

## POLYMORPHISMS OF INSULIN RECEPTOR SUBSTRATE 1 AS A RISK FACTOR FOR TYPE 2 DIABETES MELLITUS, OBESITY AND CHRONIC PANCREATITIS AMONG POPULATION OF TERNOPIIL REGION

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**Background.** The course of type 2 diabetes mellitus (T2DM), obesity and chronic pancreatitis (CP) in most cases is not isolated, so it requires broadening the knowledge about the pathogenetic links at their combined course. Despite significant advances in genome research, most of the genetic factors that cause development of T2DM are still unclear.

**Objective.** The aim of the study was to establish the prevalence of IRS1 gene polymorphism in the patients with T2DM as well as obesity and CP.

**Methods.** The study involved 33 patients with T2DM who were hospitalized in the endocrinology department of Ternopil University Hospital in 2019-2020 and 10 apparently healthy patients. Analysis of IRS1 gene polymorphism (SNP in the promoter region – rs2943640; gene localization 2q36.3) was performed on the basis of polymerase chain reaction data using specific primers.

**Results.** It was found that the frequencies of the genotype responsible for C/A polymorphism of IRS1 gene in T2DM, T2DM with obesity and in the combined course of T2DM with obesity and CP did not deviate significantly from the Hardy-Weinberg equilibrium ( $p > 0.05$ ). The patients with combined course of T2DM, obesity and chronic pancreatitis experienced a probable influence of genotypes C/C and C/A of IRS1 gene on the development of the studied comorbidity ( $p < 0.05$ ), which is confirmed by a probable difference in the dominant model of IRS1 gene inheritance only when T2DM was combined with obesity and CP compared to the control group ( $p < 0.001$ ).

**Conclusions.** The presence of the C allele in both homozygous and heterozygous states may increase the risk of T2DM comorbidity, obesity and CP in the population of Ternopil region.

**KEYWORDS:** type 2 diabetes mellitus; obesity; chronic pancreatitis; insulin receptor substrate 1; genes polymorphism.

### Introduction

Type 2 diabetes mellitus (T2DM) is a multifactorial genetic disease that causes significant morbidity and mortality worldwide [1]. Multimorbidity, the presence of two or more chronic diseases [2], is typical for patients with T2DM, which makes multimorbidity in this population a significant clinical issue. Nowakowska et al. found out that almost 75% of patients had at least one additional comorbidity at the time of T2DM diagnosis, and 44% – at least two comorbidities [3]. Other studies indicate diabetic complications in 90% [4], 91.4% [5], 84.6% [6], 44% [7] of patients with T2DM, which probably depends on the age and gender coverage of the respondents in the study.

The course of T2DM, obesity and chronic pancreatitis (CP) in most cases is not defined, so it requires broadening the knowledge about the pathogenetic links at their combined course

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[8-11]. It is obvious that T2DM is a poorly controlled epidemic that requires active research of the mechanisms of development, features of the course, methods of prevention, treatment and prevention of complications [12]. Despite significant advances in genome research, most of the genetic factors that cause development of T2DM are still unclear [13, 14]. The insulin receptor substrate (IRS) is a key central receptor in transmission of insulin signals. Several IRS polymorphisms have been identified, but the Gly to Arg 972 substitution of IRS1 probably is pathogenetically crucial in the development of T2DM [15].

Therefore, the aim of our study was to establish the prevalence of IRS1 gene polymorphism in the patients with type 2 diabetes mellitus as well as obesity and chronic pancreatitis.

### Methods

The study involved 33 patients with T2DM who were hospitalized in the endocrinology

department of Ternopil University Hospital in 2019-2020 and 10 apparently healthy patients. The distribution of groups is presented in Table 1.

There was no significant difference in age and gender between the patients of experimental groups. All patients were informed of the purpose of the clinical trial and gave written informed consent to participate in it. The privacy of the patient's identity and health has been maintained.

Verification of T2DM was performed in accordance with the recommendations of the American Diabetes Association (2019) [16]. The criteria for T2DM diagnosing were based on the rate of glycated hemoglobin (HbA1c) ( $\geq 6.5\%$ ), which was determined using the COBAS 6000 automatic biochemical analyzer (Roche Hitachi, Germany).

