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The Influence of Non-Alcoholic Fatty Liver Disease on Indicators of Arterial Stiffness and Risk of Cardiovascular Complications in Patients with Arterial Hypertension

Abstract

Aim. To determine the value of concomitant non-alcoholic fatty liver disease in patients with arterial hypertension in the progression of rigidity of the main arteries and in increase of risk of cardiovascular complications. **Material and methods.** A cross-sectional comparative study was conducted. Group 1 (n=50, 35(70%) women, average age 57,4±6,9 years) included patients with arterial hypertension and non-alcoholic fatty liver disease, group 2 (n=50, 40(80%) women, average age 56,5±7,0 years) included patients with arterial hypertension only. The groups were comparable in the main clinical and demographic indicators (p>0,05). A comparative analysis of pulse wave velocity, central aortic pressure, vascular age and a common 10-year risk of developing cardiovascular complications in both groups was performed. **Results.** As a result of the study, it was found that the metabolic index is significantly higher in patients of the main group compared with patients in the control group (p=0,0489) and there is a statistically larger number of patients with metabolic index>7,0 (58,0% vs 28,0%, p=0,0019). It was also established that systolic (121,9±10,9 mm Hg vs 115,9±8,9 mm Hg) and diastolic (82,5±9,3 mm Hg vs 77,4±8,9 mm Hg) aortic pressure, as well as the augmentation index (26,5±8,5% vs 18,6±4,2%), were significantly higher in patients with arterial hypertension and non-alcoholic fatty liver disease than in patients with isolated arterial hypertension. In the 1st group, a statistically significant increased pulse wave velocity was found both in muscular (12,0±3,1 m/s vs 10,6±1,8 m/s) and elastic (10,4±2,8 m/s vs 9,1±1,7 m/s) vessels, which indicates an increase in arterial stiffness. In addition, there was an increase in post-occlusal pulse wave velocity in this category of patients (11,0±3,3 m/s vs 9,4±1,9 m/s, p=0,0037). A significant increase in vascular age in relation to the passport age (60,4 [56,0:68,0] years vs 58,0 [53,0:60,0] years) and an increase in the 5-year risk of developing cardiovascular complications (2,4 [1,8:4,0] points vs 1,8 [0,8:4,0] points, p=0,0390) were also revealed in patients with arterial hypertension and non-alcoholic fatty liver disease compared to patients with isolated arterial hypertension. In group 1, there were fewer patients with a low risk of CVD (3 (6,0%) vs 10 (20,0%), p = 0,037) and more patients with a high risk of cardiovascular complications (22 (44,0%) vs 12 (24,0%), p = 0,034) than in the group with AH without NAFLD. **Conclusions.** Arterial stiffness was significantly higher in patients with arterial hypertension and non-alcoholic fatty liver disease than in patients with isolated arterial hypertension, which is confirmed by a statistically significant increase in pulse wave velocity and central aortic pressure. Comorbid patients have pronounced endothelial dysfunction, which is confirmed by a significant increase in the post-occlusion rate of the pulse wave. An increase in vascular age in relation

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to the passport age indicates earlier aging of blood vessels in the 1st group compared with the 2nd group. Patients in the main group have a higher incidence of a high 10-year risk of developing cardiovascular events compared with patients in the control group.

Key words: *arterial hypertension, non-alcoholic fatty liver disease, arterial stiffness, central aortic pressure, pulse wave velocity, vascular age, cardiovascular complications*

Conflict of interests

The authors declare no conflict of interests

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AH — arterial hypertension, BMI — body mass index, CAP — central aortic pressure, CVC — cardiovascular complications, DBP — diastolic blood pressure, MI — metabolic index, NAFLD — non-alcoholic fatty liver disease, PWV — pulse wave velocity, SBP — systolic blood pressure

Introduction

According to modern research, non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in Russia and abroad, diagnosed in 20-37% of the population [1, 2]. Many studies have proved that NAFLD is an independent predictor of undesirable cardiovascular events (myocardial infarction, stroke, rhythm disturbances, etc.), which is associated not only with heart remodeling, but also with changes in the architectonics and functional capabilities of the vascular wall [4].

