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Original Research

The interrelation between cardiometabolic risk biomarkers and clinical features of chronic coronary syndrome in patients with non-alcoholic fatty liver disease

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Abstract

Summary: Non-alcoholic fatty liver disease (NAFLD) is considered to be one of the states associated with metabolic syndrome that significantly worsens the course of chronic coronary syndrome (CCS). Nowadays it is important to determine the common mechanisms of CCS and NAFLD progression in order to develop a comprehensive and individualized approach to the management of patients with this comorbid pathology. **The aim of the study:** To study the interrelation between metabolic, pro-inflammatory disorders' biomarkers and endothelial dysfunction with the clinical features of CCS in patients with NAFLD. **Materials and methods:** The monocenter double open study in parallel groups' co-sex. All patients underwent a biochemical study to determine the parameters of carbohydrate, lipid spectrum, functional state of the liver, enzyme-linked immunosorbent assay to determine the content of biomarkers (adiponectin, resistin, insulin, asymmetric dimethylarginine, highly sensitive C-reactive protein), daily Holter ECG monitoring and two-dimensional echocardiography. **Results and discussion**: In CCS patients with NAFLD a significant decrease in serum adiponectin level was found (by 60% if compared to the selected control group, and by 31.6% if compared to the comparison group; $p<0.05$) and an increase in resistin level (by 48% if compared to the selected control group, and by 27% if compared to the comparison group; $p<0.05$). In patients of the main group the ratio of adiponectin/resistin was 4.89 times lower if compared to healthy individuals and 1.48 times lower if compared to CCS patients without liver pathology ($p<0.05$). There was a significant increase in the HOMA-IR index in CCS patients with NAFLD if compared to both healthy individuals and CCS patients without NAFLD – 5 times and 2.35 times, respectively ($p<0.05$). Correlation analysis revealed the interrelation between adipocytokine imbalance, endothelial dysfunction markers, systemic inflammation with metabolic disorders, and indicators of liver damage in patients with CCS comorbid with NAFLD. It was found that the level of adiponectin, resistin, ADMA, adiponectin/resistin ratio, HOMA-IR index influences the relative risk of development of atherogenic dyslipidemia, diastolic dysfunction of the LV accompanied by LV hypertrophy, vegetative imbalance, ischemic changes, and thickening of the intima-media complex development. **Conclusions:** In CCS patients with NAFLD, if compared to patients without NAFLD, a decrease in adiponectin, an increase in resistin, ADMA, HF-CRP, HOMA-IR index is observed. The obtained results of correlation analysis and estimation of relative risk confirm the clinical and pathogenetic role of the identified cluster of metabolic, pro-inflammatory disorders, and endothelial dysfunction in the progression of CCS with concomitant NAFLD.

Keywords: chronic coronary syndrome, non-alcoholic fatty liver disease, biomarkers, interrelation.

Introduction

Chronic coronary syndrome (CCS) is one of the most pressing problems in modern medicine, as it ranks first among the causes of disabling and mortality [1–3]. Along with CCS, an important medical and social problem is gastrointestinal tract disturbances, observed in 60% of people of working age [4]. The most common chronic pathology of the hepatobiliary tract is a non-alcoholic fatty liver disease (NAFLD) [5, 6]. NAFLD affects about a third of the population and up to 70% of patients with diabetes and obesity [6, 7].

NAFLD is considered to be one of the states associated with metabolic syndrome, which significantly increases the risk of cardiovascular disease. The close connection of NAFLD with insulin resistance, type 2 diabetes mellitus, and dyslipidemia has been proven [8, 9]. Metabolic syndrome (MS) is independently related to the increased risk of overall mortality in patients with NAFLD [7, 10], and vice versa, NAFLD significantly increases the risk of MS development within a 5-year period [7, 11, 12]. International experts have recognized NAFLD as the sixth criterion of metabolic syndrome and one of the main risk factors for cardiovascular disease and its complications [6, 13]. The incidence of fatty hepatosis in patients with cardiovascular disease reaches up to 90% [14].

At present, it is important to determine the common mechanisms of CCS and NAFLD progression in order to develop a comprehensive and individualized approach to the management of patients with this comorbid pathology. It is well known that the combination of CCS with NAFLD leads to a number of neurohumoral disorders which, in their turn, affect the course of both diseases due to the common pathogenetic mechanisms [14]. An important link between hepatic steatosis and CCS is the imbalance of adipocytokines [15–18]. Among them, much attention is paid to adiponectin, which has antidiabetic, antiatherogenic and anti-inflammatory effects, and resistin, which is associated with systemic inflammation and insulin resistance [15–17].

