Arterial hypertension, obesity and non-alcoholic fatty liver disease: is there any connection?

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Abstract

The combination of hypertension, obesity and non-alcoholic fatty liver disease occurs in medical practice very often. A number of studies have shown that non-alcoholic fatty liver disease increases the risk of cardiovascular disease independently of other predictors and manifestations of the metabolic syndrome. Current issues of research and identification of common pathogenic relationships of obesity, hypertension, and liver steatosis are investigated in the article. According to the analysed literature, it is indicated that insulin resistance and compensatory hyperinsulinaemia are considered as one of the key factors in the development of this comorbidity. The processes of chronic inflammation are increasing with the growth of adipose tissue volume. Some researchers believe that non-specific systemic inflammation combines arterial hypertension, increased body weight (especially abdominal obesity), steatosis, dyslipidaemia, atherogenesis and arteriosclerosis into a single syndrome. The role of non-alcoholic fatty liver disease in the growth of the thickness of the intima-media complex was studied. It is known that adipose tissue functions as an endocrine organ, expresses genes encoding bioactive substances, and secretes certain cytokines. A strong link between dysfunction of adipose tissue in patients with non-alcoholic fatty liver disease and in such conditions as metabolic syndrome and cardiovascular disease was demonstrated. The dysfunction of the endothelium is also advisable to consider as the connecting link between liver disease, obesity and hypertension. Despite some understanding of common pathogenic mechanisms for the development of non-alcoholic fatty liver disease and hypertension, this comorbid pathology remains the subject of much debate and a variety of studies.

key words: arterial hypertension, obesity, non-alcoholic fatty liver disease, insulin resistance, dyslipidaemia, non-specific systemic inflammation, endothelial dysfunction, atherogenesis.

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Introduction

The prevalence of overweight (OW) and obesity has been growing very rapidly worldwide, reaching the indicators of the epidemic. The number of patients with overweight has already exceeded 2.3 billion of the world population. 3 thousands persons with increased body weight are recorded every day [1]. Being one of the major modified risk factors (RFs) for the development of the cardiovascular (CV) system pathology, obesity leads to its rapid progression, more severe course and high frequency of complications. It is known that central (abdominal) type of obesity with the redistribution of adipose tissue in the abdominal region (compared to the lower (femoral-gluteal)) is more important RF for the development of CV diseases than the growth of the body mass index (BMI) [2–5]. The combination of hypertensive disease (HD) and obesity has a poor prognosis [2, 6–8].

According to the results of Framingham study, the chance of arterial hypertension (AH) development

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in obesity is 50% higher. Systolic blood pressure (SBP) increases in 4.4 mm Hg for every 4.5 kg of body weight in men and 4.2 mm Hg in women. The positive effects of weight loss on blood pressure (BP) have been demonstrated in several large multicentre studies, such as TOR-1, TAIM, TOMHS, XENDOS [9–13].

The urgency of the problem of obesity is also associated with the fact that it plays an important role not only in the development and progression of CV diseases, but also in the appearance of non-alcoholic fatty liver disease (NAFLD) [1]. A direct correlation between body mass index (BMI), hepatic steatosis and non-alcoholic steatohepatitis (NASH) is found (correlation coefficients are 0.35 and 0.14, respectively, $p < 0.001$) [7]. According to our data, the frequency of detection of hepatic steatosis increased progressively with the increasing body mass in 170 patients with essential hypertension (EH) stage II. Hepatic steatosis was identified in 40.0% of hypertensive patients with optimal body weight, 54.1% of patients with excess of body weight, 65.5% of patients with class I obesity and 86.7% of patients with class II obesity. The average BMI was significantly different between the groups of patients without hepatic steatosis and non-alcoholic fatty liver disease, 29 (24; 32) kg/m^2 and 32 (29; 37) kg/m^2, respectively; $p = 0.0001$. It should be noted that abdominal type of fat distribution prevailed in patients with hypertension and obesity. It was observed in more than 80% of patients. The ratio of waist circumference to hip circumference (WC/HC) was 0.97 (0.92; 1.01) in patients with hypertension and obesity in the group without steatosis and 0.99 (0.95; 1.03) in the group with hepatic steatosis, $p = 0.11$ for both groups. It should be noted that the study did not include patients with class III–IV obesity and impaired glucose tolerance (IGT) or diabetes mellitus (DM). The obtained data coincided with the results of other researchers, who studied the problems of obesity and NAFLD [1, 5, 7, 14–16].

NAFLD combines a wide range of pathological conditions from the steatohepatosis to NASH, which can progress to cirrhosis and associated life-threatening complications [17, 18]. In medical practice doctors are often faced with a combination of hypertension, obesity and liver diseases [19–24]. The comorbidity of hypertension and liver damage is the most common in metabolic syndrome (MS). Its key factors are insulin resistance and compensatory hyperinsulinaemia. They are recognized as the leading mechanisms in the pathogenesis of NAFLD.

In recent years, NAFLD has been increasingly considered as an additional independent risk factor of CV diseases and predictor of its complications [25–33]. A recent study of life expectancy among patients with NAFLD after 24 years of observation found that CV diseases were the most common cause of death in 48% of patients, while diseases associated with liver damage had a lethal outcome in 7% of patients [31]. Significantly higher levels of total cholesterol (TC), low-density-lipoprotein (LDL) cholesterol and very-low-density lipoprotein (VLDL) cholesterol, triglycerides (TG), atherogenic index, serum fasting glucose levels, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse arterial pressure (PAP) and latent myocardial ischaemia in electrocardiogram (ECG) among patients with NAFLD were recorded [5, 6, 18, 34–37]. Taking into account the lack of a clear clinical picture in the early stages of its development, NAFLD diagnosis is often carried out during the aimed examination of patients with obesity and hypertension (EH), their combination or other diseases [37, 38]. So, it is difficult to estimate its real prevalence in the population [37, 39–45]. To date, the gold standard of NAFLD diagnosis remains the tissue biopsy and biopsy scales, the most common of which is semi-quantitative NAFLD rating scale (NAS) [43].

Obesity and non-alcoholic fatty liver disease

The presence of obesity is important in the mechanisms of NAFLD formation [46]. This relationship is explained by the ability of adipose tissue to lead to the development of insulin resistance (IR), as the process of chronic inflammation increases with the increase in adipose tissue volume. The ability of insulin to inhibit the lipolysis is suppressed. This leads to the accumulation of non-esterified fatty acids' pool and deposition of triglycerides (TG) in the liver structure. Excessive accumulation of TG in the structure of hepatocytes gradually decreases the ability of insulin to suppress hepatic gluconeogenesis and TG synthesis, causing the development of hyperglycaemia, hyperinsulinaemia and dyslipidaemia [46, 47]. When the ability of hepatocytes to accumulate TG is exhausted, the damage to the liver cells will occur. Inflammatory and apoptotic pathways are activated in non-alcoholic hepatic steatosis (NAHS) and stress of endoplasmic reticulum in hepatocytes [48]. However, the role of insulin transfer in the mechanisms of liver fatty infiltration development has not been

studied. It was noted that the accumulation of fat in the liver could also be an independent factor of dyslipidaemia [44].

There may be patients who don't have excessive body weight and don't meet the minimum criteria of metabolic syndrome (MS) among the subjects with steatohepatosis and non-alcoholic steatohepatitis who are not suffering from diabetes mellitus (DM), but are in a state of insulin resistance. The received data indicate the NAFLD development among individuals with IR without signs of type 2 diabetes mellitus (DM) and with optimal body weight (OBW) [49].

Insulin resistance and non-alcoholic fatty liver disease

The research data indicate that obesity, increased serum glucose, insulin, HOMA index as well as the laboratory markers of increase in serum C-reactive protein (CRP) concentration and TG were significantly higher in the group with NAFLD in comparison with the control group. Triglycerides, in turn, support gluconeogenesis and lipid disorders in persons with NAFLD as intermediate products of metabolism of fatty acids [16].