The progression of NAFLD is closely related to the activation of atherogenesis. Against the background of steatosis transformation of the liver, the concentration of pro-atherogenic blood components (pro-inflammatory, prothrombotic and oxidative-stress substances) increases, the degree of atherogenic dyslipidemia and insulin resistance increase [3]. In turn, some authors attribute the development of insulin resistance to increased arterial stiffness [3, 5]. On the example of patients with chronic hyperglycemia and hyperinsulinemia, an increase in the activity of the renin-angiotensin-aldosterone system and the expression of receptors for angiotensin I were demonstrated, which led to hypertrophy of the vascular wall and fibrosis. In these works, to determine vascular stiffness, the researchers used pulse wave velocity (PWV) in the vessels of muscle (PWVm) and elastic type (PWVe), which closely correlated with the risk of cardiovascular events and mortality [3, 5].

At the same time, a change in aortic stiffness directly affects the indicators of central aortic pressure (CAP), which, according to some authors, are more informative than indicators of arterial pressure on the brachial artery [6, 8].

A significant number of papers on the effect of NAFLD on the development of atherosclerosis, the risk of cardiovascular diseases and complications, has been published [1, 5]. But at the same time, we did not find studies in accessible sources that would perform a comparative study of changes in aortic stiffness and blood pressure parameters in patients with arterial hypertension (AH) and NAFLD and patients with isolated AH.

Thus, the aim of our study was to determine the value of concomitant NAFLD in patients with AH in the progression of stiffness of the main arteries and an increased risk of cardiovascular complications (CVC).

Material and methods

At the planning stage of the study, aims and inclusion/exclusion criteria were determined. Results were considered clinically significant when a comparative analysis of groups of 50 patients showed a statistically significant difference in the studied parameters. **Inclusion criteria**: 45-65-year-old

patients of both sexes with AH stage I and II (with or without NAFLD). **Exclusion criteria**: patients with secondary hypertension, other liver diseases (except for NAFLD), diabetes mellitus (type 1 and 2), chronic kidney disease (CKD), obesity class II and III, and oncological or hereditary diseases.

Between September 2019 and March 2020, a cross-sectional comparative study was conducted, which included 100 patients (75 (75,0%) women, average age 57,0±7,0 years). Group 1 (n=50, 35(70%) women, average age 57,4±6,9 years) included patients with arterial hypertension and non-alcoholic fatty liver disease, group 2 (n=50, 40(80%) women, average age 56,5±7,0 years) included patients with arterial hypertension only.

The study was guided by the ethical principles of the Helsinki Declaration of the World Medical Association (2008), the Good Clinical Practice Agreement (ICH GCP). All patients signed informed consent to participate in the study and publish the results. The study was approved by the local ethics committee of Volgograd State Medical University of the Ministry of Health of the Russian Federation (protocol No. 001-2019, expert opinion No. 001/5).

Diagnosis of hypertension and the volume of antihypertensive therapy (Table 1) were carried out in accordance with the clinical recommendations of the Russian Medical Society for Arterial Hypertension [16]. At the initial examination, a history of life and disease, anthropometric data on height and weight were collected with the calculation of body mass index (BMI), waist and hips. "Office" blood pressure indicators and heart rate (HR) were recorded on both hands using OMRON M1 Compact semi-automatic blood pressure monitor (Japan). We recorded the values of «office» blood pressure on both hands and heart rate (HR) according to the standard method. Using the method of analysis of changes in bioelectric impedance (using Omron BF508 52, Japan), an analysis of body composition was carried out with an assessment of the visceral fat percentage.

Based on Russian clinical recommendations for the diagnosis and treatment of NAFLD, the comorbid pathology, NAFLD, was diagnosed in patients with hypertension [12]. For this purpose, an anamnesis of the disease, an ultrasound examination of the liver on a Siemens Sonoline G50 scanner (Germany) were analyzed, with an assessment of the echogenicity of the liver parenchyma, vascular pattern, degree of the echo signal attenuation, as well as a biochemical blood test, with an assessment of the activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), -glutamyltransferase (GGT), the level of total bilirubin in blood serum on a Liasys-2 biochemical analyzer (Analyzer Medical System S.r.l, Italy). For dynamic monitoring of the state of lipid metabolism, the levels of total cholesterol and its fractions (LDL cholesterol, HDL cholesterol) and triglycerides (TG) were determined by the enzymatic method using ASSEL kits (Italy) on a Liasys-2 biochemical analyzer (AMS, Italy).