There is a direct proven link between the severity of NAFLD, proinflammatory activation, endothelial dysfunction, and cardiovascular risk [17]. One of the modern markers of endothelial dysfunction directly related to both CCS and NAFLD is asymmetric dimethylarginine (ADMA), an endogenous inhibitor of the enzyme NO-synthetase that catalyzes the conversion of L-arginine into nitric oxide [18]. Classic biomarkers that reflect the state of systemic inflammation include C-reactive protein – a multifunctional protein synthesized by hepatocytes, alveolar macrophages, and lymphocytes present in atherosclerotic plaque under the influence of interleukin-6 [19].

Thus, today it is relevant to study the level of these biomarkers in order to clarify their clinical and pathogenetic role in comorbid pathology, as well as their interrelation with the clinical course, structural, functional, ischemic [20], and autonomic changes of the heart in patients with the chronic coronary syndrome with concomitant NAFLD.

The aim of the study

To study the interrelation of biomarkers of metabolic, pro-inflammatory disorders, and endothelial dysfunction with the clinical features of chronic coronary syndrome in patients with non-alcoholic fatty liver disease.

Materials and methods

The monocenter double open study in parallel groups involved 120 CCS patients: stable angina pectoris of the II–III functional class aged 60.0 (55.0; 64.0), of whom 67 (55%) are men and 53 (45%) are women. The selected control group included 30 healthy individuals aged 59.0 (58.0; 66.0), including 14 (46%) men and 16 (54%) women. The design of the study was agreed upon with the Commission on Bioethics of Zaporizhzhia State Medical University, with a conclusion on total compliance to moral and ethical standards of bioethics in accordance with ICH/GCP, Helsinki Declaration of Human Rights (1964), European Council Convention on Human Rights and Biomedicine 1997), as well as current legislation of Ukraine.

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Criteria for inclusion in the study: the presence of documented (verified) CCS: stable angina pectoris II–III functional class and NAFLD, written informed consent to participate in the study.

Exclusion criteria were developed to ensure reliable study results: alcoholism or liver cirrhosis, autoimmune and viral hepatitis; congenital or acquired heart defects; heart failure of the III–IV functional class by NYHA; myocardial infarction (acute, subacute periods), unstable angina; infectious diseases in the acute period; bronchial asthma or COPD; anemia (Hb<90 g/l); hypothyroidism; chronic diseases of viscera in the period of exacerbation and in decompensation stage; cancer, mental illness.

All surveyed individuals participating in the study were divided into 2 groups: 1 group (comparison) – 60 CCS patients without concomitant NAFLD; group 2 (main) – 60 CCS patients with concomitant NAFLD (steatosis or steatohepatitis). To determine the reference values of the indicators studied, the data obtained from 30 practically healthy individuals, comparable in age and sex, without cardiovascular and liver diseases, were used as controls.

The diagnosis of CCS and functional class of stable angina was based on a comprehensive analysis of complaints, physical examination data, results of laboratory and instrumental studies in full conformity with current European recommendations. Components of the metabolic syndrome in patients with CCS were determined by IDF criteria (2009). NAFLD was diagnosed according to the criteria of the World Gastroenterology Organization Global Guidelines, the adapted clinical guideline "Non-alcoholic fatty liver disease" (2014) and the unified clinical protocol of primary, secondary (specialized) medical care "Non-alcoholic steatohepatitis" (2014), after excluding other liver damage etiology. For this purpose, markers of viral hepatitis were determined, Fast-test – rapid alcohol screening test (to determine the likelihood of alcohol abuse), Fibromax test (to exclude viral, autoimmune, alcoholic liver disease affection, to determine the degree of steatosis and fibrosis) or liver puncture (to exclude other liver damage/affection causes and assess the stage of fibrosis) if needed. Patients diagnosed with non-alcoholic steatohepatitis (NASH) were forwarded to consult a gastroenterologist. According to the morphofunctional study of the liver 45 (75%) patients were diagnosed with S2–S3 steatosis stage, 15 (25%) – steatohepatitis of minimal activity. Under the METAVIR scale liver fibrosis corresponded to F0–F2 stage.

