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Features of clinical, biochemical, and sonographic parameters in patients with chronic viral hepatitis C with concomitant non-alcoholic fatty liver disease

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Abstract

Introduction. Difficulties encountered in treating patients with chronic viral hepatitis C (CHC) are associated with the presence of concomitant liver pathology, namely, fatty degeneration which contributes to the progression of HCV infection. The above circumstances prompted the authorsled to thoroughly examine this category of patients for further development of a new pathogenetically directed course of treatment.

Objective. The aim of the study was to investigate the clinical, biochemical, and instrumental features of the course of liver disease in CHC patients with concomitant non-alcoholic fatty liver disease (NAFLD).

Materials and method. The study included 339 patients with chronic hepatitis C with concomitant NAFLD, and 175 patients with CHC. Methodology: anamnestic, anthropometric and clinical, general clinical, biochemical, serological, and molecular genetic (markers of hepatitis C virus, HCV RNA PCR (qualitative and quantitative determination, genotyping), enzyme-linked immunosorbent assay, ultrasonographic examination of digestive organs, and statistical methods were used.

Results. The clinical, instrumental, and laboratory studies showed that CHC patients with concomitant NAFLD are characterized by various disorders – a violation of the functional state of the liver, a violation of carbohydrate and lipid metabolism, an imbalance of the cytokine system, as well as the presence of histological and non-inflammatory activity in the liver.

Conclusions. The presence of concomitant NAFLD in patients with CHC aggravates the clinical picture, manifesting itself in a significant lipid metabolism disorder that provokes the rapid formation of liver fibrosis. An additional complicating factor is the development of insulin resistance, leading to persistent morphological changes in the liver parenchyma.

Key words

chronic viral hepatitis C, non-alcoholic fatty liver disease, diagnostic methods

INTRODUCTION

Liver disease is a significant cause of disability and death worldwide. Chronic viral hepatis (CHC) remains one of the most critical problems of modern medicine due to its widespread, progressive increase in incidence, high level of chronicity, risk of developing liver cirrhosis and hepatocellular carcinoma, lack of specific prevention, and high cost of treatment [1, 2].

According to WHO expert estimates, the number of people infected with the hepatitis C virus is 325 million, and the number of patients dying annually due to this pathology reaches 1.4 million [3]. Therefore, the social and medical significance of this pathology determines its intensive study. According to various studies, liver steatosis is observed in almost 50% of patients infected with the hepatitis C virus. The presence of non-alcoholic fatty liver disease (NAFLD) in patients with CHC contributes to the onset and further progression of fibrosis, from the initial stages to liver cirrhosis in a short time. On the one hand, the hepatitis C virus can cytotoxically lead to direct damage to the liver or, in a genotype-specific way, to its fatty degeneration. On the other hand, the presence of such risk factors as insulin resistance (IR), diabetes mellitus, obesity, intestinal dysbiosis, and epigenomic damage, lead to the independent formation of NAFLD, which affects the development of the necrobiotic process in the liver tissue, which leads to the progression of fibrosis [4, 5, 6, 7, 8, 9, 10, 11, 12].

OBJECTIVE

The aim of the study was to investigate the clinical, biochemical, and instrumental features of the course of liver disease in CHC patients with concomitant non-alcoholic fatty liver disease (NAFLD).

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MATERIALS AND METHOD

The study included 339 patients with chronic hepatitis C (genotype 1b in the replication phase, minimal and moderate activity) with concomitant NAFLD (Group 1). The mean age of patients ranged from 32 – 58 years, average 42.13±8.64 years. Among the studied patients, women accounted for 172 (50.74%) patients and men 167 (49.26%) patients. The control Group consisted of 175 patients with CHC (Group 2). The distribution by gender was as follows: 88 (50.27±3.78)% of the examined were women, and 87 (49.71±3.78)% were men. The mean age of patients in this Group ranged from 34–56 years and averaged (46.28±7.82) years.

The patients were under observation in the clinic for the rehabilitation treatment of patients with a gastroenterological profile of the State Institution 'Ukrainian Research Institute of Medical Rehabilitation and Resort Therapy of the Ministry of Health of Ukraine' in Odesa, Ukraine.