The connection between the "fatty" liver, IR, atherosclerosis and metabolic syndrome (MS) was demonstrated [43, 50, 51]. The presence of NAFLD was associated with the elevated indicators of body mass index (BMI), waist circumference (WC), low-density-lipoprotein (LDL) cholesterol, lipoprotein (LP) and IR [52]. It is suggested that proatherogenic serum lipid profile (low high-density-lipoprotein (HDL) cholesterol; high levels of TG, small dense particles of VLDL and apolipoprotein B100), which is usually observed in patients with steatohepatosis, is responsible for this linkage [14]. The transformation of the lipid profile of blood serum with the development of type II B dyslipidaemia according to Fredrickson classification occurs in IR [53]. Enhanced synthesis of TG in the liver and excessive production of small dense particles of VLDL, which reduce the level of high-density-lipoprotein (HDL) cholesterol and contribute to the increase in the number of low density lipoproteins (LDL) particles, are considered the aetiological factors of this type of dyslipidaemia [14, 46]. The reducing of activity of lipase is also possible. This transformation occurs under conditions of insulin resistance, which triggers the development of dyslipidaemia [44].

There is a hypothesis in the literature that NAFLD may develop in the absence of insulin resistance and increased activity of lipolysis in adipose tissue. Hepatokines may be involved in cross processes between liver and adipose tissue [30].

Non-alcoholic fatty liver disease and hypertension

Recently, there have been reports about correlation between EH and NAFLD [22, 27, 48]. More than 50% of NAFLD cases were found in patients with hypertension in the absence of other risk factors for liver disease. The frequency of NAFLD in patients with isolated hypertension (without concomitant obesity and diabetes mellitus (DM)) is three times higher than in healthy persons of similar age and sex [22]. According to the results of some studies of systolic hypertension, NAFLD is an independent predictor which provokes and worsens the development of non-alcoholic steatohepatitis (NASH) [22, 27]. The greatest number of NASH cases (80%) was diagnosed in the group of non-dippers — persons with a lack of nocturnal decrease in blood pressure, which was associated with high insulin levels [54]. These data were confirmed by the results of studies, in which BP levels in patients with NAFLD and hypertension at night exceeded the daytime ones. Those patients had predominantly the circadian profile of non-dippers AP [21, 22]. Similar data were obtained in the study of Latea *et al.* (2013): pathological profiles in blood pressure [non-dippers, night-pikers (with nocturnal increase in BP)] dominated in patients with NAFLD and over-dippers (excessive nocturnal decline of BP). The frequency of having NAFLD in groups of non-dippers, night-pikers and over-dippers was higher than that in the group of dippers (patients with normal noctural decrease in BP). The severity of NASH (from moderate to severe) was higher in the group with nocturnal increase in blood pressure (night-pikers) [55].

In studies of reverse causality, the prevalence of hypertension was 37.6% in patients with NAFLD and increased to 46.7% in patients with NASH [56]. It has been suggested that the existence and development of NAFLD could change the prognosis in hypertensive patients in terms of progression of liver failure and increase the incidence of CV complications [48]. It was shown that the average intensity of liver steatosis was S2 (0.42 to 0.49) among patients with obesity and EH stage II. NASH with mild and moderate activity was associated with the development of liver tissue fibrosis (within F1 — 0.28–0.36) [57].

It was found that hypertension, particularly systolic, was an independent predictor of non-specific portal fibrosis in patients with NAFLD [22]. It was

obvious that angiotensin II had the leading role in the formation of fibrogenesis processes. It was suggested that possible implementation mechanism of such effect was the increase in profibrogenic cytokine production, that transformed the growth factor (transforming growth factor) — TGF-β1, which activated stellate cells. Angiotensin II has not only vasoconstrictor, but also prothrombogenic action. Also it is able to induce the oxidative stress. The experiment confirmed the increase in active oxygen species formation (superoxide anion) under the influence of angiotensin II. The oxidative stress products reduce the activity of nitric oxide (NO). Sometimes angiotensin II has the opposite effect in relation to NO and now it is recognized as its antagonist. According to this fact, the need for pathogenetic therapy of hypertension patients with comorbid NAFLD by angiotensin-converting enzyme (ACE) inhibitors is emphasized. They block the effects of angiotensin and aldosterone [22, 58]. The results of recent studies confirmed the positive effect of ACE inhibitors on the state of liver parenchyma. It was shown that lower degrees of fibrosis at histological examination of the liver and lower levels of transaminases in the blood plasma were found in patients receiving ACE. Those differences might be associated with the influence of ACE inhibitors on the renin-angiotensin-aldosterone system (RAAS) and effects of angiotensin II. It was local RAAS that took part in the regulation of liver fibrogenesis and in the genesis of portal hypertension formation [22, 58].

Some authors believe in the unity of pathogenetic mechanisms of hypertension development and NAFLD [22]. There is an opinion that IR and compensatory hyperinsulinaemia are important factors in the common pathogenetic mechanisms of NAFLD and hypertension development [54, 59–62]. It is shown that IR and compensatory hyperinsulinaemia are the key factors in the formation of MS [54, 61, 63]. They are also recognized as the leading mechanisms in the pathogenesis of NAFLD [59, 60, 62]. Hyperinsulinaemia, in turn, stimulates the synthesis of growth factors (platelet, insulin-like, fibroblast growth factor). That leads to the proliferation of smooth muscle cells and fibroblasts and, as a consequence, vasoconstriction and increase in blood pressure (BP) [22, 54, 61, 64]. In such conditions, the synthesis of endothelin (ET), an inhibitor of tissue activator of drug-1, increases [65]. Sympathoadrenal system (SAS) and RAAS are involved in the process. Sodium reabsorption increases in the proximal and distal tubules of nephron, which creates the background for EH development [22].

So, it is known that NAFLD and hypertension are associated with IR and MS. However, there are still unresolved issues: What is the causal relationship between the development of NAFLD and hypertension? In what way do the comorbid EH and NAFLD affect the development and course of each other? Are they parts of a single pathological process? Do they have common pathogenetic factors and mechanisms?

Dyslipidaemia and non-alcoholic fatty liver disease

Dyslipidaemia, as an important cardiovascular risk factor, exerts its influence not only on the vascular wall, but also on the physiological processes in the structure of liver. In the study by Andres-Blasco *et al.* (2015) it is indicated that NAFLD is associated not only with the components of MS such as obesity, insulin resistance and hypertension, but also with dyslipidaemia [30].

In the body there is a complex system of lipid metabolism regulation, in which each link in the reticuloendothelial system of liver plays an important role [37, 66]. The main components of hepatocellular lipids are represented by TG [67]. However, today the definitive role of triglycerides in assessing of cardiovascular risk has not yet been proven. Although, there was a highly significant direct correlations between the level of TG and smoking and the levels of total cholesterol, hylomicrones, and lipoprotein(a) (LP(a)) [39]. Graham *et al.* indicated that the level of TG in blood serum is a "signal" marker for intensive examination and determination of such RFs as abdominal obesity, hypertension, high LDL cholesterol levels and impaired glucose tolerance [68].

Lipid metabolism in the liver and its changes are involved in the development of many pathological processes, such as NAFLD, diabetes mellitus (DM) and atherosclerosis. The development of dyslipidaemia, including hypercholesterolaemia, hypertriglyceridaemia, and the increase in non-esterified fatty acids associated with the decrease in liver lipase activity were noted during the application of a high-calorie diet saturated with cholesterol (CS). This, in turn, was associated with impaired glucose tolerance, the development of an inflammatory process in liver and pancreas, and the development of steatosis [30].

The increased levels of LDL cholesterol and decrease in HDL cholesterol, increased activity of CRP, LP(a), and serum neopterin level were noted in a study that examined the subclinical markers of atherosclerosis in young men with abdominal obesi-

ty. This was associated with the presence of obesity and steatohepatosis [significant correlation was noted between the thickness of intima-media complex (TIMC) and BMI, WC, WC/WH ratio, TG level, neopterin, CRP, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), and gamma-glutamyltransferase (GGT)] [25]. According to the obtained data, the authors proposed the use of the markers of inflammation, increased levels of ALAT, ASAT, GGT and the presence of NAFLD as the predictors of subclinical atherosclerosis [25].