All patients underwent biochemical studies to determine glucose level, liver enzymes, total cholesterol (TC), triglycerides (TG), high – (HDL) and low-density (LDL) lipoprotein levels using a PLIVA-Lachema BIOLATEST reagent. Low-density lipoprotein levels were calculated under the Friedewald formula. Holter ECG daily monitoring was performed with a Cardiosens K instrument (KhAI MEDICA, Ukraine). To determine the signs of electrical instability of the heart, we investigated the number of cardiac arrhythmias per day.

Episodes of myocardial ischemia were assessed by ECG recording using two bipolar leads of the 5-electrode recorder cable. The criterion for myocardial ischemia on the ECG was a horizontal or oblique decrease in ST-segment by 1 mm or more from baseline, accompanied or not accompanied by anginal syndrome and/or its equivalents (shortness of breath, palpitations, irradiation of pain into the left shoulder blade, left hand, etc.), which was assessed due to patient diaries. The following indicators were evaluated: duration of ST-segment depression during the day (on both channels), expressed in minutes; duration of the maximum episode of depression of the ST-segment, minutes; the level of the ST-segment depression, μV, and the maximum level of depression in the form of the maximum amplitude of the offset below the isoline (on both channels), μV.

While analyzing heart rate variability (HRV), the time-domain and frequency-domain methods recommended by the Committee of Experts of the North American Society of Stimulation and Electrophysiology, the European Society of Cardiologists, and the Ukrainian Association of Cardiologists were used. Two-dimensional echocardiography and pulse-wave Doppler were performed using the Esaote MyLab 50 XVision ultrasound scanner under the generally accepted practice according to ASE/EAE

recommendations (2011). Quantitative and qualitative characteristics of the state of the intima-media complex (IMC) of the common carotid arteries (CCA) were evaluated under ultrasound visualization in B-mode. An increase in the thickness of IMC by more than 0.9 mm was considered to be a marker of atherosclerotic vascular damage.

During the 1–3 days of hospital stay, a comprehensive clinical examination was performed, with an account of complaints, anamnesis data, objective and additional (laboratory and instrumental) research methods in accordance with generally accepted standards. Determination of biomarkers serum levels was performed on the basis of the Training Medical and Laboratory Center of Zaporizhzhia State Medical University on the enzyme-linked immunosorbent assay full-plate analyzer "SIRIO S" (Italy). Serum insulin levels were examined using a kit of reagents manufactured by Monobind (USA); asymmetric dimethylarginine – Immundiagnostik (Germany); adiponectin and resistin – Mediagnost (Germany); CRP – Biomerica (USA) according to the instructions included in the kit. The HOMA index was calculated by the formula: HOMA-IR = serum insulin (μIU/ml) × plasma glucose (mmol/l)/22.5. HOMA-IR values above 2.27 are estimated as IR.

Statistical data processing was carried out using the variation statistics method with the help of the software package "Statistica 13.0" (StatSoft Inc., no JPZ8041382130ARCN10-J), under the generally accepted practice. The pattern of the distribution of the studied variables was assessed using Shapiro-Wilk's criterion. Quantitative characteristics were represented as M±m (arithmetic mean±standard error of the arithmetic mean) or Me (Q25; Q75) (median, 25, and 75 distribution quartiles) depending on the type of data distribution. Under the normal distribution, the validity of the differences was estimated using the Student's T-criterion; under the distribution different from normal, Mann-Whitney's non-parametric U-criterion was used. Assessment of the interrelation between pairs of independent indexes, expressed in a quantitative scale, was performed by calculating Pearson rank correlation coefficients (under normal distribution) or Spearman rank correlation coefficients (under a distribution different from normal). To quantify the interrelationship between the impact of a specific factor and the type of pathological changes, a relative risk (RR) analysis was performed, with a 95% confidence interval (CI) determined by constructing four-field tables. When constructing the tables the following indicators were taken into account: presence/absence of atherogenic dyslipidemia, IMC thickening of the CCA over 0.9 mm, dilation of the right and left ventricles, systolic (left ventricular ejection fraction less than 45%) and diastolic dysfunction (rated less than 1), of the left ventricle (LV), sympathetic-parasympathetic imbalance (LF/HF the ratio is higher than 2), and ischemic myocardial changes (ST-segment depression episodes significant in-depth and duration). At relative risk (RR)>1, the probability of occurrence of an adverse outcome in the group with exposure to the risk factor is higher, and at RR<1 is lower than in individuals not exposed to the risk factor. Differences were considered statistically significant at $p<0.05$.