The study used anamnestic, anthropometric, and clinical methods, and carried out a survey of general clinical, biochemical, enzyme immunoassay parameters of blood (to assess the state of metabolic processes, functional state of the liver, profile of cytokines), serological markers of viral hepatitis C and molecular genetic parameters – RNA PCR (qualitative and quantitative determination, genotyping). An ultrasonographic study of the digestive organs was also carried out to assess the state of the hepatobiliary system.

The diagnosis of CHC was established according to the International Classification of ICD-11 and the International Classification of Liver Diseases (Los Angeles, 1994), which was confirmed by the detection of total anti-HCV in the blood, and determination of the presence and amount of hepatitis C virus RNA by serum PCR.

The diagnosis of NAFLD was established based on a comprehensive examination by Order No. 826 of the Ministry of Health of Ukraine dated 6 November 2014 'On approval and implementation of medical and technological documents for standardization of medical care for chronic non-infectious hepatitis', recommendations of the European Association for the Study of the Liver, European Association for the Study of Diabetes and European Association for the Study of Obesity [13].

The dynamics of the clinical course of CHC and concomitant NAFLD were assessed based on the study of the severity of pain, dyspeptic and asthenic syndromes. To diagnose overweight, the body mass index (BMI) we calculated, and to determine the type of obesity, two indicators were measured: waist circumference (WC) and hip circumference (HC), and their ratio (WC/HC) calculated.

The functional state of the liver was assessed by biochemical parameters of blood serum. The liver pigment function was studied by determining unconjugated and conjugated bilirubin. Cytolysis syndrome was determined by the activity of indicator enzymes: alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The protein-synthetic function of the liver was assessed by determining the total protein. Cholestasis syndrome was evaluated by the activity of alkaline phosphatase (APH) and gamma-glutamyl transpeptidase (GGTP). Lipid metabolism was studied by the content of total cholesterol (TC), β-lipoproteins, low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides (TG), and atherogenic coefficient (CA) [14, 15].

The homeostatic model assessment of the HOMA-IR index (according to Matthews DR, 1985) was used. Serological markers of viral hepatitis C (HCV RNA PCR, quantification and genotyping) were used to diagnose the viral load level and genotype of HCV infection. To assess the level of fibrosis, the activity of the inflammatory process, and steatosis, the Fibro Max panel was used, a combination of five non-invasive tests: FibroTest, ActiTest, SteatoTest, NashTest, and AshTest. Used FibroTest, ActiTest, SteatoTest from this panel [16, 17].

The cytokine profile was studied by determining adiponectin using the standard kit 'Mediagnost Adiponectin ELISA E09'and leptin using the standard kit EIA-2395, Leptin (Germany). The obtained data were statistically processed using the STATISTICA 5.0 software (Stat. Soft. Inc., USA).

RESULTS

In Group 1 – 207 patients, active HCV replication (positive PCR HCV RNA) was detected, of which a low level (≤800,000 IU/ml) of the virological load was observed in 124 (59.90%) of the patients, and a high level of virological load (>800,000 IU/ml) in 83 (40.09%) patients. These patients were diagnosed with genotype 1b.

Anamnestic data analysis determined the acceptable duration of COS, which ranged from eight months to nine years. The study of the epidemiological history determined the main ways of infection of patients with HCV infection; thus, in the majority of 298 (87.91%) patients, various medical (surgical and dental interventions, transfusion of whole blood or its components, invasive medical and diagnostic procedures) and non-medical manipulations (piercing, manicure, tattooing) took place. In 41 examined patients (12.09%) it was impossible to identify the route of infection.

Concomitant diseases of the digestive system in patients were primarily represented by chronic non-calculous cholecystitis – 186 (54.86%) patients, and chronic pancreatitis – 144 (42.47%) of cases.

When interviewing patients, asthenic, dyspeptic, and pain abdominal syndromes of varying severity were identified (Tab. 1).