To determine insulin resistance, the metabolic index was calculated:

MI = [TG on an empty stomach (mmol/L) Glucose on an empty stomach (mmol/L)] / LDL cholesterol^2 on an empty stomach (mmol/L).

Based on the obtained indicator, the presence of IR is determined when the MI index is equal to or more than 7.0 [7].

The organization of the study of PWV and CAP was carried out taking into account the recommendations of the Consensus of Russian experts on the assessment of arterial stiffness in clinical practice (2016) [9]. We analyzed the wall stiffness of the main vessels of muscle and elastic types in terms of pulse wave velocity using the PolySpektr 8/E apparatus with a PWV module (Neurosoft, Russia). To determine PWVe, sphygmography was performed on the carotid-femoral segment of the arterial bed, and PWVm — on the carotid-radial. Also, the PWVm/PWVe ration was calculated, and a 3-minute compression test with reactive hyperemia (PWV test) was performed to determine the functional reserve of the muscle segment.

Daily monitoring of CAP indices was carried out using the BPLab multifunctional complex and Vasotens 24 software (Petr Telegin LLC, Russia). The following parameters were determined: average daily, daytime and nighttime values of systolic (SAPao), diastolic (DAPao), pulse aortic pressure (PAPao) and augmentation index (AI). The study included CAP protocols with a validity of more than 70% (at least 20 valid measurements in the daytime and at least 7 in the nighttime).

To calculate vascular age and the 5-year risk of cardiovascular complications, the «ADVANT

AGE» calculator (Les Laboratoires Servier, France) was used, in which, according to the method of D'Agostino R.B. et al. (2008), gender, age, smoking factor, systolic blood pressure, total cholesterol (and its fractions) and glycemia were taken into account [10]. The SCORE score was used to assess total cardiovascular risk and 10-year fatal risk [16].

For statistical processing of the obtained data, we used parametric (Student t-test for unrelated groups, mean value (M) with standard deviation (σ)) and non-parametric criteria (Mann-Whitney U-test, Fisher exact test) calculated using the statistical software package Statistica 10 (StatSoft Inc., USA). All groups of variables were checked for compliance with the law of normal distribution using the Shapiro-Wilk test. When determining the correspondence of the normality of distribution among the variables, the data are presented as M ± SD, where M is the arithmetic mean, SD is the standard deviation; in case of deviation from normality — Me (IQR), where Me is the median, IQR is the interquartile range: 25 percentile — 75 percentile. When comparing the quantitative data, we used the Student t-test for unrelated groups and the Mann-Whitney U test (for a distribution other than normal). To compare groups on a binary (qualitative) basis, a four-field table was analyzed using Fisher's exact test. The difference in group indices of more than 95% (p <0.05) was considered statistically significant.

Results and discussion

A comparison of patients of the first and second groups was made according to the main clinical and demographic indicators (Table 1). It was found that comparison groups by age and gender, quality of therapy and hypertension duration, «office» indicators of central hemodynamics were comparable (p>0,05). Reliably higher subcutaneous and visceral fat indices (p=0,0000), as well as body mass index (p=0,0048) were quite expectedly obtained in patients of the 1st group.

In the main group, there were statistically significantly more patients with class I obesity (74 % versus 6,0% (p=0,0000)), but fewer patients with overweight (20,0% against 72,0% (p=0,0000)), than in the control group. In the 1st and 2nd groups, normal weight-growth indices were determined in 6,0% and 20,0% of patients, respectively.

