Insulin receptor substrate 1 gene variations and lipid profile characteristics in the type 2 diabetic patients with comorbid obesity and chronic pancreatitis

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Objective. Type 2 diabetes mellitus (T2DM) is one of diseases that develops in a setting of polymorbid processes or more often promotes their development, forming in this spectrum the phenomenon of comorbidity. The aim of this study was to evaluate changes in the lipid panel data in T2DM patients with comorbid obesity and chronic pancreatitis (CP) taking into account the C/A polymorphism of the insulin receptor substrate 1 (*IRS1*) gene (rs2943640).

Methods. The study involved 34 T2DM patients and 10 healthy individuals. The rs2943640 *IRS1* gene polymorphism was genotyped using the TaqMan real-time polymerase chain reaction (PCR) method. Blood serum lipid panel data were determined with commercially available kits on a Cobas 6000 analyzer.

Results. In patients with only T2DM and T2DM + comorbid obesity, an association between *IRS1* gene polymorphism (rs2943640) and lipid profile abnormalities with maximum changes of the lipid characteristics recorded in C/C genotype carriers was found. Within the C/C genotype of the *IRS1* gene (rs2943640) in type 2 diabetic patients with comorbid obesity and CP, significantly lower high-density lipoprotein cholesterol (HDL-C) levels and significantly higher levels of triglycerides (TG), non-HDL-C and remnant cholesterol (RC) in relation to type 2 diabetic patients with comorbid obesity were found. At the same time, within the C/A genotype of the *IRS1* gene (rs2943640), significant changes of lipid panel data were found in type 2 diabetic patients with comorbid obesity relative to the control group ($p < 0.001$).

Conclusions. Our data indicate that the presence of the C allele of *IRS1* gene (rs2943640) in both homozygous and heterozygous states may indicate increased risk of dyslipidemia in type 2 diabetic patients with comorbidities.

Key words: type 2 diabetes mellitus, comorbidities, *IRS1* gene, lipid profile

Diabetes mellitus (DM) is the most common endocrine disease worldwide that threatens the lives of patients if not properly treated (Kaiser et al. 2018; Posokhova et al. 2018; Zheng et al. 2018; Degen et al. 2020; Almulla 2021). The International Diabetes Federation shows that 463 million people worldwide were diagnosed with DM in 2019, and 91% of them

suffered from type 2 diabetes (T2DM) and the cost of DM treatment in the world was more than 727 billion dollars. By 2045, the incidence of DM is projected to rise to 700 million, or more than 10% of the entire human population (International Diabetes Federation 2019). It should be noted that DM is not only a complex medical but also a social problem, as it

is characterized by a high risk of developing disabling complications. According to the WHO data, one person dies every six seconds from this disease and its complications on the planet (Voloshin et al. 2019). Thus, every eleventh adult on the planet has DM, most patients have T2DM, and in the coming years the prevalence of T2DM will only increase, especially in low-income countries (Kaiser et al. 2018).

On the other hand, DM is one of those diseases that develops in a setting of polymorbid processes or, more often, promotes their development, forming in this spectrum the phenomenon of pathogenetic interdependence – comorbidity (Melikhova et al. 2018; Marushchak et al. 2019; Voloshin et al. 2019). T2DM is most commonly associated with disorders such as dyslipidemia, obesity and insulin resistance (IR) (Hosseini et al. 2021). In turn, excessive abdominal fat, dysregulation of adipose tissue and inflammation are characterized by increased diabetogenic adipocytokines secretion. This group of cytokines links obesity and dyslipidemia with T2DM as they disrupt insulin action in body organs, including skeletal muscle, brain and liver (Bluher and Stumvoll 2018; Demikhova et al. 2019). Chronic pancreatitis (CP) is also linked to obesity, IR and T2DM (Hevko et al. 2020; Marushchak et al. 2021). For example, in one study 53.3% of patients with T2DM had exocrine insufficiency of the pancreas, which was determined by the levels of fecal pancreatic elastase-1 (Zhuravleva and Shekhovtsova 2016).