Table 1. Frequency of clinical syndromes in patients (%)

Syndrome	Group 1 (n = 339)	Group 2 (n = 175)	p
Asthenic syndrome	79.61	73.71	<0.05
Dyspeptic syndrome	68.73	66.86	>0.05
Abdominal pain syndrome	60.17	61.1	>0.05

Signs of asthenic syndrome dominated the clinical picture of the disease. The main manifestations of asthenic syndrome (weakness, increased fatigue) were noted by 79.61% patients of 1st Group and 73.71% of 2nd Group. Indications of dyspeptic syndrome (heartburn, bitterness in the mouth, nausea, belching with air) were identified in 68.73% patients in Group 1, and 66.86% of Group 2 simultaneously. Pain or a feeling of heaviness in the right hypochondrium dominated among the signs characterizing the abdominal pain syndrome; this was noted in 60.17% of and 61.10% of Group 2. In 39.23% patients in Group 1 and 30.28% of Group 2, intestinal dysfunction was observed.

As follows from the data obtained, in patients with chronic hepatitis C with concomitant NAFLD and chronic hepatitis C, almost the same distribution of asthenic, dyspeptic, and abdominal pain syndromes was observed. However, a slight increase in the percentage of an asthenic syndrome in the chronic hepatitis C with concomitant NAFLD Group should be noted.

An objective examination of Group 1 patients revealed pain on palpation of the right hypochondrium in 231 (68.14%) patients. Hepatomegaly was determined in 264 (77.87%) patients. In 123 (36.28%) of the examined patients, the pain was detected in the Kerah point; pain in the left hypochondrium was somewhat less – 107 (31.56%) patients. Pain on palpation of the pyloroduodenal area in 85 (25.07%) and colon sections in 68 (20.05%) patients was much less. Examination of patients of the Group 2 revealed similar symptoms. The only significant difference was a significantly lower number of hepatomegaly ($p<0.05$) (Tab. 2).

Table 2. Frequency of objective signs of the disease (%)

Signs	Group 1 (n = 339)	Group 2 (n = 175)	p
hepatomegaly	77.87	53.14	<0.05
pain in the right hypochondrium	68.14	59.71	>0.05
pain in the left hypochondrium	31.56	44.57	>0.05
pain in the pyloroduodenal area	25.07	28.57	>0.05
pain in the Kerah point	36.28	43.43	>0.05

According to the results of the anthropometric study, the average body mass index of the examined patients of Group 1 was (31.97±2.32) kg/m^2. At the same time, overweight was diagnosed in 82 (24.2%) patients, obesity of the first degree – in 212 (62.5%) patients, obesity of the second degree – in 45 (13.3%) patients. Measurement of the WC/HC ratio showed that the majority of patients – 288 (84.95%), had an android type of adipose tissue distribution, that is, abdominal obesity. Anthropometric data of patients of Group 2 did not differ significantly from those in Group 1: the average BMI was 28.49±2.78 kg/m^2, overweight was diagnosed in 50 (28.6%) patients, obesity of the first degree in 100 (57.1%) patients, obesity of the second degree in 25 (14.3%) patients.

A general blood test revealed the following changes: in 62 (18.3%) patients, an increase in the level of lymphocytes was observed, and in 54 (15.9%) of the examined patients, an increase in the level of ESR in 53 (15.6%) and an increase in the number of monocytes. The presence of thrombocytopenia was diagnosed in 42 (12.4%) patients and leukocytopenia in 31 (9.1%) patients, respectively. The rest of the general blood test parameters were within the normal range. All the studied blood parameters in Group 2 were within the normal range.

Analysis of the biochemical study of blood serum revealed a violation of the functional state of the liver in most patients (Tab 3).

Among the examined patients of Group 1, the phenomena of cytolytic syndrome dominated due to the increase in the level of ALT in 294 (86.72%) patients, and in 267 (78.76%) patients. This is significantly higher than the values of patients in Group 2, both in terms of the level of ALT and in the percentage of patients. An upward trend in the level of AST was noted in both groups, with no significant differences. Manifestations of the mesenchymal-inflammatory reaction in the form of an increase in the thymol test were significantly higher in Group 1: 42.47% patients, the average for this group was 9.13±0.87 units versus 29.6% in Group 2, and the average level – 7.63±0.92 units. Similarly, signs of cholestatic syndrome due to increased APH and GGT were significantly higher in Group 1. The albumin level did not exceed normal values in both Groups.

