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THE RELATIONSHIP OF DYSLIPIDEMIA AND INSULIN RESISTANCE IN PATIENTS WITH TYPE 2 DIABETES AND THE METABOLIC SYNDROME

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The aim of the research *was to study the relationship between dyslipidemia and insulin resistance in patients with type 2 diabetes with metabolic syndrome.*
Materials and methods: *In accordance with the aim and objectives of the study, the group of subjects consisted of 120 patients with type 2 diabetes mellitus with MS who were undergoing inpatient treatment in the endocrinology department of the KNP "Regional Clinical Hospital of the Ivano-Frankivsk Regional Council" and 15 practically healthy individuals (PHI), who made up the control group. The degree of IR was determined by waist circumference (WC), IR indices: the HOMA-IR index and the Caro index. The distribution of patients with type 2 diabetes mellitus with MS and without signs of MS was carried out, depending on the presence of NASH. The concentration of endogenous insulin (EI) was determined by the enzyme immunoassay method using an autonomous chemiluminescence analyzer Maglumi 800 with a set of reagents Maglumi "Insulin" Shanghai International Holding Corp. GmbH (Europe), Hamburg, Germany. Glycated hemoglobin (HbA1c) was determined using the "Glycosylated Hemoglobin Spl" reagent of Granum Laboratory LLC, Kharkiv, Ukraine, using a ULAB 108UV spectrophotometer. The level of triglycerides and HDL-CHD in blood serum was determined with the help of the "Cholesterol Spl" reagent of the "Granum Laboratory" LLC, Ukraine, Kharkiv, using the ER 500 enzyme immunoassay analyzer.*
Results: *calculation of generally accepted indices of insulin resistance, in particular the HOMA IR index, OT, BMI indicate the presence of significant insulin resistance in patients with type 2 diabetes with MS, while the changes were the greatest in patients with type 2 diabetes with MS and NASH. Insulin resistance syndrome contributes to lipid imbalance and is a metabolic prerequisite for the development of NASH.*
Conclusions. *The results of the study are recommended for practical use in health care: correction of dyslipidemia against the background of glycemic control*
Keywords: *type 2 diabetes, metabolic syndrome, insulin resistance, obesity, non-alcoholic fatty liver disease, non-alcoholic steatohepatosis, dyslipidemia, glycemic control in patients with type 2 diabetes with MS*

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1. Introduction

In industrialized countries, the prevalence of metabolic syndrome (MS) among people over 30 years old is 10–20 %, in the USA – 34 % (44 % among people over 50 years old). According to WHO data, the number of patients with insulin resistance (IR) syndrome, who have a high risk of developing diabetes mellitus (DM) of the 2nd type, is 40–60 million people in Europe. Obesity, type 2 diabetes and hyperlipidemia or in combination most often contribute to the development of this pathology, since all these pathological conditions are united by the IR syndrome [1, 2]. The frequency of MS symptoms in the form of a combination of cholesterol and glucose metabolism disorders and increased blood pressure in patients over 60 years of age is 42–43.5 %. According to the data of the Framingham study, it was established that the combination of 3 or more components of MS leads to an increase in the risk of CHD by 2.4 times in men and 5.9 times in women [3, 4]. The progressive course of DM is most often accompanied by the development of non-alcoholic steatohepatitis (NASH) (34–88 %), MS – in 20–81 % of cases [5]. The prevalence of non-alcoholic fatty liver disease (NAFLD) in MS is 10 %, i.e. 600 million people. NASH most often occurs during the progressive course of type 2 diabetes (34–88 %) and MS – in 20–81 % of cases [6].

The concept of NAFLD unites the spectrum of clinical and morphological changes of the liver represented by steatosis, steatohepatitis, fibrosis and cirrhosis [7]. The main pathogenetic mechanism of the development and progression of primary NASH is a violation of carbohydrate metabolism, peripheral IR of tissues, hyperglycemia, hyper- and dyslipidemia, which in turn lead to the development of NASH, hypoxia and acceleration of hepatocyte apoptosis, disruption of metabolic processes and progression of liver cell failure [8, 9]. Despite all

the diversity of established aspects of IR, the pathogenetic mechanisms remain insufficiently studied [10]. A comprehensive study of parameters of IR, dyslipidemia in patients with type 2 diabetes with MS remains relevant.

The aim of the research: to investigate the relationship between dyslipidemia and insulin resistance in patients with type 2 diabetes with metabolic syndrome.

