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Changes in the brain vessels in patients with non-alcoholic fatty liver disease and carbohydrate metabolism disorder

Abstract. *Background. The studies of brain vessels in patients with non-alcoholic fatty liver disease (NAFLD) can reveal new aspects of early detection of cerebral hemodynamic disorders, and will also allow the identification of a high-risk patients group. The purpose was to investigate the peculiarities of changes in the brain vessels in patients with NAFLD in combination with insulin resistance (IR) or type 2 diabetes mellitus (T2DM).* **Materials and methods.** *The study involved 74 patients with NAFLD (34 patients with non-alcoholic fatty hepatosis (NAFH) and 40 patients with non-alcoholic steatohepatitis (NASH)). The comparison group included 38 patients (16 patients with IR and 22 patients with T2DM). The condition of the blood flow in the brain was studied using ultrasound duplex scan of the extracranial portion of the common carotid artery (eCCA), the external carotid artery (eCA), the extracranial portion of the internal carotid artery, middle cerebral artery, the vertebral artery (VA), ophthalmic artery. The peak systolic velocity (PSV) and the time-average maximum (TAMX) of blood flow velocity in the studied vessels was determined.* **Results.** *The asymmetric damage to the vessels of the brain with more severe left ventricular dysfunction with NAFH is conspicuous; it is more pronounced in patients with the NASH stage, especially in combination with IR. Hemodynamically, the most significant changes were found in eCCA, namely, the decrease in PSV was found to be 38.1 ± 2.3 cm/s on the right, and 36.6 ± 3.4 cm/s on the left, TAMX reduction 20.4 ± 2.1 cm/s on the right, and 16.7 ± 1.8 cm/s on the left.* **Conclusions.** *The patients with NAFLD, as well as IR and T2DM had a decrease in the speed of blood flow in extracranial vessels of the brain, mainly in the eCCA, eCA and VA (segment 3). The most pronounced blood flow deficiency has been observed in patients with NASH in combination with IR, mainly on the left, especially in eCCA.*
Keywords: *non-alcoholic fatty liver disease; insulin resistance; type 2 diabetes mellitus; brain vessels*

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a clinical diagnosis that includes the presence of 5 % or more hepatic cells with fat accumulation as determined by liver imaging or biopsy in the absence of secondary causes of hepatic steatosis. NAFLD spans the spectrum of simple steatosis or non-alcoholic fatty liver to non-alcoholic steatohepatitis (NASH) which is defined histologically as hepatic steatosis, hepatic inflammation, and hepatocellular ballooning with or without fibrosis [1].

NAFLD is prevalent worldwide and is the most common chronic liver disease in Western countries. Its increasing prevalence is associated with major risk factors such as obesity, dyslipidemia, type 2 diabetes mellitus (T2DM), and the metabolic syndrome [2].

NAFLD is a systemic disorder of energy, glucose, and lipid homeostasis with hepatic manifestations [3]. Metabolic disorders, such as lipid accumulation, insulin resistance (IR), and inflammation, have been implicated in the pathogenesis of NAFLD, but the underlying mechanisms, including those that drive disease progression, are not fully understood [4]. Therefore, the non-alcoholic fatty liver disease covers a range of diseases closely related to metabolic risk factors. As of today, the commonality of pathogenic mechanisms for NAFLD and metabolic syndrome has been proven, and their association with type 2 diabetes

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mellitus, cardiovascular diseases and severe forms of liver disease, including cirrhosis and hepatocellular carcinoma, is evident [5].

It is believed that IR plays a central role in the development of NAFLD [6]. Patients with insulin resistance, as seen in obesity, metabolic syndrome, hypertension, and/or type 2 diabetes mellitus frequently exhibit endothelial dysfunction and are prone to develop arterial atherosclerosis, hypertension and metabolic disorders such as dysglycemia and elevated plasma free fatty acid levels. As a result of IR in patients with metabolic syndrome, type 2 diabetes, NAFLD, etc., endothelial dysfunction is formed, as well as vascular insulin resistance, combined with metabolic insulin resistance, that contribute to the development of hypertension and cardiovascular complications [7]. The associated physiological mechanisms are not fully appreciated yet, however, it seems that augmented oxidative stress, a physiological imbalance is a possible mechanism involved in various vascular beds with insulin resistance and hyperglycemia [8].

A growing body of literature now recognizes that deterioration in vascular function over time is a major contributor to the process of cognitive aging. Liver disease, particularly NAFLD, may be involved in the process of cognitive aging through several potential mechanisms. First, persons with NAFLD have a high prevalence of individual vascular risk factors (e.g., hypertension) that contribute to the progression of cognitive aging. Additional risk factors that may accelerate vascular aging include microvascular endothelial dysfunction in concert with high levels of liver-derived gamma-glutamyltransferase (GGT) and insulin-like growth factor-1. Second, the concurrent presence of chronic systemic inflammation and the metabolic syndrome, which are highly prevalent in NAFLD, have been shown to contribute to cognitive impairment. Finally, obesity, in particular visceral adiposity, is related to neurodegenerative, vascular, and metabolic processes that affect brain structures underlying cognitive function [9].