Lipid metabolism in the liver is regulated by protein-receptor of low density lipoprotein-6 (LRP6). Apolipoproteins recognition by receptors in neutral pH leads to the internationalization of the ligands, followed by distribution to endosome. The released particles of the ligands are transported to lysosome, where the digestive enzymes break down these ligands. The pathological pathway of IGF-1-Sp1-mTOR-SREBP1/2 is activated during the impairment of signalling protein-receptor LRP6 function. Activation of Sterol Regulatory Element Binding Protein1c (SREBP1c), involved in lipo- and adipogenesis, and SREBP2 (which activates cholesterol biosynthesis and LDL receptors) support adipogenesis and accumulation of VLDL cholesterol, which take part in the development of hyperlipidaemia and NAFLD. The state of lipid metabolism in hepatocytes depends on such pathological way of consumption as mTOR, which is supported by the serine/threonine kinase. Protein kinase B, activated by insulin, phosphorylates and suppresses tuberous sclerosis complex 2 (TSC2) a tumour suppressor. This leads to the activation of mTORC1 peptide S6, S6K and SREBP. TSC1-TSC2 complex disorder promotes SREBP-dependent lipid synthesis similarly [69, 70]. Activation of mTORX1 signalling pathway is associated with an increase in lipid synthesis and the development of non-alcoholic steatohepatosis. In addition, stimulation of the mTOR pathological pathway contributes to the insulin-dependent transcription of stearoyl-CoA desaturase (SCD1), an important enzyme that regulates the synthesis of monounsaturated fatty acids and lipogenesis in the structure of hepatocytes and lipid oxidation. It is proved in experimental work that SCD1, associated with the work of the hepatocytes, protects experimental mice from carbohydrates-induced deposition of adipose tissue and development of steatohepatosis [71].

Prognostic value of a significant increase in LP(a) in serum, as an important predictor of CV events, was confirmed in the studies that included patients with dyslipidaemia, hypertension, diabetes, the history of CV disease and non-alcoholic hepatic steatosis (NAHS) [38, 72, 73]. In parallel, the role of LP(a) as a genetic risk factor for CV disease was explained. Its value may be associated with the level of LDL cholesterol [68]. The role of hypertriglyceridaemia and increased VLDL cholesterol has been confirmed in the pathogenetic mechanisms of NAFLD formation [30, 46, 74]. LP(a) role in the development of NAFLD remained completely undetermined. The obtained data are rather contradictory. Lee *et al.* (2006) showed the decrease in LP(a) in patients with NAFLD. Also, Cankurtaran *et al.* (2007) recorded the increase in LP(a) in patients with NAFLD. Moreover, the study of lipid and carbohydrate metabolism in patients with NAFLD found that the increase in LDL cholesterol was accompanied by LP(a) concentration, CRP in serum, impaired tolerance to carbohydrates and increased levels of fasting insulin [50]. The correlation between LP(a) and IR were examined in the study in which the concentration of LP(a) was decreased more effectively in patients without IR syndrome [75].

Today, the activation of lipid peroxidation (LPO) processes in the background of an active lipogenesis in the pathogenesis of NAFLD is seen as a factor of accelerated atherosclerotic process [76]. So, foamy macrophages are formed during the modification of LDL by malonic dialdehyde (MDA) as a result of hydrolysis and esters' esterification in LDL. This contributes to the development of proinflammatory and proatherogenic reactions [77]. In the pathogenesis of NAFLD, protein-modifying effects, mediated by MDA and hydroxynonenal (HNE), manifested by the formation of protein adducts, in particular Lys-residues apo B100. This promotes the formation of atherosclerotic plaques.

Nonspecific systemic inflammation

Macrophages, accumulating in adipose tissue, are a source of local cytokine that is involved in the development of NAFLD — tumour necrotic factor α (TNF-α). Particularly intensive synthesis of TNF-α is characteristic of the visceral fat depot, which produces 2–3 times more TNF-α compared with subcutaneous adipose tissue. Infiltration of visceral adipose tissue by macrophages is observed in conditions of pronounced hypertrophy in combination with increased secretion of proinflammatory cytokines, in particular TNF-α. TNF-α, in turn, is a potent inducer of the formation of interleukin-1 (IL-1), interleukin-6 (IL-6), C-reactive protein (CRP) and other compounds with the subsequent development of insulin resistance and a cascade of

related metabolic disorders [65, 76, 78]. Adipocytes of the omentum and mesenteric area are characterized by high lipolytic ability, resulting in a massive flow of free fatty acids (FFA) and adipokines in the liver with the subsequent development of insulin resistance and dyslipidaemia. The molecules of reactive oxygen potentiate the oxidation of fatty acids in combination with the damage of hepatocytes and the production of proinflammatory cytokines. This stimulates the development of nonspecific systemic inflammation. Proinflammatory cytokines (TNF-α and IL-6) activate lipogenesis and inhibit oxidation of free fatty acids (FFA) in liver cells, resulting in increased apolipoprotein B (apoB) and VLDL. TNF-α and IL-6 inhibit the catabolism of chylomicrons and VLDL, leading to the development of significant hypertriglyceridaemia — the trigger factor of NAFLD development [79, 80]. Patients with fatty liver disease have increased levels of matrix RNA (mRNA) of TNF-α and receptors to this cytokine. TNF-α damages the metabolism of apoproteins due to the suppressive effect on the secretion of apoE and apoA1 proteins. It is necessary to mention that insulin resistance and local liver inflammation activate the macrophages of liver (Kupffer cells) that begin to synthesize proinflammatory cytokines (TNF-α, IL-12 and IFN-γ) [18]. Consequently, the metabolic disorder in the liver is the background for the development of chronic inflammatory process of low severity [33]. It is shown that it is non-specific systemic inflammation that brings together into a unitary syndrome hypertension, increased body weight (especially abdominal obesity), dyslipidaemia and atherogenesis [81]. Significant ($p < 0.001$) increase in inflammation markers (TNF-α, IL-1, IL-6) and increase ($p < 0.001$) in the circulating immune complexes' level were identified in patients with comorbidity (a combination of hypertension, obesity and NAFLD [75].

Adipose tissue and its activity

According to the approach of modern medicine, adipose tissue functions as an endocrine organ, expresses genes encoding bioactive substances, secretes certain cytokines, which are called "adipocytokines" [82]. This specifies its considerable activity in relation to metabolic processes: the larger it becomes, the more it produces hormones and biologically active substances (leptin, resistin, adiponectin, apelin, proinflammatory cytokines, growth factors, complement factors and others), that participate in inflammation processes, including atherosclerosis [8, 18, 83, 84]. An excessive amount of these molecules is associated with the alteration in insulin sensitivity. A strong link between dysfunction of adipose tissue in patients with NAFLD and such conditions as metabolic syndrome, type 2 diabetes and CV disease was demonstrated [15].

Leptin is involved in the regulation of body weight and plays a significant role in the accumulation of TG in the liver. Increase in its content is associated with the elevation of ALT levels and may be involved in the promotion of hepatocellular damage. The amount of leptin secreted is in direct proportion to the mass of adipose tissue [85]. Recently, leptin is considered as a mediator of activation of the sympathetic nervous system (SNS), which plays a role in so-called leptin-induced increase in blood pressure [86]. In obesity, leptin concentration is increased and expression of leptin receptors is reduced, which is characterized as "leptin resistance" and can be manifested both systemically and at the level of the liver [22].

The levels of resistin (another adipocytokine) in NAFLD are also elevated and associated with the histological severity of the disease. It is shown that the reduction of body weight significantly reduces its level [18, 87]. The results of the study indicate that resistin can serve as a metabolic bridge that connects inflammation and atherosclerosis [88]. It is reported that in individuals with and without diabetes the level of resistin in plasma is associated with metabolic and inflammatory markers, that include soluble receptors of TNF, IL-6 and lipoprotein-associated phospholipase. The concentration of resistin is also associated with the severity of coronary arteries' calcification, and is the independent predictor and marker of atherosclerosis [89]. The relationship between the level of resistin and the markers of endothelial dysfunction confirms the potential effects of resistin in the development of CV disease. The association between obesity, inflammation and resistin expression is complex, and a final clarification of its role requires further research.