2. Materials and methods

In accordance with the aim and objectives of the study, the group of subjects consisted of 120 patients with type 2 diabetes mellitus with MS who were undergoing inpatient treatment in the endocrinology department of the CNE "Regional Clinical Hospital of the Ivano-Frankivsk Regional Council" from 2021–2023 and 15 practically healthy individuals (PHI), who made up the control group.

The work was conducted as an open, controlled, comparative study in parallel groups, considering all provisions of the Declaration of Helsinki regarding ethical principles in research involving humans. Informed consent was signed with all study participants. The research design was approved by the Ivano-Frankivsk National Medical University Ethics Commission (Ivano-Frankivsk National Medical University Ethics Commission, protocol No. 117/20 dated 19.11.20).

To detect signs of MS in the examined persons, IDF (2005) criteria were used. In accordance with the structure of the work, elements of typological sampling (stratification randomization) were used in the controlled clinical study of patients with type 2 diabetes with MS. The distribution of patients with type 2 diabetes with MS and without MS signs was carried out depending on the presence of NASH: 2A group with type 2 diabetes with MS and NASH – 40 patients, 2B group without NASH – 32 patients; 3A group of patients with type 2 DM without MS with NASH – 26 patients, 3B group without NASH – 22 patients. The degree of IR was determined by waist circumference (WC), IR indices: the HOMA-IR (Homeostasis Model Assessment Insulin Resistance) index and the Caro index. The HOMA IR indicator was calculated according to the formula: HOMA IR=fasting blood glucose (mmol/l)×fasting blood insulin (μU/l)/22.5 [Matthew D. R., 1985]; the Caro index was calculated according to the formula: ratio: glucose (mmol/l)/insulin (μU/l). Using BMI indicators, the degree of general obesity was assessed according to the recommendations of the WHO (1997) and the International Diabetes Federation (2005). BMI was considered normal – less than 24 kg/m^2; WC – less than 80 cm in women, less than 94 cm in men; the HOMA IR indicator, which normally does not exceed 2.77, the Caro index, which normally exceeds 0.33. Mandatory scope of laboratory tests included: general clinical analysis of blood and urine, fasting blood glucose and postprandial glycemia were determined using the biosensor technology of the Acccent220S autonomous biochemical analyzer. The concentration of endogenous insulin (EI) was determined by the enzyme-linked immunosorbent assay method using an autonomous chemiluminescence analyzer Maglumi 800 with a set of reagents Maglumi "Insulin" Shanghai International Holding Corp. GmbH (Europe), Hamburg, Germany. Glycated hemoglobin (HbA1c) was determined using the "Glycosylated Hemoglobin Spl" reagent of Granum Laboratory LLC, Kharkiv, Ukraine, using a ULAB 108UV spectrophotometer. The blood lipid spectrum was studied by the content of total cholesterol (CHL), triglycerides (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol. The level of CHL, TG, HDL in blood serum was determined using the reagent "Cholesterol Spl" LLC "Granum Laboratory", Kharkiv, Ukraine, using the enzyme immunoassay "Sinnova" ER 500, China (production number ER-2FP003E). The norm for CHL was considered to be < 4.5 mmol/l, and the level of TG was considered to be < 1.7 mmol/l. Depending on the risk of unwanted cardiovascular events, the HDL norm was considered more than 1.3 mmol/l (in women), more than 1.0 mmol/l (in men). The level of LDL was calculated according to the dyslipoproteinemia diagnostic algorithm using the W. T. Friedwald mathematical formula:

$$LDL = CHL – [HDL + (TG/2.2)].$$

LDL<2.6 mmol/l for patients with moderate cardiovascular risk, <1.8 mmol/l for high cardiovascular risk, and <1.4 mmol/l for very high cardiovascular risk were considered normal. risk We also calculated the atherogenic coefficient (CA) according to the formula:

$$CA = (CHL – HDL)/HDL.$$

Determination of **C-peptide concentrations was carried out** using the enzyme-linked immunosorbent assay method in the immunological laboratory of the CNE "Regional Clinical Hospital of the Ivano-Frankivsk Regional Council" using an autonomous chemiluminescent analyzer Maglumi 800 (Calibration certificate UA/37/230526/000769, valid until May 26, 2024). with the "C-peptide" reagent set dated June 10, 2020, Shanghai International Holding Corp. GmbH (Europe), Hamburg, Germany.

Statistical analysis was carried out using the standard SPSS Statistica software package and the Microsoft Excel statistical analysis package on a personal computer, using parametric and non-parametric criteria. Correlation analysis was performed based on the determination of the parametric Pearson correlation coefficient. The reliability of the correlation was assessed by the Student's test. For non-parametric data, the statistical significance of differences between two independent groups was assessed by the Pearson test (correlation tables), Mann-Whitney, three or more - by the Kruskal-Wallis method. All statistical hypothesis testing and data analysis were performed with a confidence level of at least 0.05. If the reliability value exceeded 0.05, the comparison results and the influence of factors were considered insignificant.