When assessing the lipid spectrum (Table 2), no significant differences between the groups were established. The metabolic index is significantly higher in patients of the first group compared with patients of the 2nd group (p=0,0489). Also, in the main group there was a statistically greater number of patients with MI>7,0 (58,0 % vs 28,0 %, p=0,0019), which indicates a higher incidence of insulin resistance in this category of patients.

To assess arterial stiffness, PWV was measured. Table 3 shows the obtained PWV indicators in patients of the two groups.

In patients with AH and NAFLD, compared with patients with isolated AH, a significantly higher PWV was found vessels of both muscle type (12.0 ± 3.1 vs 10.6 ± 1.8 m/s, p = 0.0029) and elastic type (10.4 ± 2.8 vs 9.1 ± 1.7 m/s, p = 0.0220). In group 1, there were significantly more patients with exceeding the threshold level (more than 10 m/s) in vessels of elastic type (p = 0.0213) and/or muscle type (p = 0.0428), compared with patients of the 2nd group [9]. In addition, comorbid patients showed signs of endothelial dysfunction, as indicated by significantly higher values of PWV after a compression test (11.0 ± 3.3 vs 9.4 ± 1.9 m/s, p = 0.0037) [15].

In order to draw conclusions about changes in arterial stiffness, it is not enough just the indicators of PWV. For this purpose, many authors recommend to study the indicators of central aortic pressure [9]. A statistically significant increase in daytime, nighttime and daily average SBPao (p = 0.0018, p = 0.0079 and p = 0.0041, respectively), DBPao (p = 0.0053, p = 0.0178 and p = 0.0083, respectively) and AIx (p = 0.0013, p = 0.0022 and p = 0.0002, respectively) was revealed in patients of the main group compared with the control group (Table 4).

Also, in patients with AH and NAFLD vs isolated AH, a comparative analysis of the vascular age and 5-year risk of CVC was performed according to the methods described above. A significant increase in vascular age relative to the passport age was found in patients of the 1st group (60,4 [56,0:68,0] vs 58,0 [53,0: 60,0], p=0,0399). In patients of group 2, there was no significant increase in vascular age relative to the passport age (59,5 [52,0: 66,0] vs 58,0 [50,0: 64,0], p=0,3516).

Table 1. *Clinical and demographic indicators of patients included in the study*

Variable	Group 1 (patients with arterial hypertension and non-alcoholic fatty liver disease)(n=50)	Group 2 (patients with arterial hypertension without non-alcoholic fatty liver disease)(n=50)	p
Age:			
Average age, years, M±SD	57,4±6,9	56,5±7,0	0,5597
45-55 years, n (%)	19 (38,0)	22 (44,0)	0,6845
56-65 years, n (%)	31 (62,0)	28 (56,0)	
Gender:			
Women, n (%)	35 (70,0)	40 (80,0)	0,3558
Men, n (%)	15 (30,0)	10 (20,0)	
Smoking, n (%)	12 (24,0)	14 (28,0)	0,8200
BMI, kg/m^2, Me (IQR)	31,6 [30,0:33,6]	27,5 [25,0:29,1]	0,0000*
Subcutaneous fat, %, Me(IQR)	42,4 [30,2:46,9]	33,0 [21,4:41,6]	0,0000*
Visceral fat, %, Me (IQR)	12,0 [11,0:15,0]	9,0 [6,0:10,0]	0,0000*
AH duration, years, M±SD	9,1±3,5	8,7±3,2	0,2759
AH stage I, n (%)	8 (16,0)	15 (30,0)	0,0765
AH stage II, n (%)	42 (84,0)	35 (70,0)	0,0630
AH level 1, n (%)	18 (36,0)	21 (42,0)	0,3410
AH level 2, n (%)	32 (64,0)	29 (58,0)	0,3410
Total cardiovascular risk, n (%):			
Low	3(6,0)	4(8,0)	0,5000
Medium	2 (4,0)	17 (34,0)	0,0001*
High	45 (90,0)	29 (58,0)	0,0002*
Target blood pressure, n (%)	36 (72,0)	31 (62,0)	0,1976
Total risk of death from cardiovascular disease in the next 10 years , n (%):			
Low	6 (12,0)	10 (20,0)	0,2070
Medium	31 (62,0)	35 (70,0)	0,2634
High	13 (26,0)	5 (10,0)	0,0332*
10 year fatal risk, %, Me (IQR)	2,15(1,42-4,63)	1,05(0,52-2,82)	0,0043*
AH therapy, n (%)	39 (78,0)	41 (82,0)	0,8031
ACEI, n (%)	21 (42,0)	18 (36,0)	0,6820
BB, n (%)	15 (30,0)	17 (34,0)	0,8305
Diuretic, n (%)	5 (10,0)	8 (16,0)	0,5536
CCB, n (%)	18 (36,0)	23 (46,0)	0,4162
ARB, n (%)	6 (12,0)	4 (8,0)	0,7407
Concomitant pathology, n (%):			
Cholelithiasis	10 (20,0)	4 (8,0)	0,2623
Obesity I degree	37 (74,0)	3 (6,0)	0,0000*
SBP, mm Hg, M±SD	137,9±8,7	136,2±13,4	0,4362
DBP, mm Hg, M±SD	90,2±6,3	87,6±7,2	0,0532
PBP, mm Hg, M±SD	48,0±8,2	48,6±7,6	0,7146
HR, min^{-1}, M±SD	73,1±8,0	71,3±8,9	0,2984