Therefore, the studies of brain vessels in patients with NAFLD can reveal new aspects of early detection of cerebral hemodynamic disorders, and will also allow the identification of a high-risk patients group who will need to undergo a correction of existing disorders in order to prevent cardiovascular catastrophe, especially when combined with NAFLD with IR, T2DM and obesity.

The purpose of the study was to investigate the peculiarities of changes in the brain vessels in patients with NAFLD in combination with IR or T2DM.

Materials and methods

At the clinical site of the Department of Propaedeutics of Internal Diseases of the Medical Faculty of SHEI "Uzhhorod National University" (Gastroenterology and Endocrinology Department in Novak Transcarpathia Region Clinical Hospital) during 2016—2019, 74 patients with NAFLD were examined. The average age was (47.8 ± 7.9) years. They formed the basic group of the examined patients (Group 1). Patients in Group 1 were divided into subgroups, namely:

— subgroup 1.1 included 34 patients with non-alcoholic fatty hepatosis (NAFH) (20 males (58.8 %) and 14 females (41.2 %), the average age was (47.7 ± 6.8) years);

— subgroup 1.2 included 40 patients with non-alcoholic steatohepatitis (24 males (60.0 %) and 16 females (40.0 %), the average age was (48.9 ± 6.8) years).

In order to achieve the aim of the research, the patients in the basic group (Group 1) were further divided into subgroups depending on the presence of type 2 diabetes (moderate to severe) or IR (Fig. 1).

The comparison group (Group 2) included 38 patients examined without laboratory-instrumental manifestations of liver damage, which in turn were divided into 2 subgroups, namely:

— subgroup 2.1 included 16 patients with IR (10 males (62.5 %) and 6 females (37.5 %), the average age was (42.4 ± 6.9) years);

— subgroup 2.2 included 22 patients with moderate to severe T2DM (13 males (59.1 %) and 9 females (40.9 %), the average age was (46.6 ± 4.1) years).

The control group included 20 apparently healthy persons (12 males (60.0 %) and 8 females (40.0 %)), the average age was (47.6 ± 5.8) years.

All studies were performed with patients' consent (written consent for performing appropriate diagnostic and therapeutic measures was received from all of the patients), and the methodology of their implementation met the World Medical Association Declaration of Helsinki (1975) and its revised version of 1983, and European Convention on Human Rights, as well as biomedicine and legislation of Ukraine.

All the examined patients were subject to general clinical, anthropometric, instrumental, and laboratory tests. The diagnosis was verified by complaints and history taking. In anthropometric study, height, weight, and waist circumferences were determined, and body mass index (BMI) was calculated. According to WHO recommendations, patients were divided based on BMI, where BMI of 16.0 and less corresponded to an expressed deficiency of body mass; 16.0—17.9 — insufficient body mass; 18.0—24.9 — normal body mass; 25.0—29.9 — excess weight; 30.0—34.9 — class I obesity; 35.0—39.9 — class II obesity; 40.0 and above — class III obesity (morbid obesity) [10].

Ultrasound examination of the abdominal cavity was performed in all patients according to generally accepted method. Standard and biochemical blood serum tests have been performed to determine the functional state of the liver, lipid metabolism indexes and carbohydrate metabolism (glucose, insulin, glycosylated hemoglobin (HbA1c, %) indexes).
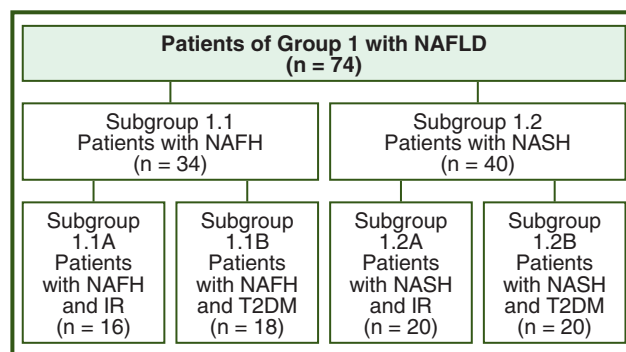

Figure 1 — Distribution of patients with NAFLD depending on the presence of IR or T2DM

NAFLD diagnosis was established in accordance with the Unified Clinical Protocol criteria (the Order of the Ministry of Health of Ukraine dated November 6, 2014, No. 826) and EASL-EASD-EASO Clinical Recommendations for Diagnosis and Treatment of NAFLD [11].

The degree of liver damage has been calculated using surrogate markers of fibrosis with the help of online calculators:

1. NAFLD fibrosis score: taking into account the age of the patients (years), BMI (kg/m^2), glucose tolerance or diabetes mellitus, alanine aminotransferase (ALT, U/L), albumin (g/L), and the number of platelets ($\times 10^9$/L). The indicator corresponds:

< −1.455: predictor of absence of significant fibrosis (F0−F2 fibrosis);

≤ −1.455 to ≤ 0.675: undetermined score;

> 0.675: predictor of presence of significant fibrosis (F3−F4 fibrosis).

