Institute Medical Ethics Committee. All patients were examined during their stay 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 (T2DM). 61 patients with T2DM (f/m 27/34) were selected for analysis (53.35 ± 1.38 years old, duration of diabetes 5.33 ± 0.67 years, glycosylated hemoglobin (Hb_{A1c}) level 7.74 ± 0.19 %, body mass index 33.28 ± 0.89 kg/m², waist-to-hip ratio 0.99 ± 0.01). Antidiabetic therapy included sulfanilamides, biguanides or their combination. Biochemical and immunoassays were conducted on the basis of the National Institute of Public Health and Environment (Bilthoven, the Netherlands) within the framework of scientific cooperation. Insulin resistance (IR) was characterized by HOMA-IR, HOMA-IR/adiponectin, adiponectin/leptin, HOMA-IR/leptin and Adipo-IR. Determination of cytosine replacement with guanine in intron 4 *SIRT1 rs7069102 (C > G)* was carried out by a polymerase chain reaction with two pairs of opposed primers. Electrophoretic fractionation allowed us to determine the following genotypes by *SIRT1 rs7069102 (C > G)*: *CC* — 391/277 b.p.; *CG* — 391/277/167 b.p.; *GG* — 391/167 b.p. Allele frequencies for the genotype studied were calculated. The normality of distribution of variables was determined by the criterion of Kolmogorov-Smirnov. To compare the indicators characterized by a normal distribution, used the odd two-sided Student's T-test, to compare the parameters with the abnormal distribution, the Mann-Whitney U-test. The χ^2 was used to statistically evaluate the differences observed between empirical and theoretical frequencies of the variation series.

Results. Despite a small number of observations, the frequency of alleles in men and women did not differ and there was a noticeable discrepancy between the distribution of genotype frequencies compared to the theoretical distribution by Hardy-Winberg equilibrium. In both men and women, a significant deviation was observed of the actual series of expected frequencies towards the accumulation of heterozygotes ($\chi^2 = 10.43$, $P = 0.005$; $\chi^2 = 11.76$, $P = 0.003$, respectively). The analysis of clinical parameters revealed that this SNP did not affect the age of diabetes manifestation, the degree of its compensation, blood pressure and the degree of obesity. At the same time, the indicators that characterize the resistance to insulin associated with adipose tissue (HOMA-IR/adiponectin, HOMA-IR/leptin, adiponectin/leptin) have undergone distinct changes. Despite some trend of greater levels of triglycerides and total cholesterol in the carriers of the *CC*-genotype, the above-mentioned IR-indices were statistically increased in the carriers of the minor *G*-allele. At the same time, they revealed a clear gender difference in manifestations of adipose tissue resistance to insulin, which was accompanied by statistically elevated tumor necrosis factor alpha (TNF- α) levels. Namely, men had much worse than women, indexes Adipo-IR (139.59 ± 17.44 vs 85.18 ± 10.48, respectively, $P < 0.05$) and adiponectin/leptin (0.23 ± 0.06 vs 0.12 ± 0.0, respectively, $P < 0.05$) against the background of statistically constant parameters of carbohydrate and lipid metabolism, as well as the same degree of obesity, while the high TNF- α levels in the group of *G*-allele carriers were associated with male gender (4.73 ± 1.30 vs 1.92 ± 0.46 ng/L in women, respectively, $0.05 < P < 0.1$).

Conclusion. The results suggest that the *C > G rs7069102* polymorphism is functional in the East Ukrainian population, since there is a shift in the frequencies of genotypes towards the accumulation of heterozygotes, and the alleles themselves are associated with metabolic differences in the studied patients. Against the background of the comparable degree of obesity and compensation of carbohydrate metabolism the *G*-allele carriers of both genders are characterized by a greater degree of insulin resistance of adipose tissue. Statistically significant intensity of low-grade inflammation has been revealed in men-carriers of *G*-allele with type 2 diabetes, which requires further research.

Key words: type 2 diabetes mellitus, sirtuin-1, overweight, single nucleotide polymorphism, insulin resistance.

ДОСЛІДЖЕННЯ ОДНОНУКЛЕОТИДНОГО ПОЛІМОРФІЗМУ ГЕНА *SIRT1* (rs7069102) У ПАЦІЄНТІВ З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ ТА НАДЛИШКОВОЮ ВАГОЮ ЗІ СХІДНОУКРАЇНСЬКОЇ ПОПУЛЯЦІЇ