Results and discussion

Changes in biomarkers that reflect metabolic, pro-inflammatory disorders, and endothelial dysfunction in CCS patients depending on the presence of concomitant NAFLD are presented in Figures 1–6.

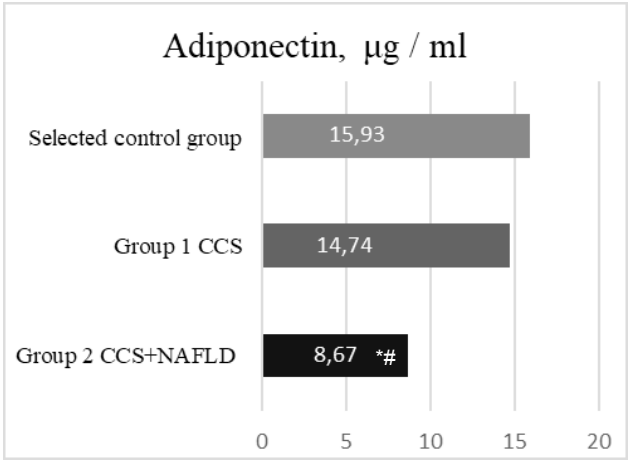

Figure 1: The level of adiponectin in CCS patients depending on the presence of concomitant NAFLD.
Note. *The probability of difference if compared to the selected control group ($p<0.05$); #The probability of the difference if compared to the patients with CCS ($p<0.05$).

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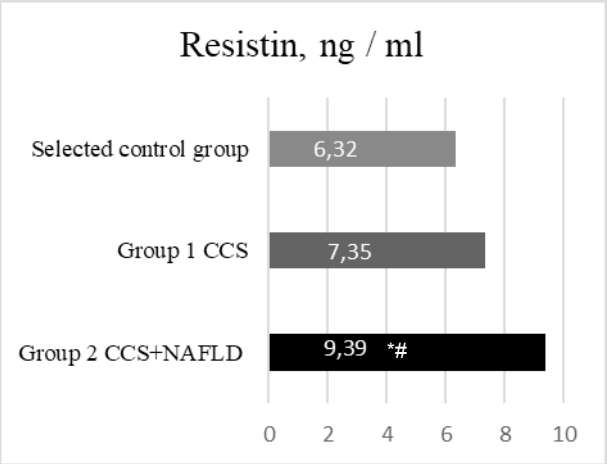

Figure 2: The level of resistin in CCS patients depending on the presence of the concomitant NAFLD.
Note.*The probability of difference if compared to the selected control group (p<0.05); #The probability of the difference if compared to the patients with CCS (p<0.05).

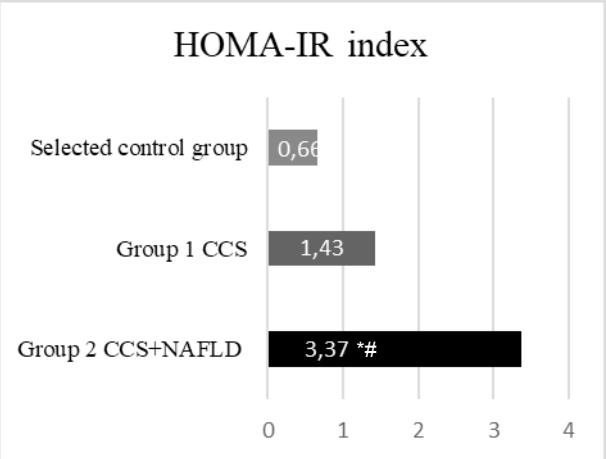

Figure 4: HOMA-IR index in CCS patients depending on the presence of concomitant NAFLD.
Note. *The probability of difference if compared to the selected control group (p<0.05); #The probability of the difference if compared to the CCS patients (p<0.05).