2. Fibrosis 4 calculator: this formula takes into account the age of a patient (years), level of ALT (U/L), AST (U/L) and platelet count ($\times 10^9$/L). Hence:

— an index lower than 1.45 — the probability of fibrosis presence is low (around 90 %);

— an index larger than 3.25 — the probability of fibrosis presence is high (around 90 %).

3. Fibrotest: here, the age (years), gender, GGT level (U/L), total bilirubin (μmol/L), apolipoprotein (g/L), haptoglobin (g/L), α2-macroglobulin (g/L) are taken into account.

Insulin resistance was determined using the HOMA-IR (homeostasis model assessment method for insulin resistance), which was calculated according to a formula (normally HOMA-IR < 2.5):

$$\text{HOMA} = \text{fasting blood serum insulin (μU/mL)} \times \text{fasting blood plasma glucose (mmol/L)} / 22.5.$$

Diagnosis of type 2 diabetes mellitus has been established according to IDF recommendations (2005), as well as taking into account the criteria of unified clinical protocol (the Order of the Ministry of Health of Ukraine dated December 21, 2012, No. 1118) [12]. The severity of T2DM was evaluated by HbA1c index (norm being up to 6.0 %).

Ultrasound evaluation of the head vessels was performed on Aloka ProSound 3500 SX (SSD-3500) (Hitachi Aloka Medical, China) apparatus using Aloka UST-5524-7.5 sensor. The condition of the blood flow in the brain was studied using ultrasound duplex scan of the extracranial portion of the common carotid artery (eCCA), the external carotid artery (eCA), the extracranial portion of the internal carotid artery (eICA), middle cerebral artery (MCA), the vertebral artery (VA), ophthalmic artery (OA). The peak systolic velocity (PSV) and the time-average maximum (TAMX) of blood flow velocity in the studied vessels was determined. For the differential diagnosis of the atherosclerotic changes in brain vessels in the examined patients, eCCA posterior wall intima-media complex thickness was measured, since this is a marker of carotid atherosclerosis. The normal thickness of the intima-media complex for all patients is less than 1.0 mm. If the thickness index of intima-media complex of CCA posterior wall in the examined patients exceeded 1.0 mm, the patients were excluded from the study, and the results were considered as manifestations of atherosclerotic lesions of the brain vessels.

The criteria for exclusion of patients from the study were also: type 1 diabetes, type 2 diabetes (moderate to severe degrees, with severe manifestations of diabetic angioneuropathy), chronic hepatitis, alcoholic, viral (hepatitis B, C, D) etiologies, autoimmune hepatitis.

The scientific research was carried out within the scientific research work framework No. 851 "Mechanisms of the formation of complications in liver diseases and pancreas, methods of their treatment and prevention" (state registration number: 0115U001103), as well as the general department topic of the Department of Propaedeutics of Internal Diseases.

The analysis and processing of the examination results were carried out using the computer program Statistics for Windows 10.0 (StatSoft Inc., USA) using parametric and non-parametric methods of evaluating the results obtained.

Results

The anthropometric study found that the prevailing majority of the examined patients of both groups had overweight or obesity of varying classification (class I−II) (Table 1).

It is worth noting that among the patients with NAFH (Subgroup 1.1) and T2DM (Subgroup 2.2) people with class I obesity prevailed (p < 0.05), while among the patients with NASH (Subgroup 1.2) and IR (Subgroup 2.1) people with overweight were determined significantly more often. At the

Table 1 — Distribution of the patients according to BMI

BMI	Group 1 (n = 74)		Group 2 (n = 38)	
	Subgroup 1.1 (n = 34)	Subgroup 1.2 (n = 40)	Subgroup 2.1 (n = 16)	Subgroup 2.2 (n = 22)
Normal weight, % 18.0–24.9 kg/m²	8.8 22.3 ± 2.7	12.5 20.3 ± 4.6*	18.8 23.7 ± 3.1	13.6 22.1 ± 4.4
Overweight, % 25.0–29.9 kg/m²	29.4 27.0 ± 4.1	45.0* 26.6 ± 3.3	50.0# 28.4 ± 3.5#	27.3 26.5 ± 2.7
Class I obesity, % 30.0–34.9 kg/m²	50.0* 33.7 ± 2.5*	25.0 31.6 ± 1.9	25.0 34.1 ± 3.3#	40.9# 31.7 ± 2.8
Class II obesity, % 35.0–39.9 kg/m²	11.8 37.9 ± 4.1	17.5 37.1 ± 3.5	6.2 38.9 ± 5.3	18.2 36.1 ± 3.2

*Notes: the difference between the indexes of Group 1 within the subgroups is significant: * — p < 0.05; the difference between the indexes of Group 2 is significant: # — p < 0.05.*

same time, among the patients from Group I, higher BMI indexes within the limits of corresponding malnutrition degree were determined in those with NAFH (Subgroup 1.1), and among patients with carbohydrate metabolism disorder — among those examined for IR (Subgroup 2.1).