Thus, IR is the most common metabolic disorder associated with only T2DM and T2DM with comorbid obesity or CP. In addition to the important contribution of environmental factors, such as diet and physical activity, genetic variants that affect insulin signaling also play an important role in IR. The insulin receptor substrate 1 (*IRS1*) gene encodes IRS1 which is a major mediator between the insulin receptor and phosphatidylinositol 3-kinase (PI3K)

in the insulin signaling pathway (Qi et al. 2011). The IRS-1 binding and phosphorylation result in the increase of the high-affinity glucose transporter-4 (GLUT4) molecules on the outer membrane of insulin-responsive tissues, including muscle cells and adipose tissue, which leads to increased glucose uptake from the blood into these tissues. Defects in muscle IRS-1 expression and function cause the disruption of the insulin signaling pathway leading to IR and DM (Menting et al. 2013; Bedair et al. 2021).

Polymorphisms in the *IRS-1* gene have been associated with IR and T2DM in different populations (So et al. 2000; Yiannakouris et al. 2012; Yousef et al. 2018). However, a study of the effects of *IRS-1* gene polymorphisms Gly972Arg and Ala513Pro on IR and T2DM in a non-obese Turkish population didn't reveal a link between these polymorphisms and risk of T2DM developing and its phenotypes (Arikoglua et al. 2014).

Studies of the *IRS-1* gene polymorphisms in the Ukrainian population of only T2DM patients or T2DM patients with comorbidities are practically absent. Therefore, the aim of our study was to evaluate changes of the lipid panel data in type 2 diabetic patients with comorbid obesity and chronic pancreatitis taking into account the C/A polymorphism of the *IRS1* gene (rs2943640).

Subjects and methods

Subjects. The study involved 34 type-2 diabetic patients hospitalized to the Endocrinology Department of Ternopil University Hospital (Ternopil, Ukraine) in 2019–2020 and 10 healthy individuals. The distribution of individuals to study groups is presented in Table 1. There were no significant age and sex differences between the groups in this study.

T2DM diagnoses were confirmed according to the 2019 Recommendations of the American Diabetes Association (ADA) (American Diabetes Association 2019). The diagnosis criteria use the level of glycated haemoglobin (HbA1c) ($\geq 6.5\%$) and glucose level. CP diagnoses were following the recommendations of the American Pancreatic Association (Conwell et al. 2014).

Body mass index (BMI) was calculated using the formula: body weight (kg)/height (m^2). Data were interpreted according to the WHO guidelines: normal weight in the range of 20.0–24.9 kg/m^2 ; overweight (pre-obesity), 25.0–29.9 kg/m^2 ; class 1 obesity, 30.0–34.9 kg/m^2 ; class 2 obesity, 35.0–39.9 kg/m^2 and class 3 obesity, $>40 kg/m^2$.

Table 1
Characteristics of the study groups (n=44).

Group	Patient cohort	n	%
1	T2DM patients with normal body weight without CP	10	22.7
2	T2DM patients with overweight/obesity without CP	14	31.9
3	T2DM patients with overweight/obesity with concomitant CP	10	22.7
4	Healthy individuals (control)	10	22.7

Abbreviations: CP – chronic pancreatitis; T2DM – type 2 diabetes mellitus.

Inclusion criteria: clinical, laboratory and instrumental signs of T2DM, CP and obesity, no sharp increase (exceeding normal activity not more than 3 times) of blood serum alpha-amylase, lipase, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma-glutamyl transferase.

Exclusion criteria from the study: signs of clinically significant neurological, mental, renal, hepatic, immune, gastrointestinal, urogenital disorder; injuries of the musculoskeletal system, skin, sense organs, endocrine system (except T2DM); or uncontrolled hematologic diseases; acute pancreatitis, unstable or life-threatening heart disease; patients with malignant neoplasms who have not been in complete remission for at least 5 years, medication (drug) and alcohol dependence.

The ethical principles included in the Declaration of Human Rights adopted in Helsinki, in 1975, and revised in 2008, were fully respected in our study. The enrolled subjects participated in this study voluntarily, completed and signed a written informed consent. Study protocol was approved by the Ethics Committee of I. Horbachevsky Ternopil National Medical University.

Methods. Level of HbA1c was determined using an automatic biochemical analyzer COBAS 6000 (Roche Hitachi, Germany) and glucose level was determined on an automatic biochemical analyzer BAS INTEGRA® 400 (Roche Diagnostics) using a standard set. Blood serum lipid panel data were measured in the Clinical laboratory of Ternopil University Hospital (Ternopil, Ukraine). Total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) were determined with commercially available kits on a Cobas 6000 analyzer (Roche Hitachi, Germany).

Friedewald's formula was used to calculate low-density lipoprotein cholesterol (LDL-C) levels (if serum TG <4.5 mmol/L) (Piepoli et al. 2016): $LDL-C (mmol/L) = TC - HDL-C - (0.45 \times TG)$. Non-HDL-cholesterol was calculated using the formula (if serum TG >4.5 mmol/L) (Piepoli et al. 2016): $non-HDL-C = TC - HDL-C$.

Remnant cholesterol (RC) was calculated using the formula (Cosentino et al. 2020): $RC (mmol/L) = TC - (HDL-C + LDL-C)$.

Genetic analysis. Genomic DNA was extracted from peripheral blood leukocytes using a commercially available DNA isolation kit (QIAamp Blood DNA Mini Kit, QIAGEN, Germany). The *IRS-1* gene rs2943640 C>A polymorphism was genotyped using the TaqMan real-time polymerase chain reaction

(PCR) method (Applied Biosystems, Foster City, CA, USA) (He et al. 2012). Quality control was performed with eight negative control and positive control samples in each 96-well plate. In addition, approximately 10% of the samples were randomly selected for further quality control, and the concordance rate was 100%. Amplification of the 25-bp *IRS-1* sequence including rs2943640 was performed by using PCR with 5'-GAAATGAGAGGAACCCTTCTAACTA-3' as the forward primer and 5'-AGGAACTCTTCTA-ACTATTAGCCC-3' as the reverse primer. Three genotypes of the rs2943640 *IRS-1* polymorphism were detected (C/C, C/A and A/A).

Statistical analysis. Study results were analyzed using STATISTICA 7.0 and MedCalc software. The Kolmogorov-Smirnov test was used to compare probability distributions (parametric or non-parametric). Quantitative values, due to their non-parametric distribution, are presented as the median, lower, and upper quartiles-Me (Lq; Uq). Comparative analysis of study groups was performed using the non-parametric Kruskal-Wallis test. Having obtained its probable values ($p < 0.05$), further pairwise comparison of groups was performed using the Mann-Whitney U-test, taking into account Bonferroni correction when assessing statistical significance.

Results

Table 2 presents the lipid panel data of patients with T2DM regardless of the presence/absence of comorbid obesity or CP, taking into account the genotypes of the *IRS1* gene (rs2943640). It was found that lipid panel data in patients with T2DM significantly differed between carriers of genotypes C/C, C/A and A/A of the *IRS1* gene in the Kruskal-Wallis test by ranks. It should be noted that all studied indices of lipid profile in patients with T2DM also significantly differed from those of the control group. In the control group, 100% of individuals were carriers of the C/A genotype of the *IRS1* gene. Thus, the level of TC was significantly higher in carriers of C/C genotype by 69.53%, in carriers of C/A by 21.05% and in carriers of A/A genotype by 51.25%, respectively; the level of LDL-C by 250.86%, 122.41% and 198.28%; TG level by 246.75%, 24.68% and 170.13%; the level of non-HDL-C by 253.64%, 94.16% and 185.71%; RC level by 242.86%, 22.86% and 168.57% relative to control. Level of HDL-C was significantly lower in C/C genotype carriers by 141.86%, in C/A carriers by 50.72% and in A/A genotype carriers by 89.09% vs control data (Table 2, Table 3).

Table 2
Lipid profile characteristics in type 2 diabetic patients taking into account the C/A polymorphism of the IRS1 gene (rs2943640).

Index	C/C	C/A	A/A	Kruskal-Wallis criterion
TC (mmol/L)	6.12 (5.88; 6.42)	4.37 (3.64; 5.20)	5.46 (4.27; 6.58)	H=23.19; p<0.001*
HDL-C (mmol/L)	0.86 (0.78; 0.94)	1.38 (0.99; 2.05)	1.10 (0.92; 1.27)	H=16.11; p<0.001*
LDL-C (mmol/L)	4.07 (3.89; 4.37)	2.58 (1.28; 3.25)	3.46 (2.44; 4.51)	H=22.11; p<0.001*
TG (mmol/L)	2.67 (2.26; 2.86)	0.96 (0.83; 2.06)	2.08 (1.14; 2.35)	H=18.88; p<0.001*
non-HDL-C (mmol/L)	5.34 (5.06; 5.56)	2.99 (1.59; 4.28)	4.40 (2.95; 5.76)	H=22.78; p<0.001*
RC (mmol/L)	1.20 (1.02; 1.30)	0.43 (0.37; 0.93)	0.94 (0.51; 1.06)	H=18.88; p<0.001*

Abbreviations: HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; RC - remnant cholesterol; TC - total cholesterol; TG - triglycerides. * - statistically significant results.

Table 3
Lipid profile characteristics of the control group taking into account the C/A polymorphism of the IRS1 gene (rs2943640).

Index/Genotype	TC (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	TG (mmol/L)	non-HDL-C (mmol/L)	RC (mmol/L)
C/C (n=0)	-	-	-	-	-	-
C/A (n=10)	3.61 (3.38; 3.82)	2.08 (1.98; 2.14)	1.16 (1.00; 1.37)	0.77 (0.71; 0.84)	1.54 (1.38; 1.72)	0.35 (0.32; 0.38)
A/A (n=0)	-	-	-	-	-	-

Abbreviations: HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; RC - remnant cholesterol; TC - total cholesterol; TG - triglycerides.

Figure 1. Serum lipid panel data of type 2 diabetic patients with comorbidities, carriers of the C/C genotype of the IRS1 gene (rs2943640). Abbreviations: T2DM - diabetes mellitus type 2; Ob - obesity; CP - chronic pancreatitis; IRS1 - insulin receptor substrate 1 gene; TG - triglycerides; HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; RC - remnant cholesterol.

A multiple comparison of the TC level between the studied genotypes of the IRS1 gene revealed a significantly higher concentration in patients with T2DM carriers of the C/C genotype (by 40.1%) relative to the carriers of the C/A genotype (p<0.001); the level of HDL-C was significantly higher in carriers of C/A genotype (by 60.5%) compared to carriers of C/C genotype (p<0.001); the level of LDL-C was significantly higher in carriers of C/C genotype (by 57.8%) compared to carriers of C/A genotype (p<0.001); the level of TG was significantly higher in carriers of C/C genotype (by 57.8%) compared to carriers of C/A genotype (p<0.001); the level of non-HDL-C was significantly higher in carriers of the C/C genotype (by 78.6%) compared to carriers of the C/A genotype (p<0.001) and the level of RC was significantly higher in carriers of the C/C genotype (by 79.1%) in relation to carriers of C/A genotype of the IRS1 gene (p<0.001). It should be noted that the maximum changes of lipid profile in patients with T2DM were recorded in carriers of C/C genotype of the IRS1 gene.

Analysis of the effect of IRS1 gene polymorphism (rs2943640) on lipid panel data did not show a clear relationship between changes of the studied lipid profile characteristics taking into account polymorphic variants of the IRS1 gene in patients with only T2DM and T2DM with comorbid obesity and CP. However, in type 2 diabetic patients with comorbid obesity, TC was significantly higher in C/C genotype

carriers (9.7%) than in C/A genotype carriers, and non-HDL-C level was significantly higher in carriers of C/C genotype (by 11.5%) relative to carriers of the C/A genotype of the *IRS1* gene. It should be noted that in patients with T2DM+obesity, carriers of the A/A genotype, relative to other polymorphic variants of the *IRS1* gene, no significant changes of lipid profile were recorded.

Analyzing the lipid panel data within the C/C genotype of the *IRS1* gene (rs2943640) in type 2 diabetic patients with comorbid obesity and CP found significantly lower HDL-C concentration (by 17.3%, $p=0.02$) and significantly higher levels of TG (by 24.8%, $p=0.04$), non-HDL-C (by 12.3%, $p=0.03$) and RC (by 24.5%, $p=0.04$), regarding type 2 diabetic patients with comorbid obesity (Figure 1).

Analyzing the lipid panel data within the C/A genotype of the *IRS1* gene (rs2943640) in type 2 diabetic patients with comorbid obesity found significantly lower HDL-C concentration (by 2.19 times) and significantly higher levels of TC (by 1.48 times), LDL-C (by 2.98 times), TG (by 2.84 times), non-HDL-C (by 2.83 times) and RC (by 2.83 times) vs control group ($p<0.001$) (Figure 2). Within the A/A genotype of the *IRS1* gene (rs2943640) no significant changes of the studied indices of the lipid panel data in type 2 diabetic patients depending on comorbid obesity or CP were found.

Comparison of the obtained lipid profile characteristics taking into account the allele status of the *IRS1* gene (rs2943640) in type 2 diabetic patients, regardless of the presence/absence of comorbidity, indicates that carriers of the C-allele of the *IRS1* gene have significantly higher TC levels (by 25.28%), LDL-C (by 41.92%), TG (by 71.09%), non-HDL-C (by 47.17%) and RC (by 70.69%), as well as lower level of HDL-C (by 32.63%) compared to carriers of A-allele of the studied gene (Table 4).