3. Research results

The analysis of the conducted studies showed that patients of all groups had a significant increase in the level of fasting blood glucose by an average of 2.0 times ($p<0.05$) compared to the control group (Table 1).

It should also be noted that all patients with type 2 diabetes with metabolic syndrome were in the stage of

subcompensation (7 %) and decompensation (93 %) before treatment. At the same time, postprandial glycemia in patients of all examined groups exceeded the PHI glycemia level by an average of 1.7 times. The results of the study of the degree of glycation of hemoglobin showed a probable increase in the relative content of HbA1c in patients of groups 2A and 2B – by 2.1 – 1.8 times, group 3A – by 1.7 times, group 3B – by 1.6 times in comparison with PHI ($p< 0.05$).

The study of insulin content in fasting blood revealed probable hyperinsulinemia in all comparison groups ($p<0.05$), which in patients of the 2A group exceeded the indicator in the PHI group by 2.2 times, in patients of the 2B group by 1.7 times ($p<0.05$). The fasting EI content exceeded the norm in groups 3A and 3B by 1.4 times and 1.2 times ($p<0.05$), respectively. The calculation of generally accepted IR indices, in particular BMI, indicates the presence of significant IR in all patients: the indicator in patients with diabetes mellitus exceeded the control by 11 % (p 3A,3B <0.05), while in patients with diabetes mellitus with MS the changes were the largest and exceeded PHI by 33 % (p 2A, 2B <0.05), (see Table 1).

The presence of visceral obesity, which is defined by waist circumference (WC) (cm) according to IDF criteria (2005), is also a characteristic of IR.

Table 1

Indicators of carbohydrate metabolism in patients with type 2 diabetes mellitus with MS

Indicator	Group 1 PHI, n=15	Group 2 A n=40	Group 2 B n=32	Group 3 A n=26	Group 3 B n=22
	M±m	M±m	M±m	M±m	M±m
Fasting blood glucose, mmol/l	4.38±0.11	9.12±0.43$^{\&\#}$	7.38±0.48$^{\&*}$	9.71±0.49$^{\&\#}$	9.49±0.87$^{\&\#}$
Postprandial glycemia, mmol/l	6.18±0.16	12.89±0.48$^{\&\#}$	10.38±0.65$^{\&*}$	10.19±0.64$^{\&*}$	10.09±1.07$^{\&*}$
Hb A I c, %	4.90±0.20	10.49±0.26$^{\&}$	8.89±0.34$^{\&*}$	8.19±0.32$^{\&*}$	8.41±0.55$^{\&*}$
IMT, kg/m^2	21.90±0.40	32.08±0.66$^{\&}$	31.83±1.20$^{\&}$	24.51±0.75$^{\&*\#}$	24.05±0.51$^{\&*\#}$
WC (cm) f	70.30±0.50	100.05±2.87$^{\&}$	96.88±4.08$^{\&}$	86.40±5.43$^{\&*}$	77.55±1.98$^{\&*\#}$
m	76.50±0.60	102.16±2.36$^{\&}$	100.38±4.67$^{\&}$	82.38±2.20$^{\&*\#}$	82.55±1.91$^{\&*\#}$
EI, micro-IU/ml	11.65±0.61	25.54±1.45$^{\&\#}$	19.55±2.28$^{\&*}$	16.38±1.75$^{\&*}$	13.89±1.31$^{*\#}$
HOMA IR index	2.28±0.08	8.10±0.68$^{\&}$	6.18±0.71$^{\&}$	3.10±0.82$^{*\#}$	2.66±0.42$^{*\#}$
Caro index	0.28±0.03	0.09±0.10	0.16±0.08	0.22±0.05	0.23±0.08
C-peptide	1.45±0.58	4.15±0.20$^{\&}$	3.00±0.29$^{\&*}$	2.69±0.49*	2.27±0.23*

Note: $^{\&}$ – statistically significant difference compared to PHI; * – a statistically significant difference compared to the indicators of the 2A group; $^{\#}$ – a statistically significant difference compared to the indicators of the 2B group

In women, WC in groups 3A and 3B increases by 19 % and 10 % compared to PHI (p 3A, 3B <0.05), while, as in group 2A and group 2B, by 30 % and 27 %, respectively. As it follows from the previous data, WC was significantly different in the group of patients with DM and MS. Clinical confirmation of the presence of peripheral tissue IR syndrome in men is a probable increase in WC in 2A, 2B groups by 25 %, 24 % compared to PHI (p 2A, 2B <0.05). Analysis of the results of calculating the Caro index showed a probable decrease in it in all patients ($p<0.05$). But the most significant degree of IR was established in patients with diabetes with MS and NASH: the Caro index was 3 times lower than the index in PHI ($p<0.05$). Such data confirming IR is a probable increase in the HOMA IR index in all observation groups, but the most significant degree of IR was established in patients with diabetes with MS and NASH: the HOMA IR index was 3.6 times higher than in PHI (p 2A<0.05).