The study of the carbohydrate metabolism indexes confirmed the presence of IR in patients in Subgroup 2.1 and T2DM in patients in Subgroup 2.2. At the same time, an increase in insulin level in patients with T2DM (moderate to severe) is a compensatory mechanism of the body for insulin resistance, as indicated by the high index of HOMA-IR in patients in Subgroup 2.1.

While characterizing carbohydrate metabolism, namely IR, at NAFLD, differences were found in patients with NAFH and NASH, namely, more severe hyperinsulinemia in patients with NAFH ((44.7 ± 6.5) U/L), which is associated with a more severe IR. Fasting glycemic indices were also higher in NAFH patients: glucose level in patients in the Subgroup 1.1A was (7.95 ± 0.24) mmol/l, and HbA1c — (7.98 ± 0.36) %.

It should be noted that more severe disorders of carbohydrate metabolism were found when combined with type 2 diabetes or IR with NAFLD than without it. In this case, the maximum deviations from the parameters of the control group were established in patients in Subgroup 1.1A (NAFH in combination with IR) (Tables 2, 3).

The Tables 4, 5 demonstrate that all examined subgroups of both groups revealed changes in the velocity of blood flow in the vessels of the brain by the results of duplex scan.

The average blood flow velocity in both external and internal carotid arteries in patients with both T2DM (Subgroup 2.2) and IR (Subgroup 2.1) was determined. The maximum deviations from the norm were found in the blood flow rates according to eCCA, namely, the decrease of PSV to (50.2 ± 2.2) cm/s on the right and to (51.0 ± 3.6) cm/s to the left in patients in the Subgroup 2.1, and to (51.0 ± 1.8) cm/s on the right and up to (50.6 ± 2.4) cm/s to the left in the patients in the Subgroup 2.2. TAMX is also believed to be significantly lower in patients with type 2 diabetes. In the study of segments 3 and 4 of VA, a blood flow deficit on both sides in patients in Group 2 was also diagnosed. It should be noted that a significant difference in the studied parameters in patients with type 2 diabetes was not detected in Group 2 (Table 4).

Patients with NAFLD revealed significant deviations from the norm in blood flow rates in the study of major vessels of the brain (Table 5). At the same time, in patients with NAFH in both 1.1A and 1.1B Subgroups, the indicators did not significantly differ from those in patients with IR ((Subgroup 2.1) or T2DM (Subgroup 2.2) without liver damage. Maximum changes in blood flow to extracranial vessels of the brain are found in patients with NASH (Subgroups 1.2). At the same time, the difference in these indicators, depending on the presence of IR (Subgroup 1.2A) or type 2 DM (Subgroup 1.2B) was not established.

The asymmetric damage to the vessels of the brain with more severe left ventricular dysfunction with NAFH is conspicuous; that is more pronounced in patients with the

Table 2 — Changes in carbohydrate metabolism in Group 2 patients (with T2DM and IR) and the control group

Index	Control group	Group 2 (n = 38)	
		Subgroup 2.1 (n = 16)	Subgroup 2.2 (n = 22)
Glucose (mmol/L)	4.51 ± 0.41	6.58 ± 0.33*	7.82 ± 0.26*
HbA1c (%)	4.38 ± 0.26	6.73 ± 0.28*	7.91 ± 0.15*
Insulin (U/L)	9.20 ± 1.14	36.21 ± 5.57**, #	19.77 ± 2.42*
C-peptide (ng/mL)	4.54 ± 0.97	16.21 ± 1.88**, +	11.73 ± 1.26**
HOMA-IR	1.71 ± 0.32	10.42 ± 2.61**,+	6.23 ± 0.40**

*Notes: the difference between the indices in patients of the Group 2 and the control group is significant: * — p < 0.05; ** — p < 0.01; the difference between the indices in patients of the Group 2 in the subgroups is significant: + — p < 0.05; # — p < 0.01.*

Table 3 — Changes of carbohydrate metabolism parameters in patients in Group 1 (patients with NAFH and NASH) depending on presence of T2DM or IR

Indicator	Participants in Group 1 with NAFLD			
	Subgroup 1.1 (n = 34)		Subgroup 1.2 (n = 40)	
	Subgroup 1.1A (n = 16)	Subgroup 1.1B (n = 18)	Subgroup 1.2A (n = 20)	Subgroup 1.2B (n = 20)
Glucose (mmol/L)	6.95 ± 0.27*	7.95 ± 0.24*	6.75 ± 0.31*	7.87 ± 0.19*
HbA1c (%)	6.88 ± 0.36*	7.98 ± 0.36*	6.80 ± 0.36*	7.89 ± 0.23*
Insulin (U/L)	44.7 ± 6.5**,+	29.7 ± 3.3**	38.4 ± 4.1**, +	21.3 ± 1.7*
C-peptide (ng/mL)	21.77 ± 2.31**	14.56 ± 1.45**, +	17.41 ± 1.67**	12.33 ± 1.22**, +
HOMA-IR	12.81 ± 3.26**	10.41 ± 2.90**	11.32 ± 2.78**, +	7.44 ± 0.23**