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Вступ. Ген сиртуїну-1, *SIRT1*, відомий як ген довголіття, серед іншого, захищає клітини від окислювального стресу та сприяє стабільності ДНК. Генетичні дослідження свідчать, що сиртуїни можуть брати участь у розвитку ожиріння у людей, оскільки було встановлено, що деякі з їх генетичних варіантів пов'язані зі збільшенням ваги та метаболічними ускладненнями. Одним з однонуклеотидних поліморфізмів (ОНП) *SIRT1*, що активно вивчається стосовно метаболічних порушень в різних популяціях, є поліморфізм *C > G* у інтроні 4 (rs7069102). Визначено, що він зчеплений з кількома мутаціями у промоторній зоні гену та з двома кодуючими ОНП у екзоні 1. Саме різним ступенем зчеплення пояснюють те, що результати відносно його функціональної ролі суттєво відрізняються поміж популяціями. **Метою** дослідження була оцінка зв'язку поліморфних варіантів гену сиртуїну-1 rs7069102 з функціонально-метаболічними характеристиками у пацієнтів з цукровим діабетом 2 типу та надлишковою масою тіла 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. Виконано ретроспективний аналіз клініко-біохімічних показників, отриманих для пацієнтів, зразки яких входять до колекції ДНК хворих на ЦД 2 типу. Для аналізу було відібрано 61 хворого на ЦД 2 типу (ж/ч: 27/34) віком ($53,35 \pm 1,38$) років, тривалістю діабету ($5,33 \pm 0,67$) років, рівнем глікозильованого гемоглобіну (HbA_{1c}) ($7,74 \pm 0,19$) %, з індексом маси тіла ($33,28 \pm 0,89$) кг/м², зі співвідношенням обсягу талії до обсягу стегон $0,99 \pm 0,01$. Антидіабетична терапія включала пероральні цукрознижувальні препарати — сульфаміламід, бігуаніди або їх поєднання. Клініко-біохімічні та імуноферментні вимірювання були проведені на базі Національного Інституту громадського здоров'я та навколишнього середовища (м. Білтховен, Нідерланди) в межах наукового співробітництва. Інсулінорезистентність (ІР) характеризували за індексом НОМА-ІР, НОМА-ІР/адипонектин, адипонектин/лептин, НОМА-ІР/лептин та Adipo-ІР.

Визначення заміни цитозину на гуанін у інтроні 4 гену *SIRT1* rs7069102 (*C > G*) здійснювали методом полімеразної ланцюгової реакції з двома парами протиставлених праймерів. Електрофоретичне фракціонування дозволило визначити наступні генотипи за геном *SIRT1* rs7069102 (*C > G*): *CC* — 391/277 п.н.; *CG* — 391/277/167 п.н.; *GG* — 391/167 п.н. Розраховували частоти алелей для дослідженого генотипу. Нормальність розподілу змінних визначили 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-Уїтні. Для статистичної оцінки розбіжностей, спостережуваних між емпіричними і теоретичними частотами варіаційного ряду, застосовувався критерій χ^2 (хі-квадрат).

Результати. Незважаючи на незначну кількість спостережень, частоти алелей у чоловіків і жінок не розрізнялися та мала місце помітна розбіжність розподілу частот генотипів порівняно до теоретичного розподілу за законом Харді-Вайнберга. Як у чоловіків, так і у жінок спостерігалася суттєва відхилення ($\chi^2 = 10,43$, $P = 0,005$; $\chi^2 = 11,76$, $P = 0,003$ відповідно) фактичного ряду від очікуваних частот у бік накопичення гетерозигот. Аналіз клінічних параметрів виявив, що даний ОНП не впливав на вік манифестації діабету, ступінь його компенсації, артеріальний тиск та ступінь ожиріння. В той же час різних змін зазнали показники, що характеризують резистентність до інсуліну, пов'язану з жировою тканиною (НОМА-ІР/адипонектин, НОМА-ІР/лептин, адипонектин/лептин). Виявилось, що незважаючи на деяку тенденцію більших рівнів тригліцеридів та загального холестерину у носіїв *CC*-генотипу, вищевказані індекси ІР були статистично збільшеними у носіїв мінорного *G*-алеля. В той же час серед них виявлено чітку статеву розбіжність у проявах резистентності жирової тканини до інсуліну, яка супроводжувалася статистично більшими рівнями фактора некрозу пухлин- α (ФНП- α). А саме, у чоловіків спостерігалася значно гірші, ніж у жінок, індекси Adipo-ІР ($139,59 \pm 17,44$ проти $85,18 \pm 10,48$ ум. од. відповідно, $P < 0,05$) та адипонектин/лептин ($0,23 \pm 0,06$ проти $0,12 \pm 0,02$ ум. од. відповідно, $P < 0,05$) на тлі статистично незмінних параметрів вуглеводного та ліпідного метаболізму, а також однакового ступеня ожиріння, тоді як високі рівні ФНП- α в групі носіїв *G*-алеля були пов'язані саме з представниками чоловічої статі ($4,73 \pm 1,3$ проти $1,92 \pm 0,46$ нг/л у жінок відповідно, $0,05 < P < 0,1$).

Висновок. Оцінка результатів дозволяє припустити, що поліморфізм *C > G* rs7069102 гену *SIRT1* є функціональним в східноукраїнській популяції, оскільки спостерігається зсув частот генотипів у бік накопичення гетерозигот, а самі алелі пов'язані з метаболічними розбіжностями у обстежених хворих на цукровий діабет 2 типу з ожирінням. Визначено, що на тлі співставного ступеня ожиріння та компенсації вуглеводного обміну носії мінорного *G*-алеля обох статей характеризуються більшим ступенем інсулінорезистентності жирової тканини. Виявлено статистично значуще більшу інтенсивність хронічного запального процесу у чоловіків-носіїв *G*-алеля, хворих на цукровий діабет 2 типу, що потребує подальших досліджень.

Ключові слова: цукровий діабет 2 типу, сиртуїн-1, надлишкова вага, однонуклеотидний поліморфізм, інсулінорезистентність.