Verification of chronic pancreatitis (CP) was based on the Unified Clinical Protocol of Primary, Secondary (Specialized) Medical Care and Medical Rehabilitation "Chronic Pancreatitis" and the recommendations of the American Pancreatic Association [15,16].

BMI was calculated by the BMI formula = body weight (kg) / height (m<sup>2</sup>). The data were interpreted according to the WHO recommendations: normal weight in the range of 20.0-24.9 kg/m<sup>2</sup>; overweight (pre-obesity) - 25.0-29.9 kg/m<sup>2</sup>; class 1 obesity - 30.0-34.9 kg/m<sup>2</sup>; class 2 obesity - 35.0-39.9 kg/m<sup>2</sup> and class 3 obesity >40 kg/m<sup>2</sup> [17].

Inclusion criteria were: clinical, laboratory and instrumental signs of T2DM, CP and obesity, no severe increase (not more than in 3 times from the upper of norm maximum) of alpha-amylase, lipase, ALT, AST, alkaline phosphatase, gamma-glutamyltranspeptidase in the blood.

Exclusion criteria from the study were: signs of clinically significant neurological, mental, renal, hepatic, immunological, gastrointestinal, urogenital disorders, musculoskeletal lesions, skin, sense organs, endocrine (except T2DM) or hematological diseases that were uncontrolled, acute pancreatitis, unstable or life-

threatening heart diseases, malignant neoplasms not in complete remission for at least 5 years, medication (drug) dependence, alcohol dependence.

Analysis of IRS1 gene polymorphism (SNP in the promoter region - rs2943640; gene localization - 2q36.3) was performed on the basis of polymerase chain reaction data using specific primers. Genomic DNA was extracted from peripheral blood leukocytes using a commercially available DNA isolation kit (QIAamp Blood DNA Mini Kit, QIAGEN, Germany). The rs2943640 IRS1 gene polymorphism was genotyped using the TaqMan real-time PCR method (Applied Biosystems, Foster City, CA, USA). Three genotypes of IRS1 polymorphism (rs2943640) were defined (C/C, C/A and A/A).

Statistical analysis of the data was performed using the STATISTICA 7.0 software. The Hardy-Weinberg equilibrium was used to verify the conformity of the genotypes of the selected samples to the general population. Comparison of the frequencies observed and expected, calculated according to the formula  $p^2 + 2pq + q^2 = 1$  (the Hardy-Weinberg equilibrium), was performed using the Pearson's chi-square  $\chi^2$ . In assessment of the reliability coefficient  $p > 0.05$ , the null hypothesis of the samples equality was taken into the account, i.e. the correspondence of the selected sample to the general population.

Comparative analysis of frequency tables was performed using the Pearson's chi-square  $\chi^2$  and two-tailed p-value for Fisher's exact test (in cases of the expected frequencies of individual indicators not exceeding 5).

To evaluate the influence of the factor (the presence of a certain genotype or allele of the gene) on the disease incidence, calculation of the odds ratio (OR), its 95% confidence interval (CI) and the reliability coefficient p-value was used.

## Results

Insulin receptor substrate (IRS) molecules are key mediators in transmission of insulin signals. Several polymorphisms have been defined in IRS genes, but only the Gly to Arg

**Table 1. Characteristic features of the study groups (n=44)**

Group №	Characteristics of the group	n	%
1	T2DM patients with normal body weight without chronic pancreatitis	9	22.7
2	T2DM patients with overweight / obesity without chronic pancreatitis	14	31.9
3	T2DM patients with overweight / obesity with concomitant chronic pancreatitis	10	22.7
4	Apparently healthy patients (control)	10	22.7

972 substitution of IRS-1 is pathogenically crucial in development of T2DM. However, other polymorphisms described in IRS-1 gene are associated with insulin resistance (IR) in T2DM. The frequency distribution of polymorphic genotypes of IRS1 gene (rs2943640) and verification of conformity with the Hardy-Weinberg population equilibrium were performed in the experimental and control groups. It was found out that the frequencies of the genotype responsible for C/A polymorphism of IRS1 gene in T2DM, T2DM with obesity and at the combined course of T2DM with obesity and CP did not deviate significantly from the Hardy-Weinberg equilibrium ( $p > 0.05$ ), while in the control group the selected sample did not correspond to the general population (Table 2).