*Notes: the difference between the indicators in patients of Group 1 and control group is significant: * — p < 0.05; ** — p < 0.01; the difference between the indices in patients of Group 1 by subgroups is significant: + — p < 0.05; ++ — p < 0.01.*

NASH stage, especially in combination with IR (Subgroup 1.2A). Hemodynamically, the most significant changes were found in eCCA and in the 3rd segment of VA, namely, the decrease in PSV was found to be (38.1 ± 2.3) cm/s on the right, and (36.6 ± 3.4) cm/s on the left, TAMX reduction to be (20.4 ± 2.1) cm/s on the right, and (16.7 ± 1.8) cm/s on the left of eCCA; reduction of PSV to (40.1 ± 2.2) cm/s on the right, and up to (35.5 ± 1.7) cm/s on the left, reduction of TAMX to (18.4 ± 1.0) cm/s on the right, and up to (18.4 ± 1.0) cm/s to the left of the 3rd segment VA.

A detailed statistical analysis enabled to establish the relationship between the violation of the blood flow in the brain vessels and IR severity.

More often, the correlation between the violation of the blood flow in the vessels of the brain (in eCCA, eCA and VA (segment 3)) and IR severity with the HOMA index was found only in patients with NASH in combination with IR (Subgroup 1.2A). In patients in Subgroup 1.1A, the dependence is established only on the parameters of blood flow on eCCA and VA, and in patients 2.1 — only on eCCA (Table 6). Consequently, IR plays a leading role in the formation of a blood flow deficit in the main vessels of the brain in patients with NAFLD.

Discussion

The obtained results indicate that NAFLD, IR, T2DM, and their combination are more likely to occur in persons with excessive body weight and obesity. The evaluation of carbohydrate metabolism indexes showed that IR is more pronounced in patients with NAFH stage than with

Table 4 — Parameters of ultrasound examination of extracranial brain blood vessels in patients with T2DM or with IR and in the control group, cm/s

Index			Participants		
Arterial segment			Control group (n = 20)	Comparison groups (Group 2, n = 38)	
				Subgroup 2.1 (IR, n = 16)	Subgroup 2.2 (type 2 DM, n = 22)
eCCA	PSV	right	73.4 ± 4.6	50.2 ± 2.2*	51.0 ± 1.8*
		left	71.7 ± 5.0	51.0 ± 3.6*	50.6 ± 2.4*
	TAMX	right	44.8 ± 3.2	38.2 ± 1.4	37.4 ± 2.2
		left	45.5 ± 3.7	37.9 ± 0.9	37.9 ± 1.8
eCA	PSV	right	61.5 ± 3.9	49.2 ± 1.7*	48.7 ± 0.9*
		left	62.9 ± 2.7	48.9 ± 1.9*	47.3 ± 2.3*
	TAMX	right	38.3 ± 2.2	31.1 ± 0.9	31.4 ± 1.6
		left	37.0 ± 3.1	30.9 ± 2.1	31.0 ± 1.5
eICA	PSV	right	53.6 ± 5.8	45.5 ± 1.7	44.9 ± 2.3*
		left	55.9 ± 5.4	45.7 ± 2.1	43.8 ± 3.7*
	TAMX	right	34.7 ± 2.0	28.7 ± 0.8	27.6 ± 1.2
		left	33.0 ± 2.6	29.0 ± 1.3	28.7 ± 1.7
MCA	PSV	right	96.4 ± 6.7	86.4 ± 3.2*	85.9 ± 2.1*
		left	91.5 ± 7.1	87.3 ± 5.5	86.9 ± 3.0
	TAMX	right	65.3 ± 2.6	60.1 ± 1.2	59.8 ± 2.0
		left	65.8 ± 3.3	60.5 ± 0.7	60.4 ± 0.9
VA, segment 3	PSV	right	46.6 ± 3.9	41.2 ± 1.1	40.9 ± 2.7
		left	46.0 ± 1.9	40.9 ± 1.6	41.3 ± 0.7
	TAMX	right	27.3 ± 1.6	20.8 ± 0.7	21.0 ± 0.5
		left	27.0 ± 1.9	21.1 ± 1.0	21.3 ± 1.2
VA, segment 4	PSV	right	57.9 ± 3.1	43.0 ± 1.8*	43.3 ± 2.3*
		left	56.8 ± 2.5	42.7 ± 2.0*	42.9 ± 1.8*
	TAMX	right	38.9 ± 3.0	28.7 ± 2.1*	27.7 ± 1.7*
		left	39.1 ± 2.6	28.0 ± 1.6*	28.2 ± 1.0*
OA	PSV	right	47.0 ± 3.1	42.4 ± 1.7	41.7 ± 2.6
		left	47.9 ± 2.6	43.4 ± 1.1	42.8 ± 1.9
	TAMX	right	24.7 ± 0.9	24.3 ± 0.5	24.4 ± 1.0
		left	25.8 ± 1.2	24.6 ± 1.4	25.0 ± 0.9