Adiponectin is collagen-like protein specific to adipose tissue, which owns antiatherogenic, anti-inflammatory and antidiabetic properties. It is adipocytokine, involved in the inhibition of NAFLD [24, 54, 75, 90–92]. Adiponectin is influenced by and affects the action of many pathophysiological mechanisms, including nonspecific systemic inflammation, increase/decrease in body weight, body constitution and chronic diseases [77]. Lower concentration of adiponectin in serum is noted in patients with NAFLD [90, 93]. There is evidence that its concentration is negatively correlated with the content of fat in the

liver. Adiponectin stimulates β-oxidation through activation of AMP-dependent protein kinase and reduces the key transcription factor of *de novo* synthesis of fatty acid. This leads to the reduced accumulation of TG in the liver. Adiponectin has antioxidant properties as an antagonist of the inflammatory mediators' effect of TNF-type and reduces the proliferation of stellate cells of the liver [91]. In several studies, the decrease in adiponectin levels is an early predictor of the development of MS and CV disease and is considered as an additional factor of high mortality rate [77]. Expression of adiponectin is impaired in patients with obesity. This may contribute to the progression of changes in liver tissue (non-alcoholic steatohepatosis (NASH) — steatohepatitis (SH) — fibrosis) or start the cascade of metabolic events with the formation of dyslipidaemia and hypertension [22]. On the other hand, some authors indicate that the elevated levels of insulin and adiponectin were recorded in patients with NAFLD [54]. It is evident that high adiponectin level is associated with the congestive heart failure and mortality [94, 95].

So, the final clarification of adiponectin and another adipokines role in the development of NAFLD and other diseases requires further researches. It is suggested that based on the adipokine levels it will be possible to predict not only the development of steatosis and the severity of NAFLD, but also AH [22].

Endothelial dysfunction

The dysfunction of endothelium may be considered as the link between the pathology of liver, obesity and hypertension [96]. The vasoregulatory role of the local fat depot around the vascular wall should be noted [97]. The vascular endothelium is an active, dynamic structure that receives the mechanical and hormonal stimuli and selects the agents which regulate vasomotor function, trigger inflammatory processes and affect haemostasis. Excess body weight and the development of abdominal obesity not only increase the frequency of other cardiovascular risk factors, including dyslipidaemia, hypertension, insulin resistance, and hyperglycaemia, but also lead to the increased activity of renin-angiotensin system, synthesis of adipocytokines, activation of the processes of nonspecific systemic inflammation, in particular increasing of TNF-α concentration level in the serum, which has a negative impact on the vascular endothelium [98].

Chronic nonspecific systemic inflammation results in a decrease in nitric oxide (NO) production by vascular endothelial cells and reduced ESVD, contributing to the invasion of LDL cholesterol in endotheliocytes and its oxidation in the vascular wall, followed by capture by macrophages with the formation of foam cells [96]. These reactions can reduce the elastic properties of the arteries and cause the development of endothelial dysfunction (ED). Different studies of the concentrations of inflammation markers such as high sensitive CRP, TNF-α, IL-6, leukocytes count in patients with NAFLD were conducted [84, 93, 99]. It was shown that nonspecific chronic systemic inflammation had led to the development of ED in patients with NAFLD [93, 96, 99]. Zitona link of immunity is considered as one of the pathogenetic factors in the formation of ED, the processes of cytolysis in hepatocytes and the subsequent development and progression of NAFLD.

The endothelium of the liver sinusoids is a highly specialized structure and phenotypically highly differentiated due to the presence of fenestration and lack of a basal membrane, which distinguishes them from other endothelial cells. Sinusoidal endothelium of the liver accounts for about 3% of the liver structure and is responsible for the clearance of liver serum molecules that pass through the sinusoid [100]. The impression of endothelial cells occurs in various liver diseases, including NAFLD. However, the relationship between the lesions of endothelial cells and NAFLD development is completely undetermined. The question about the value of the sinusoidal ED for the development of fibrosis in NAFLD remains open. The value of high-calorie diets for the development of sinusoidal ED was demonstrated in the experiment on rat metabolic syndrome model. It was shown that ED hepatic sinusoids occurred before the development of inflammation or fibrosis [101]. According to the results of other experimental studies, it was established that the impression of sinusoidal endothelial cells developed in the presence of the non-alcoholic steatohepatosis and preceded the activation of Kupffer cells and stellate cells of the liver. The obtained results indicated that the impression of sinusoidal endothelial cells was the "warning signal" of progression of simple steatosis to non-alcoholic steatohepatitis and was a prerequisite for the activation of Kupffer cells and stellate cells of the liver. This determined the development and formation of chronic liver injury [102].

The NAFLD value for the functional state of the vascular endothelium was established in the review of 11 studies. It was shown that the presence of NAFLD was associated with the reduced endothelium-dependent vasodilation (REDV), mainly in patients with obesity [103]. Long *et al.* (2015) found that fatty infiltration of the liver was

associated with REDV, the increase in the pulse wave propagation velocity (PWPV) and higher AP (samples included 2284 patients with fatty hepatosis without marked CV disease) according to the multiple correlation analysis with indices of age, sex, smoking, DM, hyperlipidaemia, blood pressure, and BMI [104]. It was also shown that the reduction of brachial artery REDV correlated with the degree of morphological changes in the liver, regardless of sex, age, insulin resistance and other MS components [105, 106]. The relationship of ED with steatohepatosis was also recorded in the study of Katsiki *et al.* (2015) that was conducted in patients with MS and NAFLD [107].

Thickness of intima-media complex

Attempts to explore the relationship between the thickness of intima-media complex (TIMC) and early manifestations of atherosclerosis in patients with NAFLD are being made. The role of NAFLD in the growth of TIMC is also being studied. It is established that TIMC is greater in patients with NAFLD in comparison with the control group, independently of other traditional RF and the presence of MS [26, 28, 93, 108]. In patients with NAFLD the TIMC value is 1.14 mm on average. It increases the risk of CV diseases. NAFLD can act as a trigger factor of the TIMC increase, and the increase in TIMC depends on the NAFLD severity [108, 109]. A meta-analysis of 8 observational studies indicated a reliable association between TIMC and CV risk. It was repeatedly noted that TIMC increase and the presence of atherosclerotic plaques of the carotid arteries might be a predictor of myocardial infarction (MI) and stroke. The ratio of TIMC and CV risk is continuum, but the criterion for a significant risk increase may be the threshold of TIMC equalled to 0.9 mm and more [110–112]. The value of fat steatohepatosis as an additional CV risk factor was confirmed by studies of Marcucci *et al.* (2010). It was noted that the presence of NAFLD along with the SBP, BMI, and WC was significantly associated with TIMC [26]. The results of the study were unexpected. It was indicated that there was no association between TIMC and well-known cardiovascular risk factors such as dyslipidaemia, increased fasting glucose levels and insulin resistance. Thus, not all cardiovascular risk factors are able to exercise the same influence on TIMC. Some of them are important for the later development of atherosclerosis, for example, the formation of atherosclerotic plaque.

Arterial stiffness

In recent years, increasing attention of researchers is focused on the arterial wall stiffness (AWS), which characterizes the structural changes of the vessels [113, 114]. The results of recent studies indicate that the old theory of AWS development (as a result of atherosclerotic changes of the vascular wall) is incorrect. Arterial stiffness develops due to arteriosclerosis, which is different from atherosclerosis and is indicated by the absence of associative relationships between the propagation velocity of the pulse wave (PVPW) and traditional cardiovascular risk factors, with the exception of age and hypertension. In addition, PVPW does not increase in the early stages of atherosclerosis and increases with the development of atherosclerotic plaques, mainly due to calcification of the arterial wall [31]. The increase in AWS in NAFLD was found [115–117]. However, the pathogenetic mechanisms of AWS formation in patients with NAFLD are completely unclear. One of the hypotheses points to the development of nonspecific systemic inflammation in patients with NAFLD, when CRP and pro-inflammatory cytokines may exercise a negative impact on the arterial wall elasticity of the arteries with large diameter. The elasticity of the arteries was lower in patients with NAFLD. No changes in the elasticity of the vascular wall were observed in patients with NAFLD and a low level of CRP. Abdominal obesity, in turn, is an unfavourable determinant not only for AWS, but also for the rising levels of CRP in patients with NAFLD [31, 115, 118–120]. Young men and middle aged persons without concomitant obesity, hypertension and diabetes were selected to explore the association between NAFLD and AWS, and to exclude the influence of age, obesity, hypertension, diabetes and other factors. The authors noted a significant increase in leukocyte count in patients with NAFLD compared with the control group. This indicates the possible involvement of inflammation in the pathogenesis of NAFLD. A significant increase in CRP index, which is independently associated with PVPW and AWS increase, confirmed the hypothesis [117]. Another point of view on the pathogenetic mechanisms of AWS increase is associated with the total blood viscosity. Blood viscosity was higher in patients with NAFLD and was independently associated with AWS, even after adjusting for other risk factors. NAFLD connection with AWS increase was presented in the study of Lee *et al.* (2012). An independent association between PVPW and NAFLD, independently of other cardiovascular risk factors, was found with the help of multivariate regression analysis [116].

The influence of NAFLD on PVPW also was discovered in the studies of Chung (2015), and Chou (2015). Overall, 2954 patients participated in the first study. It was found a reliable independent association between NAFLD and cardio-ankle vascular index [121]. Another study evaluated the association between NAFLD and AWS in healthy persons with normal glucose levels, patients with impaired tolerance to carbohydrates and newly diagnosed diabetes. The effect of NAFLD on AWS among the individuals without signs of metabolic disorders was noted. There was no such association among patients with impaired tolerance to carbohydrates and newly diagnosed DM [115]. It was established that patients with histologically confirmed diagnosis of NAFLD, assessed according to the Brunt scale (Brunt of the Global Grade), had significantly higher PVPW rates (8.2 ± 1.3 m/s versus 6.9 ± 1.3 m/s, p = 0.001), greater TIMC (0.79 ± 0.18 m/s vs. 0.67 ± 0.13 m/s, p = 0.01) and lower EDVD (1.93 ± 2.11% versus a 4.8 ± 2.43%, p = 0.001) compared with patients without NAFLD [28]. The data were confirmed by the results of a systematic review of 36 studies, 16 of which had investigated the association between NAFLD and TIMC of carotid arteries, 7 — the relationship between NAFLD and calcification of carotid arteries, 7 with ED, and the rest 6 with AWS [29].

Steatohepatosis and its metabolic consequences

What are the metabolic consequences of the steatohepatosis? Accumulation of fat in the liver causes hyperglycaemia, subclinical inflammation, dyslipidaemia and production of hepatokines, thereby leading to insulin resistance, atherosclerosis and possible dysfunction of β-cells and apoptosis. The severity of these conditions can be moderate (benign fatty infiltration of the liver). The same degree of steatosis may be accompanied by the significant liver lipotoxicity and lead to the aggravation of hyperglycaemia, inflammation, dyslipidaemia, unbalanced hepatokines production and subsequent metabolic disorders due to unestablished mechanisms [47]. The NAFLD development is closely associated with such MS components as insulin resistance, abdominal obesity, dyslipidaemia and hypertension. It is based on the impairment of mechanisms of insulin-mediated lipolysis processes inhibition and increased release of free fatty acids (FFA) from adipose tissue. A number of studies found that NAFLD increased the risk of CV diseases independently of other predictors and manifestations of MS [34].

Anthropometric characteristics of NAFLD on the background of MS were revealed. It was shown that the severity of hepatic steatosis was closely associated with BMI, WC/HC ratio and body fat percentage. The increased degree of steatosis in the presence of IR not only deteriorated the functional state of the liver, but also increased the severity of dyslipidaemia. Statistically significant direct correlations between the degree of IR and the level of AST, ALT, TH, TG, hepatic steatosis and anthropometric data showed that metabolic parameters could be considered as factors, the regulation of which affected the development and progression of NASH on the background of MS [19].

A combination of such risk factors as hyperglycaemia, dyslipidaemia, hypertension, abdominal obesity, disorders of the haemostatic system in the presence of insulin resistance creates a pathogenetic prerequisite for the disorders of CV system function in patients with NAFLD. In this aspect, the cardio-dynamic changes in NAFLD, the time of their development, the nature of the occurrence and the association with the state of the portal blood flow are very interesting [17]. Diastolic dysfunction due to the flow-dependent regulation of vascular tone can also act as a marker of subclinical atherosclerosis. The present study showed strong correlation between it and NAFLD (the greater the liver damage in NAFLD (from simple steatohepatosis, inflammation with manifestations of necrosis to the development of fibrosis), the more severe diastolic dysfunction) [22, 105, 122]. Thus, NAFLD can act as an additional predictor of CV disease.

Conclusions

A review of studies to identify the relationship between CV and NAFLD diseases indicates that NAFLD can be considered as one of the phenotypic variants of insulin resistance and MS. The participation of insulin resistance, oxidative stress, subclinical nonspecific inflammation, disorders of lipid metabolism and endothelial dysfunction in pathogenetic relationships between NAFLD and cardiovascular disease can be applied for therapeutic prospects in the treatment of these diseases [32].

The combination of AH and NAFLD are prerequisites for the progression of the pathological process, which has targeted the heart, kidneys and liver [8, 66, 103]. Taking into account the fact that NAFLD is considered within a continuum of the MS, an interesting issue is the study of the nature of changes in the CV system in such category of patients [20].

Thus, despite some understanding of common pathogenic mechanisms of NAFLD development and hypertension, this comorbid pathology is the subject of much scientific debate and various studies [6–8, 14, 20, 22, 27, 31, 32, 48, 54, 55, 57, 58, 61, 96, 121]. The question of carrying out further observations for a deeper study of pathogenesis is relevant. It is necessary to identify the ways and methods of prevention and correction of metabolic disorders, developing in these states. Today, only an individual approach to each patient with deep detailed diagnosis of main clinical and metabolic manifestations, as well as a comprehensive approach to treatment, taking into account coexisting pathologies, will help to prevent further progression of these diseases, reduce the risk of complications and improve the quality of patients' life.