Violation of lipid metabolism was observed in 100% of patients in both groups, and were unidirectional. The most remarkable differences between groups were observed in the level of increase in the concentration of total cholesterol, triglycerides, and LDL ($p<0.001$). Such changes in the blood lipid spectrum were accompanied by a decrease in HDL level, which led to a significant increase in the atherogenic coefficient, in Group 1 up to (3.29±0.36) U.

Table 3. Indicators of biochemical composition of blood (M±m).

Indicator	Level	Group 1 (n = 339)	No. of patients, %	Group 2 (n = 175)	No. of patients, %	p
Total bilirubin, μmol/l	increased normal	26.79±2.18 11.19±1.22	30.7 69.3	24.03±2.12 12.01±1.35	26.3 73.7	>0.05
Alkaline phosphatase, U/l	increased normal	148.26±2.69 98.77±2.31	36.0 64.0	131.72±2.12 79.83±2.75	29.6 70.4	<0.001
GGT, U/l	increased normal	81.33±3.18 37.82±2.29	36.0 64.0	69.83±4.17 31.82±4.38	31.1 68.9	<0.01
Thymol test, unit	increased normal	9.13±0.87 2.41±0.35	42.5 57.5	7.63±0.92 2.26±0.25	29.6 61.4	<0.001
ALT, U/l	increased normal	74.27±2.09 22.36±1.43	86.7 13.3	61.24±3.51 22.18±1.68	67.8 32.2	<0.001
AST, U/l	increased normal	54.31±2.15 19.37±1.68	78.8 21.2	48.32±2.23 20.27±2.08	61.7 38.3	>0.05
α-amylase, g/h • l	normal	23.82±1.57	100.0	29.68±2.43	100.0	<0.05
Albumin, g/l	normal	48.23±2.17	100.0	49.80±1.42	100.0	>0.05
Total cholesterol, mmol/l	increased	6.75±0.18	100.0	4.12±0.61	100.0	<0.001
Triglycerides, mmol/l	increased	2.29±0.14	100.0	1.16±0.16	100.0	<0.001
LDL, mmol/l	increased	4.31±0.25	100.0	2.30±0.21	100.0	<0.001
HDL, mmol/l	reduced	1.42±0.13	100.0	1.21±0.09	100.0	>0.05
Coefficient of atherogenicity, U	increased	3.29±0.36	100.0	1.88±0.19	100.0	<0.05

Assessment of the state of carbohydrate metabolism, according to the HOMA-IR index, revealed signs of IR in the vast majority of 279 (82.3%) patients in Group 1 (Fig. 1).

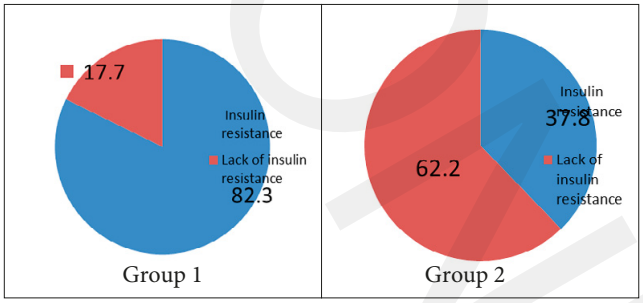

Figure 1. Frequency of determination of insulin resistance in patients of Groups 1 and 2

The average index value for Group 1 was 3.98±0.15 units. An increase in glucose levels was observed in 48.57% of the examined. Therefore, on average, the glucose level in this group of patients was 6.86±0.34 mmol/l. Basal hyperinsulinemia was detected in 43.09% of patients. The average insulin in this Group was 24.93±0.91 μU/ml.

In Group 2, the number of patients with insulin resistance was significantly less – 37.8%, and the average value of the index for the group was 3.07±0.23 units. An increase in the glucose level was registered in 28.0% of the examined. The average glucose level for this group of patients was 6.31±0.18 mmol/l. Basal hyperinsulinemia was observed in 36.0% of patients, but the average level of insulin in the entire group did not exceed the norm and was 17.79±0.92 μU/ml.

To determine the degree of histological activity in CHC patients with concomitant NAFLD, the FibroMax method was used. This technique is a unique alternative to liver biopsy, widely used in patients with diffuse liver diseases (viral hepatitis, alcoholic and non-alcoholic fatty liver disease) (Tab. 4).