*Note: the difference between the indices in patients of the Group 2 and the control group is significant: * — p < 0.05.*

Table 5 — Parameters of ultrasound extracranial brain blood vessels examination of NAFLD patients, cm/s

Index			NAFLD patients in the basic Group 1			
			Subgroup 1.1 (patients with NAFH)		Subgroup 1.2 (patients with NASH)	
Arterial segment			Subgroup 1.1A NAFH and IR (n = 16)	Subgroup 1.1B NAFH and T2DM (n = 18)	Subgroup 1.2A NASH and IR (n = 20)	Subgroup 1.2B NASH and T2DM (n = 20)
eCCA	PSV	right	49.3 ± 2.7**	49.1 ± 1.7**	38.1 ± 2.3**, #	38.0 ± 1.7**, #
		left	48.8 ± 2.7*	48.5 ± 2.0*	36.6 ± 3.4**, #	36.0 ± 2.2**, #
	TAMX	right	37.5 ± 1.8	37.9 ± 1.5	20.4 ± 2.1**, #	19.4 ± 1.7**, #
		left	37.0 ± 1.1	37.0 ± 2.1	16.7 ± 1.8**, #	15.90 ± 1.84*, #
eCA	PSV	right	48.7 ± 1.2*	47.4 ± 1.2*	45.6 ± 2.1*	45.1 ± 2.0*
		left	47.2 ± 1.4*	46.8 ± 1.4*	44.2 ± 1.9*	43.9 ± 1.7*
	TAMX	right	30.9 ± 0.8	30.6 ± 1.3	23.5 ± 2.0*, #	23.7 ± 1.7*, #
		left	29.8 ± 1.7	30.0 ± 1.8	22.1 ± 0.9*, #	21.9 ± 1.0*, #
eICA	PSV	right	45.0 ± 1.1	44.4 ± 1.6*	42.1 ± 2.3*	42.2 ± 1.8*
		left	44.7 ± 2.0	43.0 ± 3.7*	41.6 ± 1.9*	41.1 ± 0.7*
	TAMX	right	28.0 ± 0.7	27.1 ± 1.8	25.4 ± 2.1*	25.6 ± 2.2*
		left	28.1 ± 1.7	27.3 ± 1.1	24.7 ± 2.0*	24.0 ± 1.7*
MCA	PSV	right	86.2 ± 3.0*	85.7 ± 3.1*	84.7 ± 2.6*	83.9 ± 2.8*
		left	84.2 ± 3.6	85.0 ± 2.7	83.7 ± 2.9*	83.0 ± 1.6*
	TAMX	right	59.7 ± 1.0	59.0 ± 2.6	54.7 ± 1.7*	55.7 ± 1.4*
		left	58.9 ± 0.7	58.8 ± 1.8	53.2 ± 1.7*	53.1 ± 1.2*
VA, segment 3	PSV	right	40.7 ± 2.3	39.7 ± 2.5	40.1 ± 2.2	40.6 ± 2.1
		left	40.0 ± 0.6	39.2 ± 1.4	35.5 ± 1.7*	35.0 ± 1.4*
	TAMX	right	20.1 ± 0.4	20.1 ± 0.7	18.4 ± 1.0*	17.1 ± 0.9*
		left	20.3 ± 0.8	19.5 ± 1.7*	15.3 ± 1.2*	15.0 ± 1.7*
VA, segment 4	PSV	right	42.6 ± 1.7*	42.7 ± 1.4*	41.1 ± 0.7*	40.8 ± 1.1*
		left	41.5 ± 1.5*	41.0 ± 0.9*	40.2 ± 0.7*	40.1 ± 1.1*
	TAMX	right	27.9 ± 1.6*	27.0 ± 2.0*	19.8 ± 1.1*	19.2 ± 0.3*
		left	27.4 ± 1.2*	26.3 ± 0.8*	19.0 ± 0.4*	18.9 ± 0.7*
OA	PSV	right	42.8 ± 2.5	41.4 ± 1.4	41.5 ± 2.0	41.7 ± 1.6
		left	41.9 ± 2.1	40.7 ± 1.3	39.2 ± 1.6*	38.9 ± 1.1*
	TAMX	right	24.1 ± 1.2	24.0 ± 1.0	23.1 ± 1.1	23.1 ± 2.1
		left	24.3 ± 0.9	24.1 ± 0.6	23.0 ± 0.7	23.9 ± 0.8

*Notes: the difference between the indices in patients of the Group 1 and the control group is significant: * — p < 0.05, ** — p < 0.05; the difference between the indicators in patients of the Group 1 in the subgroups is significant: # — p < 0.05.*