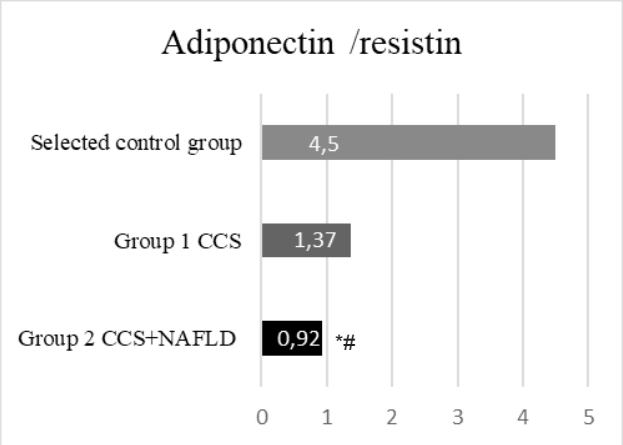

Figure 3: The adiponectin / resistin ratio in CCS patients depending on the presence of concomitant NAFLD.
Note. *The probability of difference if compared to the selected control group (p<0.05); #The probability of the difference if compared to the CCS patients (p<0.05).

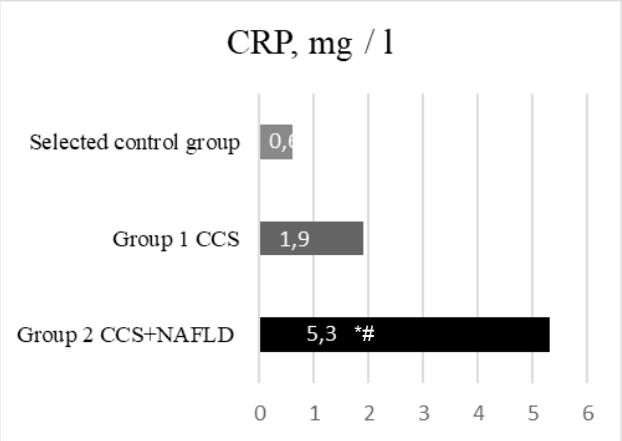

Figure 5: The level of hs-CRP in CCS patients depending on the presence of concomitant NAFLD.
Note. *The probability of difference if compared to the selected control group (p<0.05); #The probability of the difference if compared to the CCS patients (p<0.05).

In CCS patients with NAFLD, a significant decrease in serum adiponectin levels was found (60% lower if compared to healthy individuals and 31.6% lower than in the comparison group; p<0.05). At that time, the level of resistin was 48% higher than in the selected control group and 27% higher than in the comparison group (p<0.05). At the same time, patients with CCS without NAFLD did not differ significantly from healthy individuals in terms of adiponectin and resistin levels.

In patients of the main group a significant decrease in the ratio of adipocytokines was observed: adiponectin/resistin ratio was 1.48 times lower than in CCS patients without liver pathology and 4.89 times lower than in healthy individuals (p<0.05). There was also a significant increase in the HOMA index compared to healthy individuals by 5 times, with patients with CCS – by 2.35 times, respectively (p<0.05), indicating the presence of insulin resistance.

According to the CRP level the patients in the main group had an 8.9 times higher increase than in the selected control group and a 2.81 times higher increase than in the comparison group (p<0.05). It was found that in CCS patients with concomitant NAFLD, the ADMA serum level was 42% higher than in healthy individuals, and 21%

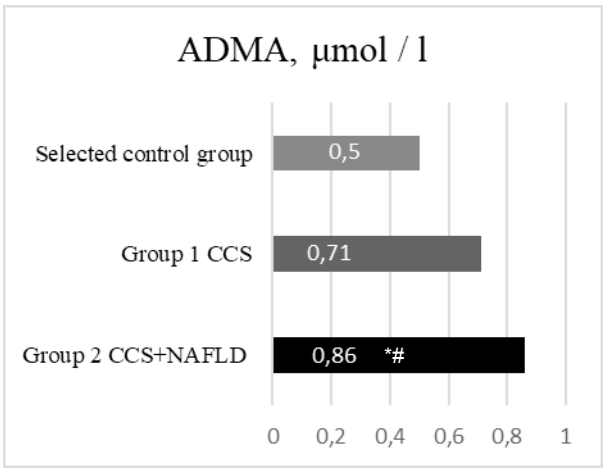

Figure 6: ADMA level in CCS patients depending on the presence of concomitant NAFLD.
Note. *The probability of difference if compared to the selected control group (p<0.05); #The probability of the difference if compared to the CCS patients (p<0.05).

higher if compared to the group of CCS patients without liver pathology (p<0.05). Thus, there is an adipocytokines imbalance in the insulin resistance background, systemic inflammation, and endothelial dysfunction in CCS patients with concomitant NAFLD, if compared to the patients without NAFLD.