Table 4. Characteristics of the stages of liver fibrosis in Groups, according to the FibroMax test (%)

Stages of fibrosis on the METAVIR scale	Average value on the FibroTest scale, (M±m)	Group 1 (n = 339)	Group 2 (n = 175)	p
F0 (no fibrosis)	0.12±0.03	23.30	46.8	<0.01
F1 (mild fibrosis)	0.34±0.02	41.88	39.7	>0.05
F2 (moderate fibrosis)	0.45±0.04	34.80	14.5	<0.01
F3 (severe fibrosis)		0	0	
F4 (cirrhosis)		0	0	

The following results were obtained: for the 79 (23.30%) patients in Group 1, according to the FibroTest, the values were 0.12±0.03 units, which corresponded to F0 (no fibrosis) according to the METAVIR scale. In 142 (41.88%) patients, the indicators corresponded to the level of F1 – 0.34±0.02 units, which can be interpreted as portal fibrosis without the formation of septa; in 118 (34.80%) of patients, the indicators corresponded to the F2 level – 0.45±0.04 units, which can be interpreted as the presence of portal fibrosis with single septa. In Group 2, the number and degree of fibrotic complications were significantly less. Thus, there were twice as many patients without signs of fibrosis – 46.8%, and only 14.5% of patients with the degree of F2. At the same time, the number of patients with mild fibrosis practically did not differ from Group 1.

To assess the degree of activity of the necro-inflammatory process, the ActiTest was used, which revealed that in 80 (23.59%) patients in Group 1 this activity was minimal (according to the METAVIR scale, corresponding to 'A1' (0.34±0.02 units). In 151 (44.54%) of patients, the activity of this process was moderate – 'A2' (0.56±0.01 units). In 98 (28.90%) of the examined patients, the activity of this process was high – 'A3' (0.78±0.03 units. In Group 2, the degree of the inflammatory process was significantly lower. In 49.7% of patients, the degree of process activity was minimal -0.31±0.06 units. Moderate activity, 0.52±0.04 units was registered in 37.8% of patients, and only 13.5% of patients had a high degree of the inflammatory process activity – 0.76±0.05 units.

Study of the cytokine profile determined the presence of hyperleptinemia in 249 (73.45%) patients Group 1. Thus, the average leptin in this group was 19.26±2.17 ng/ml. In Group 2, there were no statistically significant differences in this parameter – 69.85%, with an average value of 17.94±2.21 ng/ml. A similar situation was registered in the study of adiponectin. Hypoadiponectinemia was diagnosed in 236 (69.61%) of the examined patients in Group 1, average values – 13.08±2.34 ng/ml. In Group 2, hypoadiponectinemia was observed in 59.4% of patients, average value – 12.26±2.04 ng/ml.

DISCUSSION

According to Chaudhary, Fuda, Sainu, et al., there is a strong association between hepatitis C and hyperlipemia, fatty liver, insulin resistance, and type 2 diabetes [18]. Egyptian researchers Shawky, Mohammed, Hassan, et al., emphasize that in chronic hepatitis C there is a higher risk of insulin resistance and type 2 diabetes, compared with healthy people (without diabetes and not infected with HCV) [19]. In a study conducted in 2019 in India, researchers proved that adult patients with hepatitis C have an increased incidence of insulin resistance, compared to patients not infected with HCV [20]. Own study shows that according to the assessment of the state of carbohydrate metabolism according to the HOMA-IR index, signs of insulin resistance were detected in the vast majority of patients in Group 1 – 279 patients (82.3%), compared with Group 2 – 66 patients (37.8%).

According to a study [21] conducted on patients with NAFLD without CHC, the vast majority of patients had signs of insulin resistance (76.67%), which coincides with the data of other researchers in which the frequency of determining insulin resistance in patients with NAFLD was (74.00%) [22, 23, 24]. Interestingly, other authors [25, 26] have found a direct correlation between the level of insulin and the HOMA index (Homeostatistic Model Assessment for Insulin Resistance) with indicators characterizing the degree of morphological changes in the liver, namely, the histological activity index. In the current study, it was diagnosed that in patients with chronic hepatitis C with concomitant NAFLD, the presence of IR (Insulin Resistance) was diagnosed in (82.30%) of cases, more often than traditional indicators; which indicates that HCV infection aggravates the violation of carbohydrate metabolism. It is known that IP (Immunoprecipitation) – both virus-induced and metabolic – leads to the development

of hyperinsulinemia, which is an essential aspect of the formation of liver fibrosis. All this determines the critical role of IR in CHC patients as a factor influencing the course of the pathological process [27, 28].

