Comparison of structural and functional vascular disorders in patients with comorbidity of non-alcoholic fatty liver disease and two types of arterial hypertension

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Abstract

Background: The aim was to conduct a comparative assessment of structural and functional vascular disorders in patiets with comorbidity of non-alcoholic fatty liver disease (NAFLD) and two types of arterial hypertension (HTN).

Material and methods: The study included 329 patients 18–66 years old. All patients were divided into five groups: patients with comorbidity of NAFLD and primary HTN (121 subjects), patients with comorbidity of NAFLD and renal parenchymal HTN (88 subjects), patients with NAFLD (60 subjects), patients with primary HTN (30 subjects), patients with renal parenchymal HTN (30 people). The control group consisted of 20 healthy individuals of similar age and gender categories.

Results: In the comparative analysis of the structural and functional ultrasonographic parameters of vessels, no significant differences between two comorbidity groups NAFLD + primary HTN and NAFLD + renal parenchymal HTN were found. The influence of AH and degree of liver steatosis on ultrasound indicators of arteries in examined patients with comorbidity was evaluated by MANOVA analysis. The influence of the HTN factor and the influence of the liver steatosis factor were evaluated separately, after which the influence of the comorbidity factor, i.e., the combined influence of these factors and one or another indicator, was evaluated. The additive effect of the factors of AH and liver steatosis was identified according to the parameters: intima media thickness, pulse wave velocity in the carotid artery, pulse wave velocity in the abdominal aorta and endothelial-related vasodilation, which indicates an important comorbid effect of NAFLD and primary/renal parenchymal HTN on the structural and functional state of arteries.

Conclusions: There are no differences between the structural and functional indicators of arteries in patients with comorbidity of NAFLD + primary HTN and NAFLD + renal parenchymal HTN. The factor of the presence of HTN and the degree of liver steatosis significantly affect structural and functional indicators of the studied arteries.

Key words: structural and functional vascular alterations; non-alcoholic fatty liver disease; hypertension

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Introduction

Among the most common non-infectious diseases in the general European population, the leading positions are occupied by non-alcoholic fatty liver disease (NAFLD) and arterial hypertension (HTN), which often have a comorbid course [1, 2]. Today NAFLD is considered as a multisystemic disease, which is primarily associated with components of the metabolic syndrome (MS), associated with cardiovascular diseases (CVD) and renal abnormalities [3, 4]. Meanwhile, mechanisms for development of chronic kidney disease (CKD) in patients with NAFLD, especially when combined with HTN are not clear [3]. The comorbidity of NAFLD with renal parenchymal HTN remains insufficiently studied. The difference between the comorbidity of NAFLD on the background of primary HTN and the comorbidity of NAFLD on the background of renal parenchymal HTN remains unclear. The investigation of these differences was the aim of our research.

Material and methods

In the clinic of the Government Institution «L. T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine» (clinical base of Kharkiv National Medical University) 329 patients 18–66 years old were examined. All patients were divided into five groups. Two main groups were distinguished: a group of patients with comorbidity of NAFLD and primary HTN stage II, grade 2 (121 people), a group of patients with comorbidity of NAFLD and renal parenchymal HTN grade 2 (88 people); as well as three comparison groups: a group of patients with NAFLD (60 people), a group of patients with primary HTN stage II, grade 2 (30 people), a group of patients with renal parenchymal HTN grade 2 (30 people), who were on inpatient and outpatient treatment. In all patients, renal parenchymal HTN was diagnosed as a consequent of chronic pyelonephritis, and at the time of the study, they were in remission. Before the onset of hypertension, these patients had at least 5 years of CKD experience. The control group consisted of 20 healthy individuals of similar age and gender categories.

Inclusion criteria: NAFLD with the presence of liver steatosis of the I-III degree, with the presence or absence of steatohepatitis; primary HTN stage II, grade 2; renal parenchymal HTN grade 2 in patients with chronic pyelonephritis; chronic heart failure (CHF) 0–II functional classes; left ventricle ejection fraction > 50%; age of patients 18–66 years; glomerular filtration rate (GFR) ≥ 45 ml/min/1.73 m^2.