Discussion

Insulin resistance, a keystone of both obesity and T2DM, is a condition in which cells respond to insulin in an impaired way with respect to carbohydrate, lipid,

Figure 2. Serum lipid panel data of type 2 diabetic patients with comorbidities, carriers of the C/A genotype of the *IRS1* gene (rs2943640). Abbreviations: T2DM – diabetes mellitus type 2; Ob – obesity; *IRS1* – insulin receptor substrate 1 gene; TG – triglycerides; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; RC – remnant cholesterol.

Table 4
Lipid profile characteristics of the type 2 diabetic patients taking into account the allele status of the *IRS1* gene (rs2943640).

Index	Allele C (n=29)	Allele A (n=37)	p-value
TC (mmol/L)	5.65 (3.96; 6.12)	4.51 (3.87; 5.46)	0.025*
HDL-C (mmol/L)	0.95 (0.85; 1.38)	1.26 (0.97; 1.87)	0.026*
LDL-C (mmol/L)	3.69 (2.34; 4.07)	2.60 (1.64; 3.47)	0.030*
TG (mmol/L)	2.19 (0.86; 2.67)	1.28 (0.85; 2.16)	0.025*
non-HDL-C (mmol/L)	4.68 (2.72; 5.34)	3.18 (1.96; 4.53)	0.025*
RC (mmol/L)	0.99 (0.39; 1.20)	0.58 (0.38; 0.97)	0.025*

Abbreviations: HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; RC – remnant cholesterol; TC – total cholesterol; TG – triglycerides. * – statistically significant results.

and protein metabolism, resulting in high blood glucose levels. Insulin has many effects on metabolic processes in adipose tissue; therefore, it is one of the most important hormones regulating anti-lipolytic processes, and decrease of the cell sensitivity to its action or impairment of the insulin pathway will affect the metabolism of the adipose tissue (Yang et al. 2018; Al-Sulaiti et al. 2019; Kojta et al. 2020).

The insulin receptor substrate (IRS) proteins are adaptor proteins which play a major role in transmission of insulin-mediated signals from both the insulin and IGF-1 receptors. IRS protein family includes four proteins, namely IRS1, IRS2, IRS3, and IRS4. IRS1, the first identified among others, is encoded by a gene located on the 2q34-37 chromosome. Worth-noting that it is also transcribed as a single exon (Gorgisen et al. 2017). It had been previously shown that IRS1 was a physiological substrate of the insulin receptor and played significant role in insulin signal transmission. The phosphorylation of IRS1, specifically, its tyrosine residues, could interplay with phosphatidylinositol-3 kinase (PI3K), which phosphorylates phosphatidylinositol 2 phosphates (PIP2) into phosphatidylinositol 3 phosphates (PIP3), and recruits serine/threonine protein kinase B (AKT) to the plasma membrane through the plextrin homology domain. Following this, AKT could phosphorylate adenosine monophosphate-activated protein kinase (AMPK), which is an energy sensor in eukaryotic cells and affects GLUT4 translocation to the plasma membrane. Conversely, the dephosphorylation of IRS1 tyrosine residues can potentially inactivate the whole process of insulin signal transduction, causing IR (Copps and White 2012; Liu et al. 2020).

Moreover, mutations in the *IRS1* and *IRS2* genes are associated with T2DM and susceptibility to IR, as these factors mediate the control of various cellular processes by insulin, and dysregulation of these insulin receptor substrates is associated with PDGF-induced platelet-derived growth factor cells (Zhao et al. 2011; Copps and White 2012). In addition, the *IRS1* and *IRS2* genes have both common and different regulatory mechanisms, as double-stranded RNA-dependent protein kinase differently regulates IRS1 and IRS2 in HepG2 cells (Yang et al. 2010).

Our results indicate an association between *IRS1* gene polymorphism (rs2943640) and lipid profile abnormalities in patients with only T2DM and T2DM+obesity. Research data suggests that genetic variations near the *IRS1* gene are associated with decreased obesity, decreased IRS1 expression, and metabolic abnormalities, including IR, dyslipidemia,

risk of diabetes development, and decreased adiponectin levels (Kilpelainen et al. 2011). Shu et al. (2010) showed the association of *IRS1* (rs2943641) with T2DM, IR and hyperinsulinemia in three European populations. A study by Shalimova (2015) in the Ukrainian population of patients with comorbid pathologies (arterial hypertension and T2DM) – found that the polymorphic marker rs1801278 of the *IRS1* gene is associated with the development of T2DM, with polymorphism most influencing the violation of lipid and carbohydrate metabolism. The study by Minchenko et al. (2015) has shown that obesity affects the expression of a number of genes associated with the control of glucose metabolism and cell growth, and that IR in obesity is associated with changes in expression levels of many genes, including the *IRS1* gene, which contributes to obesity and its complications.