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References

1. Korneeva E.V. Preventive influence of orlistat on cardiovascular risk in young obese patients with obesity. Kardiovaskulyarnaya terapiya 2015; 14: 38–43.
2. Deng W.W., Wang J., Liu M.M., Wang D. Body Mass Index Compared with Abdominal Obesity Indicators in Relation to prehypertension and Hypertension in Adults. Am. J. Hypertens. 2013; 26: 58–67.
3. Da Silva J.P., Lima R.P., De Carvalno *et al.* Association between waist-to-height ratio, isolated and combined morbidities and C-reactive protein in the elderly: a clinical-epidemiological study. Int. J. Environ. Res. Public Health 2014; 11: 9595–9606.
4. Goodars D. Metabolic mediators of the effects of body-mass index, overweight and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. Lancet 2014; 383: 970–983.
5. Komshilova K.A. Abdominal obesity and non-alcoholic fatty liver disease: clinical, laboratory and morphological comparisons. Komshilova Kseniya Andreevna. Moskva 2015; 175.
6. Kostyukevich O.I. Arterial hypertension and liver disease: search of compromise. Russkiy meditsinskiy zhurnal 2011; 5: 338–334.
7. Drapkina O.M., Popova I.R. The role of obesity in the progression of hypertension and nonalcoholic fatty liver disease. Ukrayinskiy medichniy chasopis 2013; 2: 125–128.
8. Pasiyeshvili L.M., Zheleznyakova N.M., Pasiyeshvili T.M. Nonalcoholic fatty liver disease and hypertension: pathogenetic factors of the formation and progression. Hastroenterolohiya. 2014; 2: 46–49.
9. Wassertheil-Smoller S., Oberman A., Blaufox M.D., Davis B., Langford H. The Trial of Antihypertensive Interventions and Management (TAIM) Study. Final results with regard to blood pressure, cardiovascular risk, and quality of life. Am. J. Hypertens. 1992; 5: 37–44.
10. Kumanyika S.K., Hebert P.R., Culter J.A. *et al.* Feasibility and efficacy of sodium reduction in the Trials of Hypertension Prevention, phase 1. Trials of Hypertension Prevention Collaborative Research Group. Hypertension 1993; 22: 502–512.
11. Grimm R.H. Jr., Grandits G.A., Prineas R.J. *et al.* Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women. Treatment of Mild Hypertension Study (TOMHS). Hypertension 1997; 29; 29: 8–14.
12. Rumberger J.A., Brundage B.H., Rader D.J., Kondos G. Electron beam computed tomographic coronary calcium scanning: a review and guidelines for use in asymptomatic persons. Mayo Clin. Proc. 1999; 74: 243–252.
13. Torgerson J.S., Hauptman J., Boldrin M.N., Sjöström L. XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study. Diabetes Care 2004; 27: 155–161.
14. Babak O.Ya., Kolesnikova E.V., Dubrov K.Yu. Nonalcoholic steatohepatitis — "the accord" of methabolic disorders. Ukrayinskiy terapevtichniy zhurnal 2011; 1: 5–11.
15. Cusi K. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications. Gastroenterology 2012; 142: 711–725.
16. Velychko V.I., Kolotvina L.I., Hur'yeva A.M. Obesity and nonalcoholic fatty liver disease with cardiovascular risk positions in the practice of family physisions. Medytsyna transportu Ukrayiny 2014; 1: 79–82.
17. Gaskari S.A, Honar H., Lee S.S. Therapy Insight: cirrhotic cardiomyopathy. Nature Clinical Practice Gastroenterology & Hepatology 2006; 3: 329–337.
18. Yahmur V.B. Nonalcoholic fatty liver disease: modern view of pathogenesis, diagnosis and treatment. Hastroenterologiya 2013; 3: 138–147.
19. Kolesnikova O.V., Dubrov K.Yu., Krakhmalova E.O. Correlations of methabolic steatohepatitis, insulin resistance and anthropometric parameters in patients with symptoms of metabolic syndrome. Ukrayins'kyy terapevtychnyy zhurnal 2010; 3: 81–86.
20. Krahmalova E.O., Kozlov A.P. Nonalcoholic fatty liver disease and cardiovascular disease. The modern view on the problem. Ukrayins'kiy terapevtichnyi zhurnal 2010; 4: 82–85.
21. Prosolenko K.O. Features of diagnosis and treatment of nonalcoholic fatty liver disease on the background of metabolic syndrome. Ukrayins'kyy terapevtychnyy zhurnal 2010; 4: 86–92.
22. KolesnIkova E.V. Non-alcoholic fatty liver disease and hypertension: what we have achieved in the understanding of the problem. Ukrayinskiy medichniy chasopis 2014; 3: 61–66.
23. Hall J.E., do Carmo J.M., da Silva A.A., Wang Z., Hall M.E. Obesity-induced hypertension interaction of neurohumoral and renal mechanisms. Circ. Res. 2015; 116: 991–1006.
24. Kolesnikova O.V., Yares'ko M.A. Hypertension and obesity in women during perimenopause, resolved and unresolved therapeutic problems. Ukrayins'kyy terapevtychnyy zhurnal 2015; 3: 86–90.
25. Abdou A.S., Magour G.M., Mahmoud M.M. Evaluation of some markers of subclinical atherosclerosis in Egyptian Youn Adult Males with abdominal obesity. BJBS. 2009; 66: 143–147.
26. Caserta C.A, Pendino G.M., Amante A. *et al.* Cardiovascular risk factors, Nonalcoholic Fatty Liver Disease and Carotid Artery Intima-Media Thikness in an Adolescent Population in Sourthern Italy. Am. J. Epidemiol. 2010; 171: 1195–1202.
27. Tarquini R, Lazzeri C., Boddi M., Marra F., Abbate R., Gensini G.F. Non-alcoholic fatty liver disease: a new challenge for cardiologists. G. Ital. Cardiol. (Rome). 2010; 11: 660–669.
28. Vlachopoulos C., Manesis E., Baou K. *et al.* Increased arterial stiffness and impaired endothelial function in non-alcoholic fatty liver disease: a pilot study. Am. J. Hypertens. 2010; 23: 1183–1189.
29. Oni E.T., Agatstou A.S., Blaha M.J. *et al.* A systemic review: burden and severity of subclinical cardiovascular disease among those with nonalcoholic fatty liver; should we care. Atherosclerosis 2013; 230: 258–267.
30. Andres-Blasco I., Herrero-Cervera A., Vinue A. *et al.* Hepatic lipase deficiency produses glucose intolerance, inflammation and hepatic steatosis. J. Endocrinol. 2015; 227: 179–191.
31. Athyros V., Tzimalos K., Katsiki N., Doumas M., Karagiannis A., Mikhailidis D.P. Cardiovascular risk across the histological spectrum and the clinical manifestation of non-alcoholic fatty liver disease: an up date. World J. Gastroenterol. 2015; 21: 6820–6844.
32. Lim S., T.J. Oh, Koh K.K. Mechanistic link between nonalcoholic fatty liver disease and cardiometabolic disorders. Int. J. Cardiol. 2015; 201: 404–414.
33. Ponziani F.R., Pesere S., Gasparini A., Ojetti V. Physiology and pathophysiology of liver lipid metabolism. Expert Rev Gastroenterol. Hepatol. 2015; 9: 505–1067.
34. Adiels M., Taskinen M.R., Packard C. *et al.* Overproduction of large VLDL particles is driven by increased liver fat content in man. Diabetologia 2006; 49: 755–765.