While conducting the adipocytokine levels' correlation analysis, markers of endothelial dysfunction with metabolic disorders in patients with CCS comorbid with NAFLD, a reliable direct strong interrelation of adiponectin levels with HDL cholesterol (r=+0.72; p<0.05) and medium-strength feedback with the cholesterol concentration (r=-0.57; p<0.05), LDL cholesterol (r=-0.44; p<0.05), triglyceride level (r=-0.59; p<0,05), atherogenic index (r=-0,50; p<0,05) was revealed. The increase in resistin levels was associated with an increase in insulin (r=+0.42; p<0.05), glucose (r=+0.59; p<0.05) and atherogenic index (r=+0.54; p<0.05). ADMA is directly related to the level of cholesterol (r=+ 0.53; p<0.05), insulin concentration (r=+0.43; p<0.05) and HOMA-IR index (r=+0.49, p<0.05). The reliable relation between CRP levels and anthropometric parameters, carbohydrate and lipid metabolism was not specified.

Correlative interrelations between the level of CRP and alanine aminotransferase (r=+0.51; p<0.05), adiponectin and gamma-glutamyltranspeptidase (r=-0.48; p<0.05), resistin and alkaline phosphatase (r = + 0.48; p <0.05), ADMA and alkaline phosphatase (r=+ 0.63; p<0.05) were found, which indicates the relationship between adipocytokine imbalance, endothelial dysfunction, systemic inflammation with indicators of liver damage.

We further calculated the relative risk and established reliable (p<0.05) interrelations between biomarkers and factors of chronic coronary syndrome progression concomitant with NAFLD, the integrated scheme of which is presented in Figure 7.

According to the results of the relative risk analysis, the level of resistin had a probable interrelationship with the thickening of the intima-media complex (RR=1.7; CI=1.049–2.968; p<0.05). The level of ADMA exerted a significant influence on the development of atherogenic dyslipidemia (RR=2.3; CI=1.077–5.309; p<0.05), the state of diastolic LV function (RR=1.8; CI=1.036–3.422; p<0.05), ischemic changes of the myocardium (RR=1.8; CI=1.011–3.240; p<0.05), imbalance and decrease in total HRV (RR=3.8; CI=1.061–13.795; p<0.05), the thickness of the intima-media complex of the CCA (BP=2.2; CI=1.017–5.076; p<0.05).

An increase in adiponectin levels significantly increased the risk of LV diastolic dysfunction (RR=3.2; CI=1.326–7.967; p<0.05). The HOMA-IR index exerted a significant influence on the development of atherogenic dyslipidemia (RR=1.8; CI=1.050–5.484; p<0.05), myocardial ischemic changes (RR=2.4; CI=1.050–5.484; p<0.05), imbalance and decrease in total HRV (RR=2.9; CI=1.190–7.229; p<0.05).

The adiponectin/resistin ratio had a probable interrelationship with the development of atherogenic dyslipidemia (RR=3.7; CI=1.00–4.050; p<0.05), with the state of diastolic function (RR=2.4; CI=1.081–5.330; p<0.05), with the imbalance and decrease in total HRV (RR=3.0; CI=1.207–7.455; p<0.05) and with the development of left ventricular hypertrophy (RR=2.1; CI=1.183–3.882; p<0.05).

We have found the presence of adipocytokine imbalance due to a decrease in adiponectin levels and an increase in resistin levels in patients with CCS in combination with NAFLD. The association of adipocytokines with indicators of liver