Note: * — p<0,05; BMI — body mass index; ACEI — angiotensin-converting enzyme inhibitor; BB — β-blocker; CCB — calcium channel blocker; ARB — angiotensin II receptor blocker; SBP — systolic blood pressure; DBP — diastolic blood pressure; PBP — pulse blood pressure; HR — heart rate

Table 2. *Indicators of lipid, carbohydrate metabolism and metabolic index*

Index		Main group (n=50) M±σ	Control group (n=50) M±σ	ρ
Lipid spectrum	TC, mmol /L	5,4±1,3	5,6±1,1	0,4506
	HDL cholesterol, mmol /L	1,4±0,3	1,5±0,4	0,3050
	LDL cholesterol, mmol /L	3,1±1,2	3,1±1,1	0,7495
	Triglycerides, mmol/L	2,2±0,6	2,1±0,7	0,4409
	Atherogenic index	3,0±1,1	2,9±1,1	0,9040
MI		7,2±4,4	6,4±4,6	0,0489*
MI >7,0 n(%)		29(58,0)	14(28,0)	0,0019*
Glucose, mmol /L		5,7+1,1	5,3+0,8	0,1233

Note: * — ρ<0,05; TC — total cholesterol; HDL-C — high density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol; MI — metabolic index

Table 3. *Indicators of the speed of the pulse wave in patients of comparison groups*

Index	Group 1 (n=50) M±σ	Group 2 (n=50) M±σ	ρ
PWVe, m/s	10,4±2,8	9,1±1,7	0,0220*
PWVm, m/s	12,0±3,1	10,6±1,8	0,0029*
PWV sample, m/s	11,0±3,3	9,4±1,9	0,0037*
PWVm / PWVe	1,2±0,4	1,1±0,2	0,6137
PWV more than 10 m/s:			
PWVe, n (%)	24 (48,0)	12 (24,0)	0,0213*
PWVm, n (%)	34 (68,0)	23 (46,0)	0,0428*

Note: * — ρ<0,05; PWV — pulse wave velocity (m — muscle type arteries, e — elastic type arteries, sample — muscle type arteries after compression test)

Table 4. *Indicators of central aortic pressure in patients of comparison groups*

Index	Main group(n=50) M±σ	Control group(n=50) M±σ	ρ*
Average daily:			
SBPao (mm Hg)	120,9±10,9	114,9±8,9	0,0041*
DBPao (mm Hg)	81,5±9,3	76,4±8,9	0,0083*
PBPao (mm Hg)	39,4±5,8	38,6±4,3	0,4401
AIx (%)	25,5±8,5	19,6±4,2	0,0002*
Daytime:			
SBPao (mm Hg)	123,5±11,0	117,0±9,0	0,0018*
DBPao (mm Hg)	83,7±9,5	78,4±8,8	0,0053*
PBPao (mm Hg)	39,8±6,4	38,6±4,2	0,2715
AIx (%)	23,4±9,3	18,2±9,4	0,0013*
Nighttime:			
SBPao (mm Hg)	114,0±12,5	107,5±10,4	0,0079*
DBPao (mm Hg)	73,6±9,4	68,8±9,5	0,0178*
PBPao (mm Hg)	40,5±7,2	38,8±5,7	0,2120
AIx (%)	27,3±10,1	23,5±9,4	0,0022*