Exclusion criteria: other focal or diffuse diseases of the liver and kidneys, diabetes mellitus type 1 and 2, coronary artery disease, rheumatic heart disease, oncological diseases, systemic connective tissue diseases, CHF III–IV functional classes, GFR less than 45 ml/min/1.73 m^2, echo negativity.

The duration of NAFLD in the NAFLD + primary HTN comorbidity group was 9.11 ± 4.41 years versus 9.55 ± 4.84 years in the NAFLD + renal parenchymal HTN comorbidity group ($p = 0.225$). The duration of primary HTN/renal parenchymal HTN was also not significantly different — 8.90 ± 5.06 and 9.75 ± 4.55 years, respectively ($p = 0.118$).

The indicators of systolic, diastolic, mean and pulse blood pressure (BP) corresponded to the grade 2 of hypertension (which was the criterion for inclusion in the study) and were not significantly different between the two main groups according to these parameters ($p > 0.05$).

There were 93 (76.85%) patients with hypertension who received antihypertensive treatment before inclusion in the group with NAFLD and primary HTN comorbidity and 65 (73.86%) in the group with NAFLD and renal parenchymal HTN comorbidity. Most of the patients were taking ACE inhibitors and calcium antagonists.

The state of the liver parenchyma, parameters of brachial artery (BA), common carotid artery (CA) and abdominal aorta (AA) were evaluated by an ultrasound method. We performed measurements of intima-media thickness CA (IMT CA), pulse wave velocity (PWV) CA and AA according to the standard procedures. An ultrasound cuff test was used for the purpose of determining endothelial-related vasodilation (ERVD) [5]. The study was conducted on the Logiq 5 ultrasound diagnostic complex (General Electric, United States), and a sensor with a frequency of 7.5 MHz was used to scan arteries. First, a scan and measurement of the diameter of the BA was performed: the basic diameter of the BA was determined with the help of a vascular sensor. Then, for 5 minutes, the artery was compressed with a tonometer cuff under a pressure exceeding 50 mm Hg. Systolic blood pressure (SBP), repeated measurement of BA diameter was performed at 90 (60, 120, 180, 240 and 300) seconds after decompression. The response to reactive hyperemia was calculated as the difference between the maximum diameter of the artery against the background of reactive hyperemia and its initial value, expressed as a percentage. If the percentage

increase in the diameter of the artery was < 10%, it indicated a decrease in ERVD.

All obtained results were processed by the methods of variational statistics using statistical package „STATISTICA". The data were presented in the generally accepted form (M ± SD). The results were considered statistically significant at $p < 0.05$. In order to identify complex non-linear correlations, a MANOVA analysis of variance was used.

Results

Initially, an assessment of the structural and functional condition of the carotid arteries and abdominal aorta in patients with comorbidity of NAFLD and primary HTN was carried out. We also studied and performed a comparative analysis of changes in the main vessels of patients with primary HTN without NAFLD, patients with isolated NAFLD, and the control group (Tab. 1).

Abnomalities in all studied indicators were recorded in both groups of patients with hypertension. Thus, disturbances in the vascular wall were manifested by an increase in the IMT of the CA, PWV of the CA and AA, as well as a decrease in the degree of ERVD.

The PWV CA was 8.30 ± 1.17 m/s in the group of comorbidity and 7.89 ± 1.07 m/s in the group of isolated renal parenchymal HTN ($p = 0.123$). ERVD was 7.73 ± 1.52% versus 8.33 ± 1.26%, respectively ($p = 0.146$).

Significant changes in IMT CA in patients with isolated NAFLD were found — 0.78 ± 0.16 mm compared to the control group 0.63 ± 0.12 mm ($p = 0.0006$). In the presence of renal parenchymal HTN, this parameter increased even more, however, was not significantly different in the two renal parenchymal HTN groups ($p > 0.05$). Similar trends were observed in relation to PWV CA and PWV AA (Tab. 2).

The lowest rate of ERVD was recorded in the group of comorbidity 7.32 ± 1.22%, it was not significantly different from the rate of the group of isolated renal parenchymal HTN — 7.72 ± 1.21% ($p = 0.137$), however, significantly from all other groups ($p = 0.0004$).

Thus, it was recorded that the state of carotid arteries and abdominal aorta worsened in patients with comorbid course of NAFLD and renal parenchymal HTN and comparison groups. Violations of carotid arteries and abdominal aorta speed indicators, IMT CA and ERVD were detected both

Table 1. Ultrasonographic parameters of carotid arteries and abdominal aorta in patients with comorbidity of non-alcoholic fatty liver disease (NAFLD) and primary hypertension (HTN), control and comparison groups

Parameter	Groups			
	NAFLD (n = 60)	NAFLD + primary HTN (n = 121)	Primary HTN (n = 30)	Control group (n = 20)
IMT CA [mm]	0.78 ± 0.16 ^ @	0.88 ± 0.12	0.87 ± 0.11	0.63 ± 0.12* ^ @
PWV CA [m/s]	7.15 ± 1.47 ^ @	8.30 ± 1.17	7.89 ± 1.07	5.87 ± 0.98* ^ @
PWV AA [m/s]	7.26 ± 1.19 ^ @	8.45 ± 1.26	8.27 ± 0.83	6.26 ± 0.82* ^ @
ERVD (%)	10.19 ± 2.40 ^ @	7.73 ± 1.52	8.33 ± 1.26	12.88 ± 1.50* ^ @

*statistically significant differences ($p < 0.05$) in comparison with the group of isolated NAFLD; ^ statistically significant differences ($p < 0.05$) compared to the NAFLD and primary HTN comorbidity group; @statistically significant differences ($p < 0.05$) in comparison with the group of isolated primary HTN. IMT CA — intima media thickness in the carotic artery; PWV CA — pulse wave velocity in the carotic artery; PWV AA — pulse wave velocity in the abdominal aorta; ERVD — endothelial-related vasodilation

Table 2. Ultrasonographic parameters of carotid arteries and abdominal aorta in patients with comorbidity of non-alcoholic fatty liver disease (NAFLD) and renal parenchymal hypertension (HTN) and control and comparison groups

Parameter	Groups			
	NAFLD (n = 60)	NAFLD + renal parenchymal HTN (n = 88)	Renal parenchymal HTN (n = 30)	Control group (n = 20)
IMT CA [mm]	0.78 ± 0.16 ^ @	0.90 ± 0.12	0.88 ± 0.10	0.63 ± 0.12* ^ @
PWV CA [m/s]	7.15 ± 1.47 ^ @	8.33 ± 1.12	8.29 ± 1.18	5.87 ± 0.98* ^ @
PWV AA [m/s]	7.26 ± 1.19 ^ @	8.53 ± 1.30	8.93 ± 1.42	6.26 ± 0.82* ^ @
ERVD (%)	10.19 ± 2.40 ^ @	7.32 ± 1.22	7.72 ± 1.21	12.88 ± 1.50* ^ @

^ statistically significant differences ($p < 0.05$) in comparison RPAH and NAFLD comorbidity group; @statistically significant differences ($p < 0.05$) in comparison with the group of isolated renal parenchymal HTN; *statistically significant differences ($p < 0.05$) in comparison with the group of isolated NAFLD. IMT CA — intima media thickness in the carotic artery; PWV CA — pulse wave velocity in the carotic artery; PWV AA — pulse wave velocity in the abdominal aorta; ERVD — endothelial-related vasodilation

Table 3. Ultrasonographic parameters of arteries in studied groups

Parameter	Groups	
	NAFLD + primary HTN (n = 121)	NAFLD + renal parenchymal HTN (n = 88)
IMT CA [mm]	0.88 ± 0.12	0.90 ± 0.12
PWV CA [m/s]	8.30 ± 1.17	8.33 ± 1.12
PWV AA [m/s]	8.45 ± 1.26	8.53 ± 1.30
ERVD (%)	7.73 ± 1.52	7.32 ± 1.22

NAFLD — non-alcoholic fatty liver disease; HTN — hypertension; IMT CA — intima media thickness in the carotic artery; PWV CA — pulse wave velocity in the carotic artery; PWV AA — pulse wave velocity in the abdominal aorta, ERVD – endothelial-related vasodilation

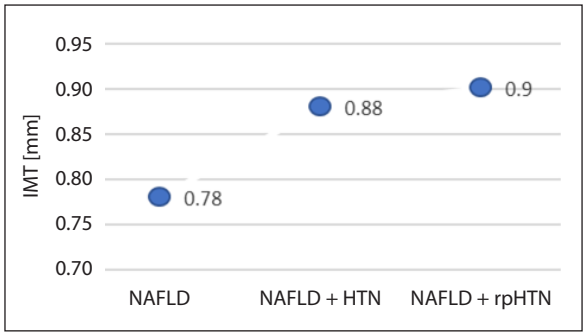

Figure 1. Associations of hypertension (HTN) factor with intima-media thickness (IMT) in the carotid arteries. NAFLD — non-alcoholic fatty liver disease; rpHTN — renal parenchymal HTN

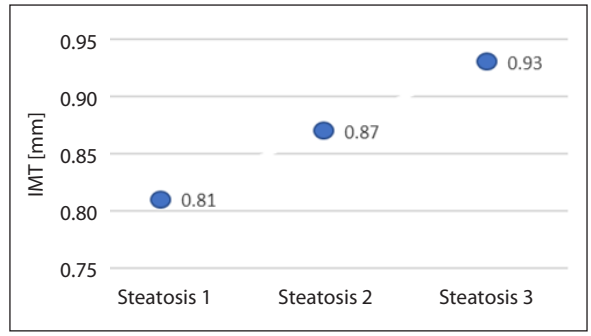

Figure 2. Associations of liver steatosis factor with intima-media thickness (IMT) in the carotid arteries

in the NAFLD group and in the renal parenchymal HTN group (more significant).

IMT CA in the NAFLD + primary HTN group was 0.88 ± 0.12 mm and was not significantly different from the NAFLD + renal parenchymal HTN parameter — 0.90 ± 0.12 cm (p = 0.138). Speed indicators in the carotid arteries and abdominal aorta also had no significant differences. Thus, PWV AA in the NAFLD + primary HTN group was 8.45 ± 1.26 m/s *vs.* 8.53 ± 1.30 m/s in patients with a combined course of NAFLD and renal parenchymal HTN (p = 0.09).

No significant difference in ERVD between the groups was also found. In patients with NAFLD in the presence of primary HTN, it was 7.73 ± 1.52% *vs.* 7.32 ± 1.22% in NAFLD + renal parenchymal HTN (p = 0.213).

Thus, in the comparative analysis of the structural and functional ultrasonographic parameters of vessels, no significant differences between these two comorbidity groups were found.

The influence of HTN and degree of liver steatosis on ultrasound indicators of arteries in examined patients with comorbidity was evaluated by MANOVA analysis. The influence of the HTN factor and the influence of the liver steatosis factor were evaluated separately, after which the influence of the comorbidity factor, i.e., the combined influence of these factors and one or another indicator, was evaluated.

A highly reliable and significant effect of the presence of HTN and liver steatosis on the indicator IMT CA was revealed (Fig. 1 and Fig. 2, respectively).