35. Lee S., Jin Kim Y., Yong Jeon T. *et al.* Obesity is the only independent factor associated with ultrasounddiagnosed non-alcoholic fatty liver disease: a cross-sectional case-control study. Scand. J. Gastroenterol. 2006; 41: 566–572.
36. Seliverstov P.V., Prihodko E.M., Dobritsa V.P., Radchenko V.G. Some issues of diagnosis, treatment and prevention of nonalcoholic fatty liver disease. Farmateka 2015; 2: 49–55.
37. Skybchyk V.A., Voytovych M.O. Nonalcoholic fatty liver disease: modern diagnostics. Hepatolohiya 2015; 1: 52–56.
38. Ghorbani A., Rafieian-Kopaei M., Hasri H. Lipoprotein (a): more than a bystander in the etiology of hypertension? A study on essential hypertensive patients not yet on treatment. J. Nephropathol. 2013; 2: 67–70.
39. Poynard T., Ngo Y., Perazzo H. *et al.* Prognostic value of liver fibrosis biomarkers: a meta-analysis. Gastroenterol. Hepatol. (N Y). 2011; 7: 445–454.
40. Poynard T., Lassailly G., Diaz E. *et al.* Performance of biomarkers fibrotest, actitest, steatotest, and nashtest in patients with severe obesity: meta analysis of individual patient data. PLoS ONE 2012; 7: e30325.
41. Kleiner D.E., Brunt E.M. Nonalcoholic fatty liver disease pathologic patterns and biopsy evaluation in clinical research. Semin. Liver Dis. 2012; 32: 3–13.
42. Grattagliano I., Ubaldi E., Napoli L. *et al.* Utility of noninvasive methods for the characterization of nonalcoholic liver steatosis in the family pracrice. The "VARES" Italian multicenter study. Ann. Hepatol. 2013; 12: 70–77.
43. Xauchy F., Fuks D., Le Bian A. Z., Belghiti J., Costi R. Metabolic syndrome and non-alcoholic fatty liver disease in liver surgery/The new scourges. World J. Hepatol. 2014: 6: 306–314.
44. Zhuravlyova A.K., Bobronnikova L.R. Predictors of fibrozis in patients with combination of non-alcoholic fatty liver disease and type 2 diabetes. Endokrinologiya 2014; 19: 134–140.
45. Alshaalan R., Aljiffry M., Al-Busafi S., Metrakos P. Hassanain M. Nonalcoholic Fatty Liver Disease: Nonsinvasive Methods of Diagnosing Hepatic Steatosis. Saudi. J. Gastroenterol. 2015; 21: 64–70.
46. Cheng S., Wiklund P., Autio R. *et al.* Adipose Tissue Dysfunction and Altered Systemic Amino Acid Metabolism Are Associated with Non-alcoholic Fatty Liver Disease. PLoS One 2015; 10: e0138889.
47. Stefan N., Schafer S., Machicao F. *et al.* Liver Fat and Insulin Resistance Are Independently Associated with the 514C>T Polymorphism of the Hepatic Lipase Gene. J. Of Clinic Endocrinol. Metab. 2005; 90: 4238–4243.
48. Kobylyak N.M., Dynnyk O.B., Kyriyenko D.V. Current approaches to diagnosis and screening of metabolic disorders in patients with nonalcoholic fatty liver disease. Mizhnarodnyy endokrynolohichnyy zhurnal 2015; 5: 89–99.
49. Stepanov Yu.M. Hepatic steatosis and steatohepatitis — the inevitability of mixed origin. Hastroenterolohyya 2014; 4: 136–142.
50. Cankurtaran M., Tayfur O., Yavuz B. *et al.* Insulin resistance and metabolic syndrome in patients with NAFLD but without diabetes: effect of a 6-month regim intervention. Acta gastroenterol. Belg. 2007; 70: 253–259.
51. Babak O.Ya., Kolesnikova E.V. Pathogenic mechanisms of non-alcoholic fatty liver disease: a focus on clinical application of ademetionin. Suchasna gastroenterologiya 2011; 3: 56–63.
52. Oganov R.G., Perova N.V., Shchel'tsyna N.V. *et al.* Signs of metabolic syndrome in combinations of hypertension with coronary risk factors. Kardiologiia 2005; 45: 27–33.
53. Khukhlina O.S. Fatty liver disease: etiology, epidemiology, course features, diagnosis, prognosis. Ukrayins'kyy medychnyy chasopys. 2006; 1: 89–95.
54. Fallo F., Dalla Pozza A., Sonino N. *et al.* Nonalcoholic fatty liver disease, adiponectin and insulin resistance in dipper and nondipper essential hypertensive patients. J. Hypertens. 2008; 26: 2191–2197.
55. Latea L., Negrea S., Bolboaca S. Primary non-alcoholic fatty liver disease in hypertensive patients. Australas. Med. J. 2013; 6: 325–330.
56. Steffen H., Demir M., Lang S., Schulte S., Tox U. High rate of undetected arterial hypertension in patients with non-alcoholic steatohepatitis (NASH). J. Hypertens. 2010; 28: 557.
57. Khukhlina O. S., Mandryk O. Ye., Antoniv A. A., Nechypay Zh. A. diagnostic markers of liver fibrosis in patients with fatty liver disease, combined with hypertension and obesity. Visnyk problem biolohiyi ta medytsyny 2013; 3: 250–253.
58. Sciacqua A., Perticone M., Miceli S. *et al.* Endothelial dysfunction and non-alcoholic liver steatosis in hypertensive patients. NMCD 2011; 21: 485–491.
59. Angelico F., Del Ben M., Conti R. *et al.* Insulin resistance, the metabolic syndrome, and nonalcoholic fatty liver disease. J. Clin. Endocrinol. Metab. 2005; 90: 1578–1582.
60. Bugianesi E., Gastaldelli A., Vanni E. *et al.* Insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: sites and mechanisms. Diabetologia 2005; 48: 634–642.
61. Hamaguchi M., Kojima T., Takeda N. *et al.* The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. Ann. Intern. Med. 2005; 143: 722–728.
62. Abdelmalek M.F., Diehl A.M. Nonalcoholic fatty liver disease as a complication of insulin resistance. Med. Clin. North Am. 2007; 91: 1125–1149.
63. Chang C.Y., Argo C.K., Al-Osaimi A.M., Caldwell S.H. Therapy of NAFLD: antioxidants and cytoprotective agents. J. Clin. Gastroenterol. 2006; 40: 51–60.
64. Lall C.G., Aisen A.M., Bansal N., Sandrasegaran K. Nonalcoholic fatty liver disease. AJR Am. J. Roentgenol. 2008; 190: 993–1002.
65. Targher G., Bertolini L., Zoppini G., Zenari L., Falezza G. Increased plasma markers of inflammation and endothelial dysfunction and their association with microvascular complications in Type 1 diabetic patients without clinically manifest macroangiopathy. Diabet. Med. 2005; 22: 999–1004.
66. Shevchuk V.V., Fediv O.I. Changes of oxidative and proxidative homeostasis in nonalcoholic steatohepatitis in patients with metabolic syndrome. Visnyk problem biolohiyi ta medytsyny 2013; 3: 276–278.
67. Radchenko V.G., Seliverstov P.V. Non-alcoholic fatty liver disease: new treatment options. Usovershenstvovannaya meditsinskaya tehnologiya. Sankt-Peterburg 2014; 11–20.
68. Graham I., Cooney M.T., Bradley D., Dunina A., Reiner Z. Dyslipidemias in the prevention of cardiovascular disease: risks and causality. Curr. Cardiol. Rep. 2012; 14: 709–720.
69. Kotronen A., Peltonen M., Hakkarainen A. *et al.* Prediction of nonalcoholic fatty liver disease and liver fat using metabolic and genetic factors. Gastroenterology 2009; 137: 865–872.
70. Go G.W. Low-Density Lipoprotein Receptor Protein-6 (LRP6) Is a Novel Nutritioanal therapeutic Target for Hyperlipidemia, Non-Alcoholic Fatty liver Disease and Atherosclerosis. Nutrients 2015; 7: 4453–4464.
71. Miyazaki H.M., Flowers M.T., Sampath H. *et al.* Hepatic srearoyl-CoA-desaturase-1 deficiency protects mice from carbohydrate-induced adiposity and hepatic steatosis. Cell. Metab. 2007; 6: 484–496.
72. Cai A., Li L., Zhang Y., Mo Y., Mai W., Zhou Y. Lipoprotein (a): A Promising Marker for Residual Cardiovascular Risk Assessment. Dis. Markers. 2013; 35: 551–559.
73. Maranhao R., Carvalho P., Strunz C.C., Pileggi F. Lipoprotein (a): Structure, Pathophysiology and Clinical Implications. Arq. Bras Cardiol. 2014; 103: 76–84.
74. Schwenzer N.F., Springer F., Schrame C., Stefan N., Machann J., Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. J. Hepatol. 2009; 51: 433–445.
75. Pasiyeshvili L.M., Khoroshavina T.F. Immune imbalance as the basis of the progression of steatohepatitis in patients with hypertension and obesity. Ukrayins'kyy terapevtychnyy zhurnal 2014; 2: 40–44.
76. Chumak A.A., Ovsyannikova L.M., Kubashko A.V., Sarkisova E.O. Features of the molecular mechanisms of nonalcoholic fatty liver disease progression. Ukrayins'kyy medychnyy chasopys 2013; 6: 33–39.
77. Babak O. Ya., Klimenko N. N. Physiological and pathophysiological role of adiponectin in the complex regulation of the metabolism and the development of cardiovascular diseases. Ukrayinskiy terapevtichniy zhurnal 2010; 2: 94–100.