The corresponding frequencies for the genotypes of IRS1 gene were as follows: 66.7% for C/A and 33.3% for A/A in the experimental

group 1; 21.4% for C/A, 64.3% for C/A and 14.3% for A/A in the group 2; 70.0% for C/A, 10.0% for C/A and 20.0% for A/A in the group 3 and 100.0% for C/A in the control group (Table 3).

The frequencies of alleles of IRS1 gene in the patients involved in the study are presented in Table 2. In the patients with T2DM the allele C predominated, in the patients with T2DM + obesity + CP – allele A, while in the patients with T2DM + obesity and in the control group, the C allele and the A allele were almost equal.

The obtained results, presented in Table 4, indicate the absence of a statistically significant relationship between the factor (presence of alleles C or A) and the disease incidence ( $p > 0.05$ ).

Evaluation of the reliability coefficient in the analysis of odds ratio showed probable influence of the genotypes C/C and C/A of the IRS1 gene on development of T2DM combined with

**Table 2. Polymorphism of IRS1 genes (rs2943640) according to the Hardy-Weinberg equilibrium in T2DM and its comorbidity**

Genotypes		T2DM (Group 1)		T2DM+obesity (Group 2)		T2DM+obesity+CP (Group 3)		Control	
		Expected	Present	Expected	Present	Expected	Present	Expected	Present
Polymorphism of IRS1 gene (rs2943640)									
Homozygotes that are common	C/C	1	0	4,0	3	6.4	7	2.5	0
Heterozygotes	C/A	4	6	7.0	9	3.2	1	5	10
Homozygotes that are rare	A/A	4	3	3.0	2	0.4	2	2.5	0
$\chi^2, p$		$\chi^2=2.25; p>0.05$		$\chi^2=1.20; p>0.05$		$\chi^2=2.45; p>0.05$		$\chi^2=10.00; p<0.01^*$	

**Table 3. Frequency of the alleles of the IRS1 genes (rs2943640) in T2DM and its comorbidity**

Frequency of alleles	T2DM (group 1)		T2DM+obesity (group 2)		T2DM+obesity+CP (group 3)		Control	
	n	%	n	%	n	%	n	%
Polymorphism of IRS1 gene (rs2943640)								
Allele C	6	33.33	15	53.57	16	80.00	10	50.00
Allele A	12	66.67	13	46.43	4	20.00	10	50.00
$p_F$ (patients/control)	$p_F=0.342$		$p_F=0.999$		$p_F=0.096$		-	

**Table 4. The odds ratio for alleles in different study groups in T2DM and its comorbidity**

Group	IRS1 gene (rs2943640)					
	Allele C			Allele A		
	OR	95 % CI	p	OR	95 % CI	p
T2DM (Group 1)	0.50	0.13-1.86	>0.05	2.00	0.54-7.45	>0.05
T2DM+obesity (Group 2)	1.15	0.37-3.64	>0.05	0.87	0.27-2.73	>0.05
T2DM+obesity+CP (Group 3)	4.00	0.98-16.27	>0.05	0.25	0.06-1.02	>0.05

obesity and CP ( $p < 0.05$ ) (Table 5). This is confirmed by a probable difference in the dominant model of IRS1 gene inheritance only in the group with combination of T2DM as well as obesity and CP compared with the control group (reliability coefficient for the chi-square  $p < 0.001$ ). Thus, the presence of the C allele in both homozygous and heterozygous states may increase the risk of T2DM comorbidity, obesity and CP (Table 6).

It should be noted that in recessive models of IRS1 gene inheritance in T2DM, T2DM +

obesity and T2DM + obesity + CP no significant differences were established compared with the control group, but there was also a tendency to increase in the probability of development of these diseases in the presence of C allele (Table 7).