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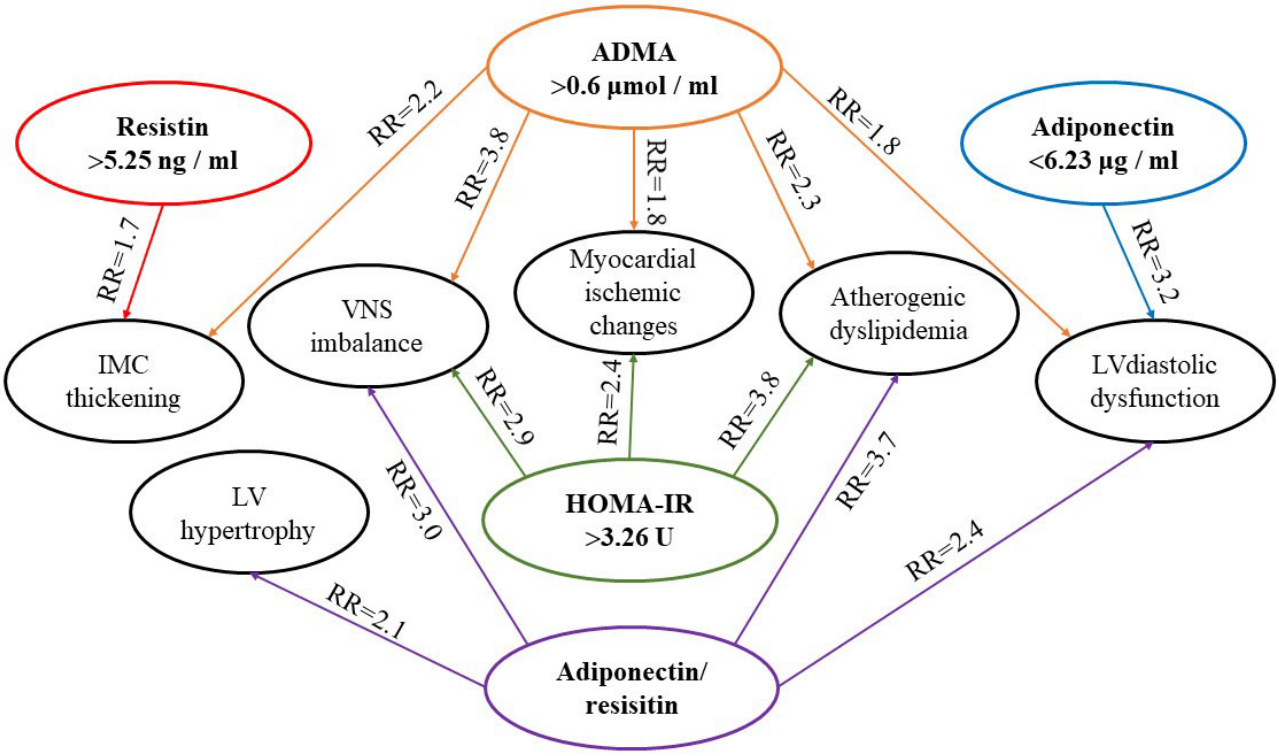

Figure 7: The interrelationship between biomarkers and the clinical course of CCS with concomitant NAFLD. IMC – intima-media complex, LV – left ventricle, RR – relative risk, ADMA – Asymmetric dimethylarginine, HOMA-IR – Homeostasis Model Assessment of Insulin Resistance, VNS – vegetative nervous system, RR – relative risk.

damage, clinical course, structural–functional, ischemic, and autonomic changes in the hearts in patients with CCS with concomitant NAFLD was also found, indicating their importance in the progression of these combined diseases. The data obtained are confirmed by a number of studies indicating the clinical significance of hypoadiponectinemia as a risk factor for cardiovascular disease and NAFLD [16, 17, 21]. It has been established that adiponectin levels are reduced and inversely correlated with the severity of inflammation and liver damage in patients with NAFLD, and adiponectin has been shown to reduce steatosis in high-calorie diets, obesity, and insulin resistance [16, 22]. It has been found that adiponectin inhibits the differentiation of preadipocytes, reduces gluconeogenesis in the liver, increases the oxidation of fatty acids in muscles and reduces IR. In addition, adiponectin exerts a direct effect on endothelial function by reducing endothelial cell damage and stimulating nitric oxide production, as well as an indirect one through membrane-bound receptors and adapter molecules of endothelial cells [15, 16]. The effect of adiponectin on the process of remodeling of cardiomyocytes can be explained by its ability to reduce the degree of hypertrophy through stimulation of the signaling pathway dependent on AMP kinase in cardiomyocytes [23].