On the other hand, Vassy et al. (2014) did not find any influence of a common genotype, which included 65 gene loci, including the *IRS1* gene (rs2943640), on the occurrence of T2DM among individuals with a BMI greater than 30 kg/m² compared to those with a BMI below 30 kg/m.

We found a link between the C allele of the C/C genotype of the *IRS1* gene (rs2943640) and the maximum changes in the lipid profile of the type 2 diabetic patients. Rung et al. (2009) also identified a single rs2943641C>T SNP, located ca. 500 kb downstream from the *IRS1* gene, as a T2DM risk factor locus, with the major C-allele being associated with increased risk of T2DM by 19%. Importantly, the rs2943641 C allele was clearly associated with increased fasting- and glucose-stimulated hyperinsulinemia and decreased insulin sensitivity (Rung et al. 2009).

Interestingly, carriers of the C/C genotype of the rs2943641 SNP in *IRS1* gene, according to Qi et al. (2011), are more successful in weight loss and IR decreasing than individuals without this genotype, while fed high-carbohydrate and low-fat diet. These results indicate a possible long-term effect of the rs2943641 C/C genotype on improving IR under the above mentioned diet.

The potential mechanisms underlying this effect are unknown, but may be associated with lipid-induced IR (Samuel et al. 2010; Chernatska et al. 2019). It became increasingly evident that chronic free fatty acids (FFAs) blood plasma elevation played a critical role in the impairment of insulin-associated glucose uptake during obesity, as well as in T2DM (Christiansen et al. 2008; Marushchak et al. 2017). Elevated levels of FFAs impaired glycogen synthesis, transport

and utilization of glucose in hepatocytes, adipocytes, and skeletal myocytes. Furthermore, lasting exposure of FFAs induced the production of variety of inflammatory factors, as well as activation of c-Jun N-terminal kinase, which accelerated β -oxidation of FFAs, brought excessive electron flux into the mitochondrial respiratory chain, and subsequently led to the generation of reactive oxygen species (Gao et al. 2010). All mentioned above factors would damage the insulin signaling molecules by lowering the phosphorylation levels of IRS and AKT, and impair the expression and translocation of GLUT4, ultimately resulting in the defective mechanisms of glucose uptake and utilization (Zhang et al. 2019).

Previous studies by a number of research groups have shown that prolonged diets high in fat and elevated levels of FFAs in blood plasma impair insulin signaling by altering IRS1 phosphorylation, leading to decreased activation of IRS1-associated PI3K activity (Yu et al. 2002; Frangioudakis et al. 2005). The results of our study, which indicate an association of rs2943640 polymorphism of the *IRS1* gene with lipid profile abnormalities in T2DM patients, may also be associated with IRS1-associated PI3K activity.

This study involved a small sample size; because of it, significant relationships between study factors were difficult to establish. The patients included

in T2DM+obesity and T2DM+obesity+ P groups, were not randomly selected, potentially resulting in selection bias. While we cannot support the assumption that study participants represent the population of type 2 diabetic patients with comorbid obesity and CP in Ternopil region, but obtained results give grounds for further studies with larger sample sizes reflecting a more inclusive population.

In conclusion, in patients with only T2DM and T2DM+comorbid obesity, an association was found between *IRS1* gene polymorphism (rs2943640) and lipid profile abnormalities, with maximum changes of the lipid panel data recorded in C/C genotype carriers. Within the C/C genotype of the *IRS1* gene (rs2943640) in type 2 diabetic patients with comorbid obesity and chronic pancreatitis, significantly lower HDL-C levels and significantly higher levels of TG, non-HDL-C and RC in relation to type 2 diabetic patients with comorbid obesity were found. At the same time, within the C/A genotype of the *IRS1* gene (rs2943640), significant changes of lipid panel data were found in type 2 diabetic patients with comorbid obesity relative to the control group ($p < 0.001$). Thus, the presence of the C allele of *IRS1* gene (rs2943640) in both homozygous and heterozygous states may indicate increased risk of dyslipidemia in type 2 diabetic patients with comorbidities.

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