### Discussion

It is established that genes are crucial in development of T2DM. Researchers have suggested the interaction between many genetic factors and environmental factors that

**Table 5. The odds ratio for genotypes in different study groups in T2DM and its comorbidity**

Group	Genotype					
	Polymorphism of IRS1 gene (rs2943640)					
	CC		CA		AA	
	OR	95 % CI	OR	95 % CI	OR	95 % CI
T2DM (Group 1)	1.11	0.02-61.38	0.09	0.01-2.00	11.31	0.50-256.21
T2DM+obesity (Group 2)	6.39	0.29-138.94	1.73	0.03-99.96	4.20	0.18-97.55
T2DM+obesity+CP (Group 3)	71.40*	3.00-1696.84	0.002*	0.001-0.13	6.18	0.26-146.79

Note. \* –  $p < 0.05$ .

**Table 6. Dominant model of IRS1 gene inheritance (rs2943640) in T2DM and its comorbidity**

Genotypes	Experimental group	Control	$p_F$	OR	95% CI	p
	%	%				
T2DM (Group 1)						
C/C	0	0	–	1.11	0.02–61.38	>0.05
C/A+A/A	100.00	100.00		0.90	0.02–50.25	>0.05
T2DM+obesity (Group 2)						
C/C	21.43	0	0.239	6.39	0.29–138.94	>0.05
C/A+A/A	78.57	100.00		0.16	0.01–3.40	>0.05
T2DM+obesity+CP (Group 3)						
C/C	80.00	0	<0.001*	71.40	3.00–1696.84	0.008*
C/A+A/A	20.00	100.00		0.01	0.001–0.33	0.008*

Note. \* – statistically significant results.

**Table 7. Recessive model of IRS1 inheritance (rs2943640) in T2DM and its comorbidity**

Genotypes	Experimental group	Control	$p_F$	OR	95 % CI	p
	%	%				
T2DM (Group 1)						
C/C+C/A	66.67	100.00	0.087	0.09	0.01–2.00	>0.05
A/A	33.33	0		11.31	0.50–256.21	>0.05
T2DM+obesity (Group 2)						
C/C+C/A	85.71	100.00	0.493	0.24	0.01–5.53	>0.05
A/A	14.29	0		6.18	0.26–146.79	>0.05
T2DM+obesity+CP (Group 3)						
C/C+C/A	80.00	100.00	0.474	0.16	0.01–3.85	>0.05
A/A	20.00	0		6.18	0.26–146.79	>0.05

contribute to the disease development [20]. However, there are only isolated data in the literature on the role of IRS1 polymorphism (rs2943640) in increased susceptibility to T2DM. Thus, Langenberg C et al. presented the results of the InterAct study, which proved the effect of C allele of IRS1 gene polymorphism (rs2943640) on the risk of T2DM development [21]. In the study prepared by Liu J and et al. 8 SNPs associated with T2DM were found, including rs2943640 variant of IRS1 gene, which was also associated with body mass index [22].

A study of the physical activity genetics made by Loos RJ et al., which included IRS1 (rs2943640) among the studied genes, showed an increased interaction of the gene with the risk of diabetes, in particular, a dependence on genetic susceptibility to insulin resistance [23]. Another interesting result of this study is the established data on the higher genetic risk of T2DM in individuals with the highest level of physical activity that is consistent with the large-scale study of Langenberg et al. (24), in which the predicted effect of T2DM genetic risk was the strongest among young, lean, and physically active individuals [21]. It should be noted that according to Karaderi T. et al., rs2943640 variant of IRS1 gene is associated with decreased BMI [24]. Our results prove the effect of C allele of IRS1 gene (rs2943640) on the increased susceptibility to the combination of T2DM+obesity+CP, but there is no probable effect of the factor (alleles C and A) on development of only T2DM and T2DM+obesity. There are no data in the literature on the role of IRS1 gene (variant rs2943640) in increased susceptibility to CP.

