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Dyslipidemia and nonalcoholic fatty liver disease in rheumatoid arthritis patients

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Liver damage in patients with immunoinflammatory rheumatic diseases is one of the urgent problems of modern medicine. Mostly, nonalcoholic fatty liver disease (NAFLD) is developed in patients with rheumatoid arthritis (RA) with high clinical and immunological activity of the disease. Despite the presence of a large number of studies devoted to the problem of the development of dyslipidemia and liver steatosis in RA, information about their mechanisms and prevalence of risk factors remains controversial and requires further research.
The objective: **to analyze the state of lipid metabolism in patients with RA in combination with NAFLD and without signs of liver damage.**
Materials and methods**. 156 persons who were divided into two groups took part in the study. The main group included 126 patients with RA, the control group – 30 persons without autoimmune pathology.**
To determine the parameters of lipid metabolism, the participants underwent a blood laboratory test to study the parameters of the lipidogram. An ultrasound examination (USE) of the liver was performed for study the state of the hepatobiliary system.
Results**. Based on the results of liver USE, it was found that the majority of patients with RA have an increased liver size and liver fatty infiltration (steatosis) of various degrees of severity. I degree steatosis was determined in 30 (38.96%) patients with RA, II degree – in 28 (36.36%) and III degree – in 19 (24.67%) RA patients. As for the control group, steatosis I degree was diagnosed in only 1 (3.33%) person, II degree – 1 (3.33%) individual.**
The results of the lipidogram study showed that patients with RA and steatosis have elevated serum triglycerides.
An increased total cholesterol was found in patients with RA and NAFLD. Analysis of low-density lipoprotein (HDL) cholesterol levels showed that RA and NAFLD patients had HDL levels 18.00% lower compared to controls and 21.01% lower compared to RA patients without NAFLD. An increased LDL in patients with RA and NAFLD indicates the risk of development of atherosclerosis and cardiovascular diseases in this group of people.
Conclusions**. In 77 (61.10%) examined RA patients, liver steatosis of various degrees was detected by ultrasound examination. The combination of RA with NAFLD is associated with more pronounced proatherogenic dyslipidemias compared to patients with RA without NAFLD. Hepatic steatosis is associated with a significant increase in TG and LDL cholesterol levels and an increased atherogenicity.**
A standard clinical and laboratory and instrumental examination of patients with RA should include an assessment of the state of the liver (ultrasound examination, laboratory parameters) and lipid metabolism for further application of therapeutic and preventive non-medicinal and medicinal algorithms for the correction of detected disorders.
Keywords: *rheumatoid arthritis, nonalcoholic fatty liver disease, lipid metabolism, dyslipidemia.*

Дисліпідемія та неалкогольна жирова хвороба печінки у пацієнтів з ревматоїдним артритом

Л. В. Хіміон, І. В. Климась

Однією з актуальних проблем сучасної медицини є ураження печінки у пацієнтів з імунозапальними ревматичними захворюваннями. Найчастіше неалкогольна жирова хвороба печінки (НАЖХП) розвивається у хворих на ревматоїдний артрит (РА) з високою клініко-імунологічною активністю хвороби. Незважаючи на наявність великої кількості досліджень, присвячених проблемі розвитку дисліпідемії та стеатозу печінки при РА, інформація про їхні механізми і поширеність факторів ризику залишається суперечливою та потребує подальших досліджень.
Мета дослідження: аналіз стану ліпідного обміну у хворих на РА у поєднанні з НАЖХП та без ознак ураження печінки.
Матеріали та методи. У дослідженні взяли участь 156 осіб, яких було розподілено на дві групи. До основної групи увійшли 126 хворих на РА, до групи контролю – 30 осіб без аутоімунної патології.
Для вивчення показників ліпідного обміну учасникам дослідження проводили лабораторне дослідження крові з визначенням показників ліпідограми. Для характеристики стану гепатобіліарної системи проведено ультразвукове дослідження (УЗД) печінки.
Результати. На підставі результатів УЗД печінки виявлено, що у більшості хворих на РА спостерігається збільшення розмірів печінки та жирова інфільтрація печінки (стеатоз) різного ступеня важкості. Стеатоз I ступеня зафіксовано у 30 (38,96%) хворих на РА, II ступеня – у 28 (36,36%) та III ступеня – у 19 (24,67%) хворих на РА. Щодо групи контролю, то лише в 1 (3,33%) особи виявлений стеатоз I ступеня і в 1 (3,33%) – стеатоз II ступеня.
Результати дослідження ліпідограми продемонстрували, що у пацієнтів із РА та стеатозом у сироватці крові спостерігається підвищення рівня тригліцеридів.
У хворих на РА і НАЖХП зафіксовано підвищення вмісту загального холестерину. Аналіз показників вмісту холестерину ліпопротеїдів низької щільності (ЛПВЩ) продемонстрував, що у пацієнтів з РА та НАЖХП рівень ЛПВЩ на

18,00% нижче порівняно з контролем та на 21,01% нижче порівняно з показниками групи пацієнтів з РА без НАЖХП. Підвищення рівня ЛПНЩ у хворих на РА та НАЖХП свідчить про наявність ризику розвитку атеросклерозу та серцево-судинних захворювань у цій групі осіб.