According to the HTN factor, F was 20.49 (p = 0.0003), according to the liver steatosis factor, F = 25.55 (p = 0.0005). From the point of view of the comorbidity analysis of primary HTN/renal parenchymal HTN and NAFLD, it was also important to establish the fact of the combined effect of factors on the IMT CA parameter — F = 2.82 (p = 0.034).

According to the two-factor MANOVA analysis, a significant influence of the hypertension factor on PWV CA was established — F = 26.18 (p = 0.0002) (Fig. 3 and Fig. 4). The degree of liver steatosis also had a significant effect on the CA speed index — F = 37.95 (p = 0.0003). It is important that the influence of these factors also adds up — F = 2.43 (p = 0.028).

The state of the PWV AA parameter was analyzed. The trend persisted. Factor HTN had a significant effect on PWV AA — F = 25.15 (p = 0.0002); liver steatosis factor was F = 18.18 (p = 0.0004). As in relation to PWV CA, in relation to PWV AA, the additive effect of both factors was recorded F = 2.76 (p = 0.042).

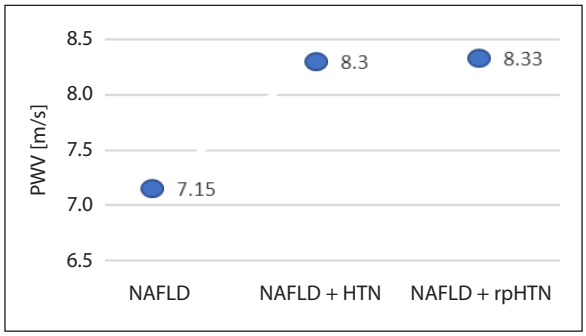

Figure 3. Associations of hypertension (HTN) factor with pulse wave velocity (PWV) in the carotid artery. NAFLD — non-alcoholic fatty liver disease; rpHTN — renal parenchymal HTN

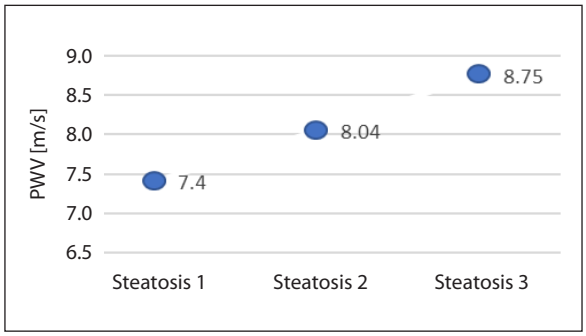

Figure 4. Associations of liver steatosis factor with pulse wave velocity (PWV) in the carotid artery

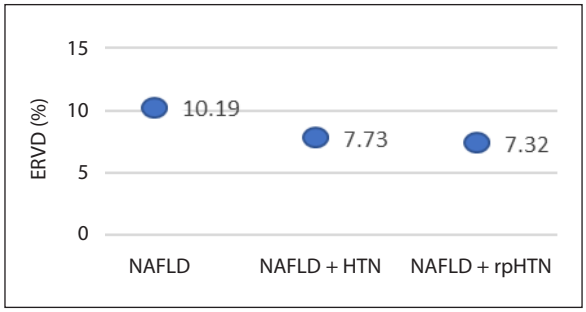

Figure 5. Associations of hypertension (HTN) factor with endothelial-related vasodilation (ERVD). NAFLD — non-alcoholic fatty liver disease; rpHTN — renal parenchymal HTN

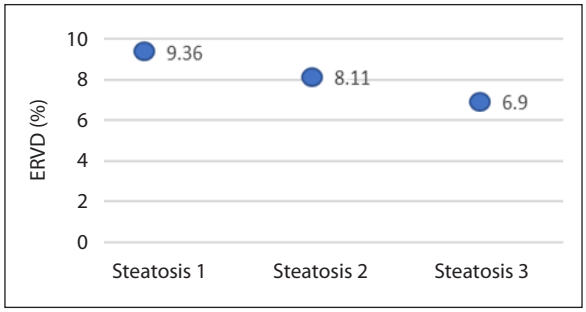

Figure 6. Associations of liver steatosis factor with endothelial-related vasodilation (ERVD)

The final indicator was the ERVD, which characterized the condition of the endothelium in the studied patients (Fig. 5 and Fig. 6).