There are some limitations in this study that need to be considered when interpreting its results: the sample size is too small, so it is difficult to find significant relationships between

the data; inclusion into the experimental groups only of patients with comorbidity T2DM+obesity and T2DM+obesity+CP; patients were not randomly selected generating a potential selection bias. Therefore, we cannot exclude the hypothesis that the evaluated patients do not represent the whole population of the patients with comorbid T2DM, but these results are the first step in finding genes for increased susceptibility to the studied pathology, they reflect a more heterogeneous real-world population characteristic in clinical practice.

### Conclusions

The patients with combined course of T2DM, obesity and chronic pancreatitis have a probable influence of genotypes C/C and C/A of IRS1 gene on development of the studied comorbidity ( $p < 0.05$ ) that is confirmed by a probable difference in the dominant model of IRS1 gene inheritance only when T2DM is combined with obesity and CP compare to the control group ( $p < 0.001$ ). Thus, the presence of the C allele in both homozygous and heterozygous states may increase the risk of T2DM comorbidity, obesity and CP in the population of Ternopil region.

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### Conflict of Interest

The authors declare no conflict of interest.

### Author Contributions

*Hevko U.P.* – methodology, software, validation, formal analysis, investigation, resources, data curation, visualization, writing – original draft, writing – reviewing and editing.

*Marushchak M.I.* – conceptualization, visualization, supervision, writing – reviewing and editing.

## ПОЛІМОРФІЗМ СУБСТРАТУ ІНСУЛІНОВИХ РЕЦЕПТОРІВ 1 ТИПУ ЯК ФАКТОР РИЗИКУ РОЗВИТКУ ЦУКРОВОГО ДІАБЕТУ 2 ТИПУ, ПОЄДНАНОГО З ОЖИРІННЯМ ТА ХРОНІЧНИМ ПАНКРЕАТИТОМ У НАСЕЛЕННЯ ТЕРНОПІЛЬСЬКОЇ ОБЛАСТІ

**У.П. Гевко, М.І. Марущак**

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І.Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ,  
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**Вступ.** Перебіг цукрового діабету 2 типу (T2DM), ожиріння та хронічного панкреатиту (CP) в більшості випадків не є ізолюваним, тому потребує поглиблення знань стосовно патогенетичних

ланок при їх поєднаному перебігу. Незважаючи на значні успіхи у дослідженнях геному, більшість генетичних факторів, що спричиняють розвиток T2DM, залишаються невизначеними.

**Мета дослідження** – встановити поширення поліморфізму гена субстрату інсулінових рецепторів 1 типу (IRS1) у хворих на T2DM у поєднанні з ожирінням та СР.

**Методи дослідження.** У дослідження було включено 33 хворих на T2DM, які перебували на стаціонарному лікуванні в ендокринологічному відділенні Тернопільської університетської лікарні у 2019-2020 рр. та 10 практично здорових осіб. Аналіз поліморфізму гена IRS1 (SNP у промоторному регіоні – rs2943640; генна локалізація 2q36.3) проведено на підставі даних полімерної ланцюгової реакції з використанням специфічних праймерів.

**Результати.** Встановлено, що частоти генотипу, що відповідає за С/А поліморфізм гена IRS1 при T2DM, T2DM з ожирінням та при поєднаному перебігу T2DM з ожирінням та СР суттєво не відхилялися від рівноваги Харді–Вайнберга ( $p > 0,05$ ). У хворих на поєднаний перебіг цукрового діабету 2 типу, ожиріння та хронічного панкреатиту виявляється вірогідний вплив генотипів С/С та С/А гена IRS1 на розвиток досліджуваної коморбідності ( $p < 0,05$ ), що підтверджується вірогідною відмінністю у домінантній моделі успадкування IRS1 гену тільки при поєднанні T2DM з ожирінням та СР порівняно з групою контролю ( $p < 0,001$ ).

**Висновки.** Наявність алелі С як в гомозиготному, так і в гетерозиготному станах може підвищувати ризик виникнення коморбідності T2DM, ожиріння та СР.

**КЛЮЧОВІ СЛОВА:** цукровий діабет 2 типу; ожиріння; хронічний панкреатит; субстрат інсулінових рецепторів 1 типу; поліморфізм гена.

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