Analysis of the conducted studies showed the presence of hypercholesterolemia in all comparison groups ($p<0.05$) (Table 2). In patients of group 2A, CHL exceeded the rate of healthy people by 2 times, while in patients, groups 2B, 3A, and 3B, the level of CHL exceeded the norm by 1.6, 1.6, and 1.3, respectively (p2B, 3A, 3B< 0.05) times (Table 2).

A similar trend of changes was observed in relation to the content of TG in the blood: in patients of the 2A group, the TG content exceeded the indicator in the PHI group by 4.3 times, while in the patients of the 2B, 3A and 3B groups, the level of TG content exceeded the norm by 4.1; 3.0 and 1.7 (p2B, 3A, 3B<0.05) times, respectively.

The concentration of LDL exceeded the normative indicators in patients of the 2A group – by 2.2 times in women and by 2.4 times in men, in the 2B group – by 2.1 times, in the 3A group – by 1.8 times in women and by 2.0 times in men, 3B groups – 1.7 times in women and 1.7 times in men compared to the control ($p<0.05$) and the presence of a probable difference between 2A group and 3B groups in women ($p<0.05$). In the group of men with type 2 diabetes and NASH, a significantly higher level of LDL was observed compared to all groups of patients ($p<0.05$). The content of HDL in blood in patients of the 2A comparison group was significantly reduced by 44 % in women and by 43 % in men, in patients of the 2B group by 36 % in women and by 36 % in men (p <0.05), in the 3A group – by 22 % in women and by 19 % in men, in group 3B – by 25 % in women and by 17 % in men, which probably did not differ compared to PHI ($p>0.05$). When calculating the indices of lipid balance, in particular the coefficient of atherogenicity and according to the formula: CA=(CHL–HDL)/HDL), a significant degree of imbalance was established in all comparison groups ($p<0.05$): in patients of 2A group, KA was higher than the indicator in PHI is 3.8 times in women and 3.1 times in men, 2B group patients – 3.2 times in women and 3.4 – in men, 3A group patients – 2.1 times in women and 2, 3 in men, 3B group – 2.9 times in women and 1.7 in men.

Table 2

Indicators of the blood lipid spectrum in patients with type 2 diabetes with MS

Indicator	f/m	PHI, n=15 group 1	Group 2 A, n=40	Group 2 B, n=32	Group 3 A, n=26	Group 3 B, n=22
		M±m	M±m	M±m	M±m	M±m
CHL, mmol/l		3.60±0.20	7.19±0.21$^{\&\#}$	5.98±0.23$^{\&*}$	5.81±0.13$^{\&*}$	4.60±0.36$^{\&*\#}$
TG, mmol/l		1.20±0.16	5.19±0.17$^{\&}$	4.97±0.21$^{\&}$	3.61±0.12$^{\&*\#}$	2.07±0.35$^{\&*\#}$
HDL, mmol/l	f	1.53±0.17	0.87±0.09$^{\&}$	0.99±0.11$^{\&}$	1.20±0.27	1.15±0.18
	m	1.43±0.13	0.82±0.08$^{\&}$	0.92±0.12$^{\&}$	1.17±0.08	1.19±0.25
LDL, mmol/l	f	1.78±0.21	3.98±0.28$^{\&}$	3.80±0.37$^{\&}$	3.28±0.34$^{\&}$	3.16±0.27$^{\&*}$
	m	1.79±0.27	4.26±0.26$^{\&}$	3.58±0.28$^{\&}$	3.19±0.18$^{\&*}$	2.02±0.29$^{*\#}$
CA	f	1.48±0.19	5.68±0.33$^{\&}$	4.70±0.39$^{\&}$	3.12±0.44$^{\&*\#}$	4.34±0.25$^{\&*}$
	m	1.69±0.28	5.24±0.29$^{\&}$	5.88±0.28$^{\&}$	3.95±0.09$^{\&*\#}$	2.87±0.43$^{\&*\#}$

Note: $^{\&}$ – statistically significant difference compared to PHI; * – statistically significant difference compared to indicators 2A; $^{\#}$ – statistically significant difference compared to indicators 2B

At the same time, we established a statistically significant difference in comparison with the indicators of 2A and 2B groups ($p<0.05$). Correlation analysis, which showed the presence of a direct correlation between WC in women and indicators: CHL, blood TG and CA. A direct correlation between WC and CHL indicators (r=0.5526, p=0.003), WC and TG (r=0.4456, p=0.002), WC and CA (r=0.4812, p =0.022).

We proved a direct correlation between BMI and CHL indicators (r=0.3653, p=0.0258), BMI and TG (r=0.3388, p=0.0021), BMI and CA in women (r =0.2435, p=0.0271), a direct correlation between total cholesterol and the level of endogenous insulin (r=0.3246, p=0.00001), between TG and the level of EI (r=0.4085, p=0.00001), between CA in men and the level of EI (r=0.3243, p=0.00376) and HOMA IR and CHL (r=0.3788, p=0.0001), HOMA IR and TG (r=0.42361, p=0.00001), HOMA IR and CA in women (r=0.32671, p=0.0423), HOMA IR and CA in men (r=0.4034, p=0 .0269), sufficiently indicates the connection of IR with changes in the blood lipid spectrum and visceral obesity.

4. Discussion of research results

Despite all the variety of established aspects of IR, the pathogenetic mechanisms remain insufficiently studied. A comprehensive study of IR parameters and dyslipidemia in patients with type 2 diabetes with MS remains relevant. The data we obtained prove the connection of IR with changes in the blood lipid spectrum. We found that the prerequisites for the development of IR in patients with type 2 diabetes mellitus with MS are probable fasting and postprandial hyperglycemia, hyperinsulinemia, an increase in the degree of glycation of hemoglobin, primary tissue IR, i.e., a decrease in the sensitivity of peripheral tissues to insulin. A decrease in the intensity of reverse transport of cholesterol from tissues to the liver due to insufficient synthesis of HDL and a significant level of hypercholesterolemia in the composition of LDL and hypertriacylglyceridaemia creates conditions for the development and progression of liver steatosis. The obtained data indicate that IR syndrome contributes to lipid imbalance and is a metabolic prerequisite for the development of NASH. The liver plays an important role in metabolic processes, interconversion of carbohydrates, proteins, lipids, nucleotides, provides immunological and toxicological control [6, 9]. Along with this, it should be emphasized that there is insufficient data in the literature on the role of dyslipidemia in the development of insulin resistance in patients with type 2 diabetes with MS depending on the presence of NASH. We proved that a feature of patients with NASH on the background of MS with type 2 diabetes was the formation of the most significant degree of IR. Lipid imbalance was pronounced in patients with NASH on the background of MS with type 2 diabetes. Therefore, the metabolic prerequisites for the development of IR in patients with type 2 diabetes mellitus with MS are probable hypercholesterolemia, hypertriglyceridemia, an increase in the content of LDL and a decrease in the content of HDL in the blood. A feature of patients with type 2 diabetes with MS in combination with NASH was the presence of significant IR and dyslipidemia.

The obtained results of our study indicate a close connection and interdependence of carbohydrate and lipid metabolism disorders and IR.

Our research results agree with the data of other authors, who prove the relationship between dyslipidemia and IR in patients with type 2 diabetes [1, 6, 8].

The results of the study are recommended for practical use in health care: correction of dyslipidemia against the background of glycemic control.

The conditions of martial law in Ukraine did not affect the conduct of the research and the obtained results.

Study limitations. All patients with type 2 diabetes in this study had poor glycemic control. It has been proven that hyperglycemia is associated with dyslipidemia. Age and gender, duration of diabetes, severity of DM, obesity, bad habits, duration of hypertension, genetic factors may be important in the study of both lipid metabolism and compensation of DM. This requires a larger sample and study duration.

Prospects for further research: study of correlational relationships of blood lipid spectrum parameters, insulin resistance and pro-inflammatory cytokines.

5. Conclusions

1. The calculation of generally accepted indices of insulin resistance, in particular the HOMA IR index, WC, BMI indicates the presence of significant insulin resistance in patients with type 2 diabetes with MS, while

the changes were the greatest in patients with type 2 diabetes with MS and NASH.

2. Insulin resistance syndrome contributes to lipid imbalance and is a metabolic prerequisite for the development of NASH.

3. The results of the study are recommended for practical use in health care: correction of dyslipidemia against the background of glycemic control.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this study, including financial, personal, authorship, or any other, that could affect the study and its results presented in this article.

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Data availability

The manuscript has associated data in the data repository.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the presented work.

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