Table 6 — Correlation between parameters of blood flow in great brain blood vessels and IR based on HOMA-IR index

Parameters of examined vessels		HOMA-IR		
		Subgroup 1.1A (NAFH and IR)	Subgroup 1.2A (NASH and IR)	Subgroup 2.1 (IR)
eCCA	PSV	r = 0.47; p < 0.05	r = 0.92; p < 0.01	r = 0.76; p < 0.01
	TAMX	r = 0.50; p < 0.05	r = 0.88; p < 0.01	r = 0.64; p < 0.05
eCA	PSV	–	r = 0.74; p < 0.01	–
	TAMX	–	r = 0.69; p < 0.05	–
VA, segment 3	PSV	r = 0.56; p < 0.05	r = 0.57; p < 0.05	–
	TAMX	r = 0.62; p < 0.05	r = 0.49; p < 0.05	–

NASH (according to the HOMA index: (12.81 ± 3.26) and (11.32 ± 2.78), respectively). Thus, IR is the key mechanism in the progression of lesions of various organs and systems, including the vascular bed, in patients with metabolic disorders with NAFLD.

Various studies paid attention to psychological status, cognitive impairment, as well as their association with changes in the structure of the brain (with a decrease in the volume of white matter) and the severity of fibrosis at NAFH (B. Filipović et al., 2018) [13]. It is believed that cerebral hemodynamics due to disruptions in the microcirculation can lead to structural changes in the brain that underlie cognitive impairment (L.B. VanWagner et al., 2017) [9].

According to A. Rasool et al. (2017), all patients with NAFLD should be subjected to a study of the intima-media complex of the posterior wall of the common carotid artery, since NAFLD is associated with carotid atherosclerosis and, consequently, coronary atherosclerosis [14]. In the study of Y.J. Lee et al. (2018), NAFLD was associated with a subclinical form of cerebrovascular atherosclerosis in an asymptomatic general population of Korean men. Higher prevalence of subclinical form of cerebroid-cardiac atherosclerosis was observed in patients with NAFLD compared with controls without NAFLD. In addition, NAFLD was associated with a higher risk of atherosclerosis in large vessels [15]. Another study (L. Airaghi et al., 2018) also examined subclinical cerebrovascular lesions in patients with NAFLD, but without risk factors for atherosclerosis [16].

The results obtained by us testify to the impairment of the vascular pool of the brachiocephalic trunk in patients with NAFLD, type 2 diabetes and IR. There was no significant difference between the indicators of cerebral hemodynamics in patients with type 2 diabetes and IR (without liver damage). In fact, it does not differ from the data and results of patients with NAFLD (regardless of the presence of IR or DM). Our data indicate the maximum slowing of blood flow to the vessels of the brain in patients with NAFLD at the stage of steatohepatitis (regardless of the presence of IR or DM). In this case, asymmetry with more pronounced deceleration of velocity indicators to the left is revealed.

Consequently, insulin resistance plays a leading role in the formation of vascular tract defects in patients with metabolic disorders (liver steatosis, obesity, T2DM, etc.). Vascular changes are more pronounced in patients with NASH, which is probably due to a decrease in functional reserve of the liver, which in turn contributes to the reduction of the production/deactivation of vascular active biological substances, which together with the IR is the basis of the vascular system damage, including cerebral hemodynamics.

Further research is needed to better understand the progression of vascular lesions in NAFLD and in the carbohydrate metabolism, taking into account risk factors, severity of liver damage, IR and type 2 diabetes as well as cognitive impairment in these patients.

Conclusions

1. The patients with NAFLD (NAFH and NASH), as well as IR and T2DM had a decrease in the velocity of blood flow in extracranial vessels of the brain, mainly in the common carotid artery, external carotid artery and vertebral artery (segment 3).

2. There was no statistically significant difference between the indicators of cerebral hemodynamics in patients with IR, type 2 diabetes mellitus (mild course) and NAFH (regardless of type of IR or DM).

3. The most pronounced blood flow deficiency has been observed in patients with NASH in combination with IR, mainly on the left, especially in eCCA (PSV reduction to (38.1 ± 2.3) cm/s on the right and up to (36.6 ± 3.4) cm/s on the left, and also TAMX decrease to (20.4 ± 2.1) cm/s on the right and to (16.7 ± 1.8) cm/s on the left).

Conflicts of interests. Authors declare the absence of any conflicts of interests that might be construed to influence the results or interpretation of their manuscript.

Contribution of the authors
Sirchak Ye.S. — conception and design of the study; analysis of obtained data; *Griga V.I.* — collection and processing of data, text writing; *Kurchak N.Yu.* — collection of the material; *Kutsenko A.Yu.* — performance of ultrasound investigation of great brain vessels.