78. Dschietzig T., Brecht A., Bartsch C., Baumann G., Stangl K., Alexiou K. Relaxin improves TNF-a-induced endothelial dysfunction: the role of glucocorticoid receptor and phosphatidylinositol 3-kinase signaling. Cardiovasc. Res. 2012; 95: 97–10.
79. Kravchenko N.A., Klimenko N.N. Mechanisms of development of cardio-metabolic syndrome in obesity. Problemi endokrinnoyi patologiyi 2012; 1: 84–93.
80. Kovalenko V.M., Talayeva T.V., Kozlyuk A.S. Metabolic syndrome: as a factor in cardiovascular risk: mechanisms of progression the principles of diagnosis and treatment. Ukrayins'kyy kardiolohichnyy zhurnal 2013; 5: 80–87.
81. McMaster W.G., Kirabo A., Madhur M.S., Harrison D.G. Inflammation, Immunity, and Hypertensive End-Organ Damage. Circ. Res. 2015; 116: 1022–1033.
82. Wozniak S.E., Gee L.L., Wachtel M.S., Frezza E.E. Adipose tissue: the new endocrine organ? A review article. Dig. Dis. Sci. 2009; 54: 1847–1856.
83. Estep J.M., Baranova A., Hossain N. *et al.* Expression of cytokine signaling genes in morbidly obese patients with non-alcoholic steatohepatitis and hepatic fibrosis. Obes. Surg . 2009; 19: 617–624.
84. Sur G., Floca E., Kudor-szabadi L. Sur M.L., Sud D., Samasca G. The relevance of Inflammatory Markers in Metabolic Syndrome. Maedica (Buchar.) 2014; 9: 15–18.
85. Dubielski Z., Zamojski M., Wiechecki B., Mozenska O., Petelczyc M., Kosior DA. The current state of knowledge about the dipping and non-dipping hypertension. Arterial Hypertens. 2016; 20: 33–43.
86. Hall J.E., da Silva A.A., Brandon E. *et al.* Pathophysiology of obesity hypertension and target organ injury. In: Lip G.Y.P., Hall J.E. (eds.). Comprehensive Hypertension. Elsevier, New York 2007: 447–468.
87. Anty R., Lemoine M. Liver fibrogenesis and metabolic factors. Clin. Res. Hepatol. Gastroenterol. 2011; 35: 10–20.
88. Gnacinska M., Malgorzewicz S., Lysiak-Szydlowska W., Sworczak K. The serum profile of adipokines in overweight patients with metabolic syndrome. Endokrynol. Pol. 2010; 61: 36–41.
89. Lemoine M., Ratziu V., Kim M. *et al.* Serum adipokine levels predictive of liver injury in non-alcoholic fatty liver disease. Liver Int. 2009; 29: 1431–1438.
90. Day C.P. From fat to inflammation. Gastroenterology 2006; 130: 207–210.
91. Harwood H.J. Jr. The adipocyte as an endocrine organ in the regulation of metabolic homeostasis. Neurophatmacology 2012; 63:57–75.
92. Parfenov N. S. Tanyanskyy D. A. Adiponectin: befenit influencce on the metabolic and cardio-vascular disorders. Arteryal'naya hypertenzyya 2013; 1: 84–96.
93. Dogru T., Genc H., Tapan S. *et al.* Plasma fetuin-A is associated with endothelial dysfunction and subclinical atherosclerosis in subjects with nonalcoholic fatty liver disease. Clin. Endocrinol. (Oxf). 2013; 78: 712–717.
94. Wild S.H., Byrne C.D., Tzoulaki I. *et al.* Metabolic syndrome, haemostatic and inflammatory markers, cerebrovascular and peripheral arterial disease: The Edinburgh Artery Study. Atherosclerosis 2009; 203: 604–609.
95. Kalhan S.C., Guo L., Edmison J. *et al.* Plasma metabolic profile in nonalcoholic fatty liver disease. Metabolism 2011; 60: 404–413.
96. Villanova N., Moseatiello S., Ramilli S. *et al.* Endothelial dusfunction and cardiovascular risk profile in nonalcoholic fatty liver disease. Hepatology 2005; 42: 473–480.
97. Yarmysh N.V., Hroznaya L. N. Endothelial dysfunction and its regulatory factors. Visnyk problem biolohiyi ta medytsyny 2014; 3: 37–43.
98. Mitchenko O.I., Kornats'ka A.H., Romanov V.Yu., Sopko O.V. Endothelial function and thickness of intima — media in women with metabolic syndrome on the background of polycystic ovaries. Ukrayins'kyy kardiolohichnyy zhurnal 2013; 3: 82–89.
99. Bahcecioglu I.H., Yalniz M., Ataseven H. *et al.* Levels of serum hyaluronic acid, TNF-α and IL-8 in patients with nonalcoholic steatohepatitis. Hepatogastroenterology 2005; 52: 1549–1553.
100. Arias I.M., Boyer J.L., Chisari F.V. *et al.* The liver: Biology and pathobiology. Lippincott Williams & Wilkins, Philadelphia 2001; 437–453.
101. Pasarin M., La Mura V., Gracia-Sancho J. *et al.* Sinusoidal Endothelial Dysfunction precedes inflammation and fibrosis in a model of NAFLD. PloS One 2012; 7: e32785.
102. Miyao M., Kitani H., Ishida T. *et al.* Pivotal role of liver sinusoidal endothelial cells in NAFLD/NASH progression. Lab. Invest. 2015; 95: 1130–1144.
103. Fan Y., Wei F., Show Y., Zhang H. Association of non-alcoholic fatty liver disease with impaired endothelial function by flow-mediated dilation: a meta-analysis. Hepatol. Research. 2016; 46: 165–173.
104. Long M.T., Wang N., Larson M.G. *et al.* Nonalcoholic fatty liver disease and vascular function cross analysis in the Framingham heart study. Arterioscler. Thromb. Vasc. Biol. 2015; 35: 1284–1291.
105. Schindhelm R.K., Diamant M., Bakker S.J. *et al.* Liver alanine aminotransferase, insulin resistance and endothelial dysfunction in normotriglyceridaemic subjects. Eur. J. Clin. Invest. 2005; 35: 369–374.
106. Fracanzani A.L., Valenti L., Bugianesi E. *et al.* Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. Hepatology 2008; 48: 792–798.
107. Katsiki N., Milehalidis D.P. Emerging Vascular Risk Factor in Women: any differences from men. Curr. Med. Chem. 2015; 22: 3565–3579.
108. Cai J., Zhang Sh., Huang W. Association between nonalcoholic fatty liver disease and carotid atherosclerosis: a meta-analysis. Int. J. Clin. Exp. Med. 2015; 8: 7673–7678.
109. Brea A., Mosquera D., Martin E., Arizti A., Cordero J.L., Ros E. Nonalcoholic fatty liver disease is associated with carotid atherosclerosis: a case-control study. Arterioscler. Thromb. Vasc. Biol. 2005; 25: 1045–1050.
110. Nambi V., Chambless L., Folsom A.R. *et al.* Carotid intima-media thickness and presence or absence of plague improves prediction of coronary heart disease risk: THE ARIC (Atherosclerosis Risk In Communities study). J. Am. Coll. Cardiol. 2010; 55: 1600–1607.
111. Nagvi T.Z., Lee M.S. Carotid intima-media thickness and plague in cardiovascular risk assessment. JACC Cardiovasc. Imaging 2014; 7: 1025–1038.
112. Kuzminova N.V., Osovska N.Y., Lozinsky S.E., Knyazkova I.I. Characteristics of changes and clinical and instrumental predictors of the severity of structural remodelling of carotid arteries in hypertensive patients. Arterial Hypertens. 2016; 20: 60–67.
113. Yingchoncharoen T., Limpijankit T., Jongjirasiri S., Laothamatas J., Yamwong S., Sritara P. Arterial stiffness contributes to coronary artery disease risk prediction beyond the traditional risk score (RAMA-EGAT score). Heart Asia 2012; 4: 77–82.
114. Brant L., Hamburg N.M., Barreto S.M., Benjamin E.J., Ribeiro A.L. Relation of Digital Vascular Function, Cardiovascular Risk Factor and Arterial Stiffness: The Brazilian Longitudinal Study of Acute Health (ELSA-Brasil) Cohort Study. J. Am. Heart Assoc. 2014; 3: e001279
115. Chou C.Y., Yang Y.C., Wu S.S., Sun Z.J., Lu F.N., Chang C.J. Non-alcoholic fatty liver disease associated with increased arterial stiffness in subjects with normal glucose tolerance but not prediabetes and diabetes. Diab. Vasc. Dis. Res. 2015; 12: 359–365.
116. Lee Y.I., Shim J.Y., Moon B.S. *et al.* The relationship between arterial stiffness and nonalcoholic fatty liver disease. Dig. Dis. Sci. 2012; 57: 196–203.
117. Yu X., Zhao Y., Song X., Song Z. Association between nonalcoholic fatty liver disease and arterial stiffness in the non-obese, non-hypertensive, non-diabetic young and middle-aged Chinese population. J. Zhejiang Univ. Sci. B. 2014; 15: 879–887.
118. Ozturk K., Kurt O., [Dogan] T. *et al.* Pentraxin 3 is a predictor for fibrosis and arterial stiffness in patients with nonalcoholic fatty liver disease. Gastroenterol. Res. Pract. 2016; 2016: 1417962.
119. Pierce G.L., Zhu H., Darracott K. *et al.* Arterial Stiffness and Pulse-Pressure Amplification in Overweight Obese African-American Adolescents Relation with Higher Systolic Pulse Pressure. Am. J. Hypertens. 2013; 26: 20–26.
120. Dzyak G.V., Kolesnik E.L. Vascular wall stiffness and atherosclerotic changes of carotid arteries in men suffering from hypertension. Ukrayinskiy terapevtichniy zhurnal 2015; 2: 16–23.
121. Chung G.E., Choi S.Y., Kim D. *et al.* Nonalcoholic fatty liver disease as a risk factor of arterial stiffness measured by the cardioankle vascular index. Medicine/Baltimor 2015; 94:e654.
122. Lewis J.R., Mohanty S.R. Nonalcoholic fatty liver disease: a review and update. Dig. Dis. Sci. 2010; 55: 560–578.