This study confirms the position of Negro et al. and Persico et al. [29, 30] in that HCV infection is a risk factor for the development of IR. In a comparative assessment of biochemical activity in Group 1 with a predominance of patients with IR, the number of patients with excess ALT levels was almost three times more than in Group 2. For patients of the 1st Group, not only a change in the permeability of hepatocyte membranes is characteristic, but also the destruction of the organelles of the liver cells themselves, as well as damage to the biliary pole of hepatocytes and the development of cholestasis syndrome, determined by the level of GGT and ALP, which are significantly higher than in the 2nd Group. Fatty degeneration of hepatocytes against the background of an altered lipid composition of membranes could contribute to a change in the activity of biochemical processes in liver cells (including gluconeogenesis).

Against the background of IR, the damage to hepatocytes is aggravated, leading to persistent morphological changes in the liver. This position is confirmed by a significant increase in the level of results in the thymol test, reflecting the activity of mesenchymal inflammation. Since in the patients of Group 1 the progression of fibrosis occurred more often than in Group 2, it can be assumed that HCV influences the formation of liver fibrosis. These data are confirmed by other researchers [31, 32, 33]. In this case, fibrosis is formed as a result of the accumulation of triglycerides by the liver cell; on the one hand, this occurs against the background of dyslipidemia, characterized by an increase in the level of TG (thyroglobulin) and LDL cholesterol, which are considered as HCV-specific receptors, and on the other hand, as a result of a violation of the functional activity of the hepatic microsomal triglyceride transfer protein (MTP) [34].

From a study by Maqsood et al. in Pakistan among 320 adults with hepatitis C, 45.0% were diagnosed with dyslipidemia. At the same time, together with the presence of dyslipidemia, age and increase in BMI were shown to be statistically significant [35]. According to researchers in Mexico [36], lipid profile disorders in patients with hepatitis C can contribute to liver steatosis and excessive lipid deposition in hepatocytes According to researchers in Croatia [37], severe HCV infection affects the severity and progression of liver fibrosis, insulin resistance, and lower response rates to interferon therapy, and also contributes to the development of hepatocellular carcinoma (HCC). The revealed decrease in the content of HDL in the blood serum in most of the examined patients may be associated with a violation of the conversion of cholesterol into its esters as a result of a deficiency of the LCAT enzyme, which naturally occurs with hepatocellular damage. In addition, a decrease in HDL cholesterol can be caused by a lack of phospholipids in the body and a violation of their synthesis by the liver [38].

At the same time, there are other data in the literature concerning the characteristics of lipid metabolism in patients with chronic hepatitis C [39]. Thus, Dudnik et al. revealed a significant increase in the level of TG, total cholesterol and LDL cholesterol, and a decrease in the level of HDL cholesterol in patients with genotype 3a, compared with similar indicators in patients with genotype 1 of the virus. Moroz et al. established a relationship between the degree of liver steatosis according to the data of puncture biopsy, and a decrease in the content of total cholesterol, LDL, and an increase in the level of TG in the blood serum of such patients. At the same time, Bobrova, having studied the lipidograms of 32 CHC patients, did not reveal any disorders in lipid metabolism in the majority (75%) of them. In the remaining (25%) patients, the most common manifestation of these was an increase in the level of total cholesterol in the blood serum, as well as, to a lesser extent, LDL and VLDL.

Thus, both the results of the current study and data of other authors indicate a violation of lipid metabolism in the majority of CHC patients [40, 41].

CONCLUSIONS

The presence of concomitant NAFLD in patients with CHC aggravates the clinical picture, manifesting itself in a significant lipid metabolism disorder that provokes the rapid formation of liver fibrosis. An additional complicating factor is the development of IR, leading to persistent morphological changes in the liver parenchyma.

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