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Зміни судин головного мозку в пацієнтів із неалкогольною жировою хворобою печінки й порушенням вуглеводного обміну

Резюме. *Актуальність.* Дослідження судин головного мозку в пацієнтів із неалкогольною жировою хворобою печінки (НАЖХП) може розкрити нові аспекти щодо раннього виявлення порушень церебральної гемодинаміки, а також дозволить визначити групу хворих високого ризику. *Мета дослідження:* дослідити особливості зміни судин головного мозку в пацієнтів із НАЖХП у поєднанні з інсулінорезистентністю (ІР) чи цукровим діабетом (ЦД) 2 типу. *Матеріали та методи.* Обстежено 74 пацієнтів із НАЖХП (34 хворі з неалкогольним жировим гепатозом (НАЖГ) та 40 хворих з неалкогольним стеатогепатитом (НАСГ)). Група порівняння включала 38 пацієнтів (16 хворих з ІР та 22 пацієнтів з ЦД 2 типу). Стан кровотоку в судинах головного мозку вивчали за допомогою ультразвукового дуплексного сканування екстракраніального відділу загальної сонної артерії (ЗагСА), зовнішньої сонної артерії (ЗовСА), екстракраніального відділу внутрішньої сонної артерії, середньої мозкової артерії, вертебральної артерії (ВА), очної артерії. Визначали пікову систолічну швидкість (ПСШ) та середню за часом максимальну швидкість кровотоку (ТАМХ) в досліджуваних судинах. *Результати.* Звертає на себе увагу асиметричне ураження судин головного мозку з більш вираженим дефіцитом кровотоку зліва при НАЖХП, що більш виражене у хворих зі стадією НАСГ, особливо у поєднанні з ІР. Гемодинамічно найбільш значущі зміни встановлено в ЗагСА, а саме виявлене зниження ПСШ до $(38,1 \pm 2,3)$ см/с справа та до $(36,6 \pm 3,4)$ см/с зліва, зниження ТАМХ — до $(20,4 \pm 2,1)$ см/с справа та до $(16,7 \pm 1,8)$ см/с зліва. *Висновки.* У хворих із НАЖХП, а також із ІР та ЦД 2 типу виявлене зниження швидкісних показників кровотоку по екстракраніальних судинах головного мозку, переважно по ЗагСА, ЗовСА та ВА (сегмент 3). Найбільш виражений дефіцит кровотоку встановлений у хворих на НАСГ у поєднанні з ІР, переважно зліва, особливо по ЗагСА.

Ключові слова: неалкогольна жирова хвороба печінки; інсулінорезистентність; цукровий діабет 2 типу; судини головного мозку

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Изменения сосудов головного мозга у пациентов с неалкогольной жировой болезнью печени и нарушением углеводного обмена

Резюме. *Актуальность.* Исследование сосудов головного мозга у пациентов с неалкогольной жировой болезнью печени (НАЖБП) может раскрыть новые аспекты раннего выявления нарушений церебральной гемодинамики, а также обнаружить группу больных высокого риска. *Цель исследования:* изучить особенности изменений в сосудах головного мозга у пациентов с НАЖБП в сочетании с инсулинорезистентностью (ИР) или сахарным диабетом (СД) 2 типа. *Материалы и методы.* Обследовано 74 пациента с НАЖБП (34 больных с неалкогольным жировым гепатозом (НАЖГ) и 40 больных с неалкогольным стеатогепатитом (НАСГ)). Группа сравнения включала 38 пациентов (16 больных с ИР и 22 пациента с СД 2 типа). Состояние кровотока в сосудах головного мозга изучали с помощью ультразвукового дуплексного сканирования экстракраниального отдела общей сонной артерии (ОСА), наружной сонной артерии (НСА), экстракраниального отдела внутренней сонной артерии, средней мозговой артерии, вертебральной артерии (ВА), глазной артерии. Определяли пиковую систолическую скорость (ПСС) и среднюю по времени максимальную скорость кровотока (ТАМХ) в исследуемых сосудах. *Результаты.* Обращает на себя внимание асимметричное поражение сосудов головного мозга с более выраженным дефицитом кровотока слева при НАЖБП, что более выражено у больных со стадией НАСГ, особенно в сочетании с ИР. Гемодинамически наиболее значимые изменения установлены в ОСА, а именно выявлено снижение ПСС до $(38,1 \pm 2,3)$ см/с справа и до $(36,6 \pm 3,4)$ см/с слева, снижение ТАМХ — до $(20,4 \pm 2,1)$ см/с справа и до $(16,7 \pm 1,8)$ см/с слева. *Выводы.* У пациентов с НАЖБП, ИР и СД 2 типа выявлено снижение скоростных показателей кровотока по экстракраниальным сосудам головного мозга, преимущественно по ОСА, НСА и ВА (сегмент 3). Наиболее выраженный дефицит кровотока установлен у больных НАСГ в сочетании с ИР, преимущественно слева, особенно по ОСА.

Ключевые слова: неалкогольная жировая болезнь печени; инсулинорезистентность; сахарный диабет 2 типа; сосуды головного мозга