For HTN factor — $F = 98.07$ ($p = 0.0001$), for liver steatosis factor — $F = 85.07$ ($p = 0.0002$). The interaction of two factors also provided a significant effect on ERVD — $F = 5.42$ ($p = 0.007$).

Discussion

In our study, in the groups of isolated HTN and renal parenchymal HTN, vascular abnormalities were evident, and its presence fairly correspond to previous reports [6–8].

The role of NAFLD in the cardiovascular risk has recently been widely tested [6, 9]. On top of well-known metabolic risk factors associated with NAFLD (insulin resistance, dyslipidemia), the role of genetic factors, intestinal microbiota abnormalities, and endothelium dysfunction have recently been discussed [9, 10]. The latter appears to be the most powerful in the the development of CVD in NAFLD patients. The main factors that can aggravate and promote endothelial dysfunction in these patients are lipotoxicity, inflammation, oxidative stress and early apoptotic processes [9, 10].

Federico at al., 2016 proposed an inverse relationship between endothelial dysfunction and NAFLD. Endothelial dysfunction may contribute to metabolic hepatopathy due to reduced nitric oxide bioavailability and consequent activation of hepatic stellate cells and sinusoidal thrombosis [9].

In a review and meta-analysis by P. Theofilis at al., 2022, the results of 96 studies were analyzed and it was found that the rate of ERVD was significantly lower in patients with NAFLD compared to the control group ($p < 0.001$). At the same time, this indicator was worse in patients with non-alcoholic steatohepatitis, compared to the liver steatosis group ($p = 0.003$) [6].

In our study, negative effects of these two diseases on vascular properties and endothelial dysfunction were confirmed. Apparently, we now report that cummulation of the factors of liver steatosis and HTN may also be important.

On the other hand, another important disease, the occurrence of which has been proven to be influenced by both hypertension and NAFLD, is CKD. It

can affect the vascular properties, disrupt the lining of endothelial cells by various mechanisms, such as: an increase in matrix metalloproteinases that disrupt the interaction of endothelial cells with each other, restructuring of the F-actin, decreasing bioavailability of nitrous oxide and others. Concurrently, at later stages of the course of CKD the regeneration of the endothelium is disturbed [12].

There are hypotheses saying that in the initial stages, CKD is independently associated with vascular smooth muscle dysfunction but not with endothelial dysfunction [13].

Considering the data on such close relationships on the "artery–kidney–liver" axis, it was interesting to compare the groups of patients with comorbidities of NAFLD + primary HTN and NAFLD + renal parenchymal HTN. However, we did not detect any differences, although one would expect them in patients with renal parenchymal HTN resulting from potential long course of chronic pyelonephritis. We assume, the lack of differences may be related to the fact that our patients did not have advanced stages of CKD (maximum IIIA stage).

Limitations of the study

Patients enrollement included subjects with HTN stage 2, and/or NAFLD with the presence of steatosis of the I–III degree, with the presence or absence of steatohepatitis. Perhaps, with more/less advanced HTN, as well as with more advanced NAFLD we can have other severity of structural and functional indicators in the studied arteries. It should also be noted that in our study, we evaluated only one of the variants of renal parenhymal arterial hypertension — in patients with chronic pyelonephritis. It can be assumed that arterial hypertension in other renal parenchymal diseases would have a different effect on the nature of changes in the arteries.

Conclusions

We found no differences between the structural and functional vascular properties in patients with such types of comorbidity as NAFLD + primary HTN and NAFLD + renal parenchymal HTN (on base of initial stages of chronic kidney disease – not more than IIIA). However, the degree of liver steatosis may furhter affect structural and functional properties of the vascular bed.

Conflict of interest

None declared.

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