Note: * — ρ<0,05; SBPao — systolic aortic pressure; DBPao — diastolic aortic pressure; PBPao — pulse aortic pressure; AIx — augmentation index

As shown in table 1, patients with hypertension and NAFLD, compared with patients with isolated hypertension, a statistically significant increase in 10-year fatal risk was found (2.15 [1.42: 4.63] and 1.05 [0.52: 2.82] %, p = 0.0043). In addition, in the 1st group, slightly fewer patients were observed with low (6 (12.0%) vs 10 (20.0%), p = 0.2070) and moderate (31 (62.0%) vs 35 (70.0%), p = 0.2634), but significantly more patients with high (13 (26.0%) vs 5 (10.0%), p = 0.0332) overall cardiovascular risk than in 2nd group.

Mitchell GF, et al. (2016) in their publication noted an increase in the stiffness of the main arteries in patients with NAFLD, based on changes in the parameters of CAP and PWV. Changes in vascular stiffness in patients of this category were associated primarily with an increase in the level of atherogenic agents, activation of the renin-angiotensin-aldosterone system, and dishormonal disorders. In our study, no significant difference in lipid metabolism were established between groups. It was found that patients of the main group had a statistically more significant increase in the metabolic index and a greater frequency of insulin resistance compared with patients in the control group. Our study found that comorbid patients have a statistically significant increase in stiffness of the main arteries, both in the vessels of the muscular and elastic types. In the main group, a significantly larger number of patients was noted with PWV values exceeding the threshold level of 10 m/s, which indicates a high risk of developing cardiovascular complications in this category of patients. Chou C. Y., et al. (2015) note that these changes are present in patients without AH, regardless of the presence or absence of clinical signs of metabolic syndrome and/or diabetes mellitus. In addition, in patients of the first group, daytime, nighttime, and daily average systolic aortic pressure, diastolic aortic pressure, and the augmentation index were significantly increased, which also indicates an increase in the rigidity of the main arteries in this category of patients.

Also, in patients with AH and NAFLD, in comparison with patients with isolated AH, a more pronounced violation of endothelial function is noted, which is confirmed by an increase in post-occlusal PWV. Gurfinkel, Yu.I. et al. (2009) indicate that endothelial cells are highly sensitive to the speed of blood flow and an increase in blood flow causes deformation of endothelial cells, which increases the production of NO.

A significant increase in the indicators of vascular age relative to the passport age in comorbid patients is noted, which is associated with a greater severity of atherosclerosis and arteriosclerosis in this category of patients. Protasov K.V. et al. (2011) indicate that this indicator can be used to assess the risk of development and timely diagnosis of complications of arterial hypertension. In addition, the researchers found that the vascular age, compared with the passport age, is more closely correlated with damage to the heart and blood vessels. A significantly higher 5-year risk of developing cardiovascular complications confirms the greater severity of the condition of patients with hypertension and NAFLD compared with patients with isolated hypertension.

Conclusions

1. Arterial stiffness was significantly higher in patients with AH and NAFLD than in patients with isolated AH, which is confirmed by a statistically significant increase in the parameters of PWV and central aortic pressure.
2. Comorbid patients have signs of endothelial dysfunction, which is confirmed by a statistically significant increase in post-occlusion PWV.
3. An increase in vascular age in relation to the passport age indicates earlier vascular aging in the main group compared with the control group.
4. Patients with hypertension and NAFLD have a higher incidence of a high 10-year risk of developing cardiovascular events compared with patients with isolated hypertension.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Statsenko M.E. (ORCID ID: https://orcid.org/0000-0002-3306-0312): writing text, editing and approval for publication

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