Висновки. У 77 (61,10%) обстежених хворих на РА за допомогою УЗД виявлено стеатоз печінки різного ступеня. Поєднання РА з НАЖХП асоціюється з більш вираженими проатерогенними дисліпідеміями порівняно із пацієнтами з РА без НАЖХП. Стеатоз печінки пов'язаний з істотним підвищенням рівнів ТГ і холестерином ЛПНЩ та збільшенням атерогенності.

Стандартне клініко-лабораторне та інструментальне обстеження хворих на РА має включати оцінку стану печінки (УЗД, лабораторні показники) та ліпідного обміну для подальшого застосування лікувально-профілактичних немедикаментозних і медикаментозних алгоритмів корекції виявлених порушень.

Ключові слова: *ревматоїдний артрит, неалкогольна жирова хвороба печінки, ліпідний обмін, дисліпідемія.*

Frequent development of liver damage, including non-alcoholic fatty liver disease (NAFLD), in patients with rheumatoid arthritis (RA) is one of the significant scientific and practical problems, actively investigated during last decade. RA course is manifested by systemic immunological (autoimmune) inflammation, which accompanied by a wide range of extra-articular organs damage, of which liver pathology is prominent, including NAFLD. Most often, NAFLD develops in RA patients with high clinical and immunological activity of the disease (Wendt M.M.N., de Oliveira M.C. et al., 2019). According to a meta-analysis, 1 in 3 patients with RA had NAFLD, which is comparable to the overall prevalence in the general population (Zamani M., Alizadeh-Tabari S. et al., 2023), at the same time in ultrasound studies after adjustment for all main NAFLD risk factors, RA was found to be an independent risk factor significantly associated with moderate to severe liver steatosis, with the odds ratio of 2.24 compared to healthy controls [14].

There is an increasing evidence suggesting an association between liver disease and inflammatory arthritis. Although only a few number of studies evaluated the mechanisms of development of NAFLD in inflammatory joint diseases. Most of the studies carried out to investigate liver damage in patients with inflammatory arthritis have been mainly focused on the possible hepatotoxic effect of methotrexate (Ogdie A., Grewal S.K. et al., 2018).

RA can be associated with a number of extra-articular manifestations or comorbidities, including cardiovascular diseases, gastrointestinal, kidney, and lung disorders, metabolic alterations (obesity, type 2 diabetes mellitus, metabolic syndrome, dyslipidemia), infections, osteoporosis, tumors, and depression [2, 20, 24]. In addition, the liver injury might be considered as an extra-articular manifestation of these inflammatory arthritis, especially the development of NAFLD [7]. However, there is some controversy between the occurrence of liver pathology as an extra-articular manifestation or as a result of hepatotoxicity of anti-inflammatory and disease-modifying treatment [4].

At present, the pathophysiological link between liver damage and inflammatory arthritis is unknown, although the potential mechanisms can involve adipocytokines, altered lipid profile, obesity and the treatment administered.

It is recognized that RA is associated with alterations in lipid pattern. These alterations are derived from the effect of inflammatory response and mainly translated into a deregulation in the levels of cholesterol, triglycerides, LDL-C and HDL-C that are directly involved in the development of atherosclerosis [4, 5]. It is noteworthy to mention the existence of the RA-associated "lipid paradox" in which from the one hand there is an inverse association between cholesterol and cardiovascular risk and secondly, treatments aimed to reduce inflammation induce certain elevations in lipid levels [10, 27]. It is possible that liver steatosis can increase the frequency of the drugs hepatotoxic adverse events in RA patients. The vice versa is also possible, but results of the studies focused on evaluation of influence of methotrexate cumulative dose on the NAFLD development are conflicting [8].

Hyperlipidemia is considered as an important risk factor for the development of various pathologies, in particular, NAFLD (Lambert J.E., Ramos-Roman M.A. et all., 2014). One of the reasons for the development of NAFLD is an imbalance between the intrahepatic production of TG, obtained mainly from plasma fatty acids that enter the liver, and the removal of intrahepatic triglycerides as part of VLDL-C (Vaziri N.D., 2016).

In turn, NAFLD can also lead to dyslipidemia, the most common manifestation of which is the "lipid triad": low high-density lipoprotein cholesterol (HDL-C), elevated low-density lipoprotein cholesterol (LDL-C), and hypertriglyceridemia (Xu M.X., Ge C.X., et al., 2019). At the same time, each component of this triad can indicate the severity of NAFLD and is an independent risk factor for other pathologies. Among all classes of lipoproteins, low- and high-density lipoproteins deserve special attention, as they are of great importance in assessing the state of the liver in NAFLD. LDL-C is synthesized in the liver and is the main transport form of cholesterol in the liver, adrenal glands and other organs and tissues. It is believed that up to 70% of all transported plasma cholesterol is accounted for by LDL-C [17, 19].

It is known that in RA patients cardiovascular risk is higher, atherosclerosis develops earlier than in general population and NAFLD can be the hepatic manifestation of the systemic dysmetabolic process. In case of its further progression it can significantly alter drugs metabolism and drugs tolerance which can negatively impact treatment efficacy.

At the most cases, chronic inflammatory process observed in the body during this pathology contribute to disorders of the blood lipid spectrum in RA. Current studies have shown that in active RA, disturbances the lipid profile are characterized by an increase in the concentration of total cholesterol and a decrease in HDL cholesterol, which leads to an increase in the atherogenