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The glycemic profile in patients with non-alcoholic steatohepatitis and type 2 diabetes depending on diabetic kidney disease

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Abstract. ***Background.*** *State of carbohydrate metabolism and severity of insulin resistance in the comorbid course of non-alcoholic steatohepatitis (NASH) and diabetic kidney disease (DKD) in patients with type 2 diabetes mellitus (DM2) is due to the cascade of possible transformation of NASH into liver cirrhosis. The purpose is to study the interaction of changes in glucose and insulin homeostasis, the degree of insulin resistance and insulin sensitivity, the degree of hemoglobin glycosylation on the clinical course of NASH associated with DM depending on the presence of DKD and its stage.* ***Materials and methods.*** *One hundred and eight patients with NASH and comorbid DM2 were examined. The average age of patients was 58.2 ± 6.1 years. There were 63 women (58.3 %) and 45 men (41.7 %). Depending on the presence of DKD, 4 groups of patients were formed, who were randomized by age, sex, activity of cytolytic syndrome. The comparison group consisted of 30 healthy individuals of the appropriate age and sex. The degree of hepatic steatosis and its nature were determined using SteatoTest, ASH and NASH-Test kits (BioPredictive, France). The stage of liver fibrosis was determined using FibroTest (BioPredictive, France), a set of markers for quantitative biochemical evaluation of fibrosis.* ***Results.*** *In patients with NASH, DM2 and DKD stage I–II, we found a significant decrease in serum albumin by 9.0 % ($p < 0.05$); glomerular filtration rate (GFR) and urine albumin, on the contrary, increased significantly, by 1.5 times ($p < 0.05$) compared to those in the control group, which indicates the phenomenon of hyperfiltration and is specific to the initial stage of DKD. When NASH is combined with DM2 and DKD stage III, a significant decrease in serum albumin by 1.2 times ($p < 0.05$) is reported; GFR and albuminuria were significantly increased, by 1.4 and 11.7 times ($p < 0.05$), respectively, compared to the control group. In patients with NASH, DM2 and DKD stage IV, we found a significant decrease in serum albumin by 1.4 times ($p < 0.05$), it was significantly increased by 30.2 times ($p < 0.05$) compared to the indicator in the control group, and the GFR, on the contrary, was significantly reduced by 1.7 times ($p < 0.05$), which indicates the progression of DKD.* ***Conclusions.*** *Disorders of glucose homeostasis due to insulin resistance are one of the probable risk factors for the progression of non-alcoholic steatohepatitis and type 2 diabetes mellitus in the presence of stage I–IV diabetic kidney disease.*

Keywords: *non-alcoholic steatohepatitis; type 2 diabetes mellitus; diabetic kidney disease; insulin resistance*

Introduction

The worldwide prevalence of non-alcoholic steatohepatitis (NASH) is estimated to have reached 25 % or more in adults [1]. NASH is prevalent in obese individuals, but may also affect non-obese insulin-resistant individuals. NASH is associated with a 2- to 3-fold increased risk of developing type 2 diabetes (DM2), which may be higher in patients with more severe liver disease — fibrosis increases this risk [2, 3]. In NASH, not only the close association with obesity, but also the impairment of many metabolic pathways, including decreased hepatic insulin sensitivity and insulin secretion, increase the risk of developing DM2 and related comorbidities [4, 5]. Conversely, patients with diabetes have a higher prevalence of steatohepatitis, liver fibrosis and end-stage liver

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disease. Genetics and mechanisms involving dysfunctional adipose tissue, lipotoxicity and glucotoxicity appear to play a role [6, 7].

State of carbohydrate metabolism and the intensity of insulin resistance (IR) in the comorbid course of NASH and diabetic kidney disease (DKD) in patients with DM2 is due to possible transformation of NASH into liver cirrhosis [8]. Non-alcoholic steatosis of the liver and NASH are considered the most common liver pathology, which in developed countries is observed in 20–30 % of the adult population [9]. It is proved that the most common cause of NASH is obesity and DM2 [10]. The combination of NASH and DM2 increases the risk of liver cirrhosis and hepatocellular carcinoma by 2–2.5 times [11].

Diabetic nephropathy is one of the leading causes of end-stage renal disease in industrialized countries [12]. Since 2007, the National Foundation for Kidney Disease Initiative to Improve the Quality of Kidney Disease Treatment has proposed the use of the term "diabetic kidney disease" instead of "diabetic nephropathy" [13]. In addition, patients with diabetes often develop non-specific renal lesions such as asymptomatic bacteriuria, pyelonephritis, renal carbuncle, apostematous nephritis, renal abscess, renal tuberculosis, necrotic papillitis or papillary necrosis, which significantly aggravate the disease.

The purpose of the study was to examine the interaction of changes in glucose and insulin homeostasis, the degree of IR and insulin sensitivity, the degree of glycosylation of hemoglobin on the clinical course of NASH on the background of diabetes mellitus depending on the presence of DKD and its stage.

Materials and methods

One hundred and eight patients with NASH with comorbid DM2 were examined. The average age of patients was 58.2 ± 6.1 years. There were 63 women (58.3 %) and 45 men (41.7 %). Depending on the presence of DKD, 4 groups of patients were formed, which were randomized by age, sex, activity of cytolytic syndrome. The division into groups of examined patients is given in Table 1. The comparison group consisted of 30 practically healthy people (PHP) of the appropriate age and sex.

The diagnosis of NASH was established in accordance with the unified clinical protocol approved by the Order of the Ministry of Health of Ukraine No. 826 of 06.11.2014, in the presence of criteria for exclusion of chronic diffuse liver disease of viral, hereditary, autoimmune or drug origin as the cause of cytolytic, cholestatic and mesenchymal also the results of ultrasonographic examination of the liver. The degree of hepatic steatosis and its nature were determined using a ratified kit SteatoTest, ASH and NASH-Test (BioPredictive, France). The stage of liver fibrosis was determined by using a set of markers for quantitative biochemical evaluation of fibrosis FibroTest (BioPredictive, France).

Diagnosis of DM2 was performed in accordance with the unified clinical protocol approved by the Order of the Ministry of Health of Ukraine No. 1118 of 21.12.2012. Diagnosis and treatment of CKD was carried out according to the recommendations of clinical guidelines SI "Institute of Nephrology of the NAMS of Ukraine" (2012). Calculation of the glomerular filtration rate (GFR) was performed using a GFR calculator of the Institute of Nephrology of the National Academy of Medical Sciences of Ukraine on the average of three calculated indicators: creatinine clearance according to the Cockcroft-Gault formula, MDRD and CKD-EPI [14].

The state of carbohydrate metabolism was determined by the level of fasting blood glucose and blood glucose 2 hours after a meal (postprandial glucose) by glucose oxidase method; fasting insulin content (DRG System) by enzyme-linked immunosorbent assay; content of glycated hemoglobin (HbA1c) in the blood using standard reagent kits Simko Ltd (Lviv). The degree of IR was determined by the value of the body mass index (BMI), HOMA-IR index and tissue sensitivity index to insulin was calculated using the HOMA2 Calculator Version 2.2 Diabetes Trials Unit University of Oxford (United Kingdom).

Statistical analysis was performed according to the type of study and the types of numerical data that were obtained. The normality of the distribution was checked using Lilliefors, Shapiro-Wilk tests and the method of direct visual evaluation of histograms of the distribution of eigenvalues. Quantitative values that had a normal distribution are presented as mean (M) ± standard deviation (S). Discrete values are presented in the form of absolute and relative frequencies (percentage of observations to the total number of subjects). For comparisons of data that had a normal distribution, we used parametric tests with the assessment of Student's t-test, Fisher's F-test. In the case of an abnormal distribution, the calculation of the Mann-Whitney rank U-test was used, and for multiple comparison, the Wilcoxon T-test was used (in the case of the study of dependent groups). Pearson correlation analysis in the parametric distribution and Spearman's rank correlation coefficient in case of the distribution of indicators that were significantly different from the normal one were used to assess the degree of dependence between the variables. For statistical and graphical analysis of the obtained results we used software packages Statistica for Windows version 8.0 (StatSoft inc., USA), Microsoft Excel 2007 (Microsoft, USA).

Table 1. Distribution of examined patients with non-alcoholic steatohepatitis and type 2 diabetes mellitus depending on the presence of DKD and its stage

Number of examined patients		Comorbidity, DKD stages							
		NASH with DM2 without DKD		NASH with DM2 and DKD stage I–II		NASH with DM2 and DKD stage III		NASH with DM2 and DKD stage IV	
n	%	n	%	n	%	n	%	n	%
108	100	28	25.9	27	25.0	28	25.9	25	23.1

Results

Analysis of renal function in patients with NASH with diabetes without DKD (group 1) indicates a normal level of albumin in the blood, normal GFR and albuminuria (Table 2). At the same time, in patients with NASH, DM and DKD I–II (group 2) found a significant decrease in the serum albumin by 9.0 % ($p < 0.05$), GFR and the content of albumin in the urine, on the contrary, significantly increased by 1.5 times ($p < 0.05$) compared with PHP (Table 2), which indicates the phenomenon of hyperfiltration and inherent in the initial stage of DKD.

In patients with NASH, DM and DKD III (group 3) found a significant decrease in blood albumin by 1.2 times ($p < 0.05$), GFR and albuminuria were significantly increased by 1.4 and 11.7 times ($p < 0.05$), respectively, compared with the indicator in PHP (Table 2).

In patients with NASH, DM and DKD IV (group 4), we found a significant decrease in the serum albumin by 1.4 times ($p < 0.05$), the serum albumin was significantly increased by 30.2 times ($p < 0.05$) compared with the PHP (Table 2), and the GFR, on the contrary, was significantly reduced — by 1.7 times ($p < 0.05$), which indicates the progression of CKD and DKD.

Glycemia, insulinemia and IR indices in patients with NASH with DM2 are shown in Table 3. Patients of all groups found a significant probable increase in fasting glycemia: in group 1 — by 1.6 times, in 2 — by 1.8 times, in group 3 — by 2.5 and in group 4 — by 2.7 times ($p < 0.05$) compared to the indicator in PHP. Examination of the serum insulin revealed a significant hyperinsulinemia, which in patients of the group 1 exceeded the indicator in the group of PHP by 1.9 times, in patients of the second group — by 2.4 times, in the third group — by 2.9 and in the fourth group — by 3.3 times ($p < 0.05$) (Table 3).

The above processes resulted in significant changes in IR and peripheral tissue sensitivity to insulin.

In particular, the violation of peripheral tissue sensitivity to insulin in patients with NASH and DM indicates a significant increase in the HOMA-IR index (in groups 1, 2, 3 and 4 — by 2.2, 2.7, 3.5 and 4.0 times, respectively; $p < 0.05$), as well as an adequate decrease in S ($p < 0.05$) with a significant difference between groups 1, 2 and 3, 4 ($p < 0.05$) (Table 3). At the same time, there was no difference between the indicator of another marker of IR — BMI in patients of different groups ($p > 0.05$), but the indicator in all groups of patients exceeded the data in PHP by 1.3 times ($p < 0.05$) (Table 3).

The consequence of chronic fasting and postprandial hyperglycemia was an increase in HbA1c in these observation groups (in groups 1, 2, 3 and 4 — by 1.6, 1.9, 2.4 and 2.5 times, respectively; $p < 0.05$) with a significant difference between groups 1, 2 and 3, 4 ($p < 0.05$).

Analysis of glucose and insulin homeostasis in relation to markers of liver damage, indicators of functional status of the liver and kidneys in patients with NASH with DM2 and DKD IV indicates that postprandial hyperglycemia and

Table 2. Indicators of the functional state of the kidneys in patients with NASH, type 2 diabetes depending on the presence of DKD and its stage (M ± m)

Indicators	PHP (n = 30)	Groups of examined patients			
		NASH with DM2 without DKD (n = 28)	NASH with DM2 and DKD I–II stages (n = 27)	NASH with DM2 and DKD III stage (n = 28)	NASH with DM2 and DKD IV stage (n = 25)
Blood albumins, g/l	40.9 ± 1.3	39.1 ± 0.8	37.2 ± 0.9[a]	32.3 ± 0.8[a, b, c]	28.2 ± 0.9[a, b, c, d]
GFR, ml/min/1.73 m^2	95.3 ± 1.6	91.5 ± 2.1	145.0 ± 2.0[a, b]	134.6 ± 2.3[a, b, c]	57.0 ± 1.2[a, b, c, d]
Urine albumin, mg/day	18.4 ± 0.7	20.3 ± 0.5	28.4 ± 1.6[a, b]	210.5 ± 8.7[a, b, c]	543.1 ± 24.9[a, b, c, d]

Notes (here and in Table 3): the difference is significant: [a] — in comparison with the indicator in the control group ($p < 0.05$); [b] — compared to the indicator in patients with NASH with DM2 ($p < 0.05$); [c] — in comparison with the rate in patients with NASH with DM, DKD I–II ($p < 0.05$); [d] — compared to the indicator in patients with NASH with DM2, DKD III ($p < 0.05$).

Table 3. Indicators of blood glucose and blood insulin, glycated hemoglobin, IR indices in patients with NASH, type 2 diabetes mellitus depending on the presence of DKD and its stage (M ± m)

Indicators	PHP (n = 30)	Groups of examined patients			
		NASH with DM2 without DKD (n = 28)	NASH with DM2 and DKD I–II stages (n = 27)	NASH with DM2 and DKD III stage (n = 28)	NASH with DM2 and DKD IV stage (n = 25)
Fasting glucose, mmol/l	4.23 ± 0.27	6.82 ± 0.31[a]	7.78 ± 0.24[a, b]	10.52 ± 0.27[a, b, c]	11.58 ± 0.44[a, b, c, d]
Fasting insulin, mIU/l	9.92 ± 2.17	19.35 ± 2.15[a]	23.50 ± 1.21[a]	28.97 ± 1.53[a, b, c]	32.39 ± 1.15[a, b, c]
HbA1c, %	4.07 ± 0.23	6.70 ± 0.31[a]	7.63 ± 0.43[a]	9.95 ± 0.52[a, b, c]	10.37 ± 0.47[a, b, c]
HOMA-IR2	1.23 ± 0.26	2.65 ± 0.35[a]	3.28 ± 0.24[a]	4.26 ± 0.21[a, b, c]	4.98 ± 0.20[a, b, c]
S, %	81.61 ± 7.24	37.82 ± 3.27[a]	30.55 ± 3.12[a]	23.50 ± 2.87[a, b]	20.11 ± 2.18[a, b, c]
BMI, kg/m^2	23.08 ± 1.65	29.21 ± 1.19[a]	30.42 ± 1.33[a]	30.79 ± 1.49[a]	29.88 ± 1.45[a]

Table 4. Correlations of markers of damage and functional parameters of the liver, kidneys with indicators of glucose homeostasis and insulin content in the blood, indices of insulin resistance in patients with NASH

Indicator	Fasting glucose	Postprandial glucose	Insulin	HOMA-IR	BMI	HbA1C
Alanine aminotransferase	0.50*	0.55*	0.29	0.57*	0.22	0.53*
Alkaline phosphatase	0.39*	0.41*	0.15	0.42*	0.17	0.36*
Thymol test	0.42*	0.47*	0.26	0.53*	0.28	0.55*
Steatotest	0.64*	0.71*	0.34*	0.74*	0.59*	0.69*
Albumins	–0.37*	–0.42*	–0.33*	–0.49*	–0.32*	–0.46*
Blood creatinine	0.56*	0.63*	0.44*	0.63*	0.43*	0.57*
GFR	–0.51*	–0.57*	–0.41*	–0.61*	–0.47*	–0.51
Albuminuria	0.48*	0.52*	0.35*	0.58*	0.38*	0.48*

Note: * — the level of correlations is statistically significant (p < 0.05).

insulinemia, as well as the degree of IR in a weak relationship increase with increasing intensity of cytolysis, cholestasis, mesenchymal inflammation, and are factors of mutual burden of NASH and DM2 with DKD (Table 4).

Thus, the most significant metabolic prerequisites for the development of NASH on the background of DM are probable fasting and postprandial hyperglycemia, hyperinsulinemia, increased HbA1c, tissue IR. One of the risk factors for the progression of NASH and the background of DM is the presence of DKD, as impaired carbohydrate metabolism and the degree of IR in these conditions are more significant compared to the course of NASH in the absence of DKD ($p < 0.05$). The progression of DKD from stage I to IV on the background of DM2 in comorbidity with NASH depends on the degree of supracardiac, postprandial hyperglycemia and the degree of IR (HOMA-IR) ($p < 0.05$).

Discussion

The article presents a theoretical generalization of the results of the study of IR in patients with NASH in comorbidity with DM2 in the presence of DKD and depending on its stage. It was found that disorders of glucose homeostasis due to IR is one of the significant risk factors for the progression of NASH and DM in the presence of DKD I–IV serum insulin level — 2.9 vs. 1.9 times, HbA1c — 2.3 vs. 1.6 times and the degree of IR (increase in HOMA by 3.4 vs. 2.2 times) under these conditions are more significant in comparable with the course of NASH with DM in the absence of DKD ($p < 0.05$).

Indicators of postprandial glycemia and insulinemia, as well as the degree of IR in patients with NASH and the background of DM2 with DKD IV affect an increase in the intensity of cytolysis, cholestasis, mesenchymal inflammation, contribute to the development of hepatic steatosis, as well as renal dysfunction. The progression of DKD from stage I–II to stage IV on the background of DM2 and NASH depends on the level of hyperglycemia and the degree of IR ($p < 0.05$).

The main pathogenetic basis of NASH on the background of DM is a violation of the sensitivity of insulin receptors to membranes of insulin-sensitive organs (liver and skeletal muscle) to the hormone, disorders of transport and utilization of glucose from the circulatory system [15, 16].

It has been proved that in DM2 the organism is rebuilt into an alternative energy supply — by catabolism of fat in visceral fat depots, as a result of which a significant amount of free fatty acids enters the systemic circulation and is sent to the liver [17, 18]. Due to significant inhibition of β-oxidation of free fatty acids in hepatocytes in DM2, neutral fat in the form of triacylglycerols accumulates in hepatocytes and forms the pathomorphological basis of micro- or macrovesicular steatosis of the liver and, at the same time, deepens [19].

At the same time, the effect of DKD depending on its stage on the glycemic and insulin profile, the state of IR in NASH on the background of DM is still poorly understood, although disorders of glucose homeostasis may accelerate apoptosis of hepatocytes and podocytes, hyper- and dyslipidemia, early development and endothelial dysfunction, activation of inflammatory processes, fibrosing reactions in the liver and kidneys [20].

Conclusions

Metabolic prerequisites for the development of NASH on the background of diabetes mellitus are probable fasting and postprandial hyperglycemia (1.6 times, $p < 0.05$), hyperinsulinemia (1.9 times, $p < 0.05$), an increase in the degree of HbA1c (1.6 times, $p < 0.05$), IR (increase in HOMA by 2.2 times, $p < 0.05$) compared with healthy individuals.

Disorders of glucose homeostasis due to IR is one of risk factors for the progression of NASH and diabetes mellitus in the presence of DKD.

Indicators of postprandial glycemia and insulinemia, as well as the degree of IR in patients with NASH and DM2 with DKD IV affect an increase in the intensity of cytolysis, cholestasis, mesenchymal inflammation, and are factors of mutual burden of NASH and DM2 with DKD.

The progression of DKD from stage I–II to IV on the background of DM in combination with NASH depends on the degree of postprandial hyperglycemia and the degree of IR (HOMA-IR) ($p < 0.05$).

Ethical approval. The research was carried out taking into account the main provisions of the GCP (1996), the Helsinki Declaration of the World Medical Association on the ethical principles of scientific medical research with human participation (1964–2013), the Council of Europe Convention on Human Rights and Biomedicine (1997) Ministry of Health of Ukraine No. 616 of August 3, 2012, and a positive conclusion of the Commission on Biomedical Ethics of Bukovinian State Medical University (No. 1, September 22, 2019).

Consent to participate. Written informed consent was obtained from the patients.

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Глікемічний профіль у пацієнтів із неалкогольним стеатогепатитом і цукровим діабетом 2-го типу залежно від стадії діабетичної хвороби нирок

Резюме. ***Актуальність.*** Стан вуглеводного обміну й ступінь інсулінорезистентності при коморбідному перебігу неалкогольного стеатогепатиту (НАСГ) та діабетичної хвороби нирок (ДХН) у пацієнтів із цукровим діабетом 2-го типу (ЦД2) зумовлені можливою трансформацією НАСГ в цироз печінки. ***Мета:*** вивчити взаємовплив змін гомеостазу глюкози й інсуліну, ступеня інсулінорезистентності та чутливості до інсуліну, ступеня глікозилювання гемоглобіну на клінічний перебіг НАСГ на тлі ЦД2 залежно від наявності ДХН та її стадії. ***Матеріали та методи.*** Обстежено 108 хворих на НАСГ із коморбідним ЦД2. Середній вік пацієнтів становив 58,2 ± 6,1 року. Жінок було 63 (58,3 %), чоловіків — 45 (41,7 %). Залежно від наявності ДХН сформовано 4 групи пацієнтів, які були рандомізовані за віком, статтю, активністю цитолітичного синдрому. Групу порівняння становили 30 практично здорових осіб відповідного віку та статі. Ступінь стеатозу печінки та його природу визначали за допомогою наборів SteatoTest, ASH та NASH-Test (BioPredictive, Франція). Стадію фіброзу печінки визначали з використанням набору маркерів для кількісної біохімічної оцінки фіброзу FibroTest (BioPredictive, Франція). ***Результати.*** У пацієнтів із НАСГ, ЦД2 та ДХН I–II ст. встановлено достовірне зниження вмісту альбумінів у крові на 9,0 % ($p < 0,05$), швидкість клубочкової фільтрації (ШКФ) та вміст альбумінів у сечі, навпаки, достовірно зросли — в 1,5 раза ($p < 0,05$) порівняно з показником у контрольній групі, що свідчить про гіперфільтрацію, притаманну початковим стадіям ДХН. За коморбідності НАСГ, ЦД2 та ДХН III ст. встановлено достовірне зниження вмісту альбумінів у крові в 1,2 раза ($p < 0,05$), ШКФ та рівень альбумінурії були достовірно підвищені — відповідно в 1,4 та 11,7 раза ($p < 0,05$) порівняно з показником у контрольній групі. У пацієнтів із НАСГ, ЦД2 та ДХН IV ст. встановлено істотне зниження вмісту альбумінів у крові в 1,4 раза ($p < 0,05$), він був достовірно підвищений у 30,2 раза ($p < 0,05$) порівняно з показником у контрольній групі, а ШКФ, навпаки, істотно знизилася в 1,7 раза ($p < 0,05$), що вказує на прогресування ДХН. ***Висновки.*** Розлади гомеостазу глюкози внаслідок інсулінорезистентності є одним із достовірних факторів ризику прогресування неалкогольного стеатогепатиту на тлі цукрового діабету 2-го типу за наявності діабетичної хвороби нирок I–IV стадій.

Ключові слова: неалкогольний стеатогепатит; цукровий діабет 2-го типу; діабетична хвороба нирок; інсулінорезистентність