In our study, in patients with CCS and NAFLD, an increase in resistin, a peptide hormone belonging to the cysteine-enriched proteins class of the RELM family, also called ADSF (Adipose Tissue-Specific Secretory Factor) was found. This can be explained by the fact that resistin is another important cytokine involved in the pathogenesis of NAFLD, as its main target organ is the liver. The interrelation between resistin and components of the metabolic syndrome and its role in NAFLD has been studied in a number of studies [17, 24]. A positive correlation was found between the degree of obesity, insulin resistance, and increased resistin level [24, 25]. The increase in serum levels of resistin in patients with NAFLD and the presence of a positive relationship between inflammation in the liver and the severity of fibrosis have been proven [26]. Currently, much attention is also paid to

the pleiotropic effects of resistin and its biological functions: participation in systemic inflammation, endothelial dysfunction, thrombosis, angiogenesis, smooth muscle cell dysfunction, and more. Therefore, it is suggested that resistin may act as a link between inflammation, metabolic syndrome, and CCS [27].

According to the study results, it was found that in patients with CCS comorbid with NAFLD, if compared to patients without structural and functional changes in the liver, more pronounced manifestations of insulin resistance according to the HOMA-IR index were observed, which had significant relationships with the risk of imbalance and reduced ANS variability, ischemic changes in the myocardium, atherogenic dyslipidemia and the development of endothelial dysfunction. The data obtained confirm the important role of insulin resistance in the pathogenesis of CCS. Thus, according to current data, IR promotes the formation of triglycerides, low- and very-low-density lipoproteins, their transportation into the vascular wall [28, 29], as well as collagen formation and proliferation of vascular smooth muscle cells, activation of systemic inflammation and endothelial dysfunction, which is the basis of the CCS progression.

The results also coincide with the opinion of some authors that among patients with NAFLD there is a higher frequency of registration of insulin resistance and other components of the metabolic syndrome compared to patients without NAFLD [30]. It is important to note that the close pathogenetic link of NAFLD with obesity, insulin resistance (IR), hypertension, and dyslipidemia allows us to consider non-alcoholic fatty degeneration as a hepatic manifestation of MS [25, 26, 30]. Moreover, it is currently believed that not only can IR lead to NAFLD, but the fatty liver disease itself can cause hepatic IR [27].

In our study of markers of systemic inflammation and endothelial dysfunction, serum ADMA was higher in patients with HCV with concomitant NAFLD than in patients without NAFLD and was likely to be associated with hepatic function, metabolic disturbances, and CCS progression factors, the persistence of systemic inflammation by the level of hs-CRP. This may indicate the pathogenetic significance of these markers in the development and the CCS progression with the concomitant NAFLD. According to Hill M. A., et al. (2021), the development of endothelial dysfunction is a universal tissue response to insulin resistance and inflammatory stress, which are characteristic of both CCS and NAFLD [30]. It is established that the generally accepted indicators of endothelial dysfunction (endothelium-dependent vasodilation, circulating endotheliocytes) progressively deteriorate with the increasing severity of liver damage and are associated with changes in its functional state [30]. Elevated levels of ADMA have been found in various cardiovascular diseases, including CCS. According to recent studies, elevated plasma ADMA levels are associated with risk factors for CCS such as hypertension, type 2 diabetes, insulin resistance, hypercholesterolemia, hypertriglyceridemia, hyperhomocysteinemia, etc. [30, 31].

Thus, NAFLD in patients with CCS is associated with accelerated development of atherosclerosis, insulin resistance, imbalance of the adipokine profile, activation of systemic inflammation, endothelial and autonomic dysfunction, cardiovascular remodeling, which is confirmed by our results of correlation analysis and calculation of relative risk.

Conclusions

In patients with CCS with NAFLD, if compared to patients without NAFLD, there are more pronounced manifestations of metabolic disorders: imbalance of adipocytokines (decrease in adiponectin and increase in resistin), insulin resistance backgrounded by endothelial dysfunction and persistence of systemic inflammation, which have the interrelations with indicators of liver damage.

The level of adiponectin, resistin, ADMA, adiponectin/resistin ratio, HOMA index impacts the relative risk of development of atherogenic dyslipidemia, diastolic dysfunction of the LV accompanied by LV hypertrophy, vegetative imbalance, ischemic changes, and thickening of the intima – media complex development.

The obtained results of correlation analysis and calculation of relative risk confirm the

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clinical and pathogenetic role of the identified cluster of metabolic, pro-inflammatory disorders, and endothelial dysfunction in the CCS progression of CCS with concomitant NAFLD.

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Conflict of Interest

The authors declare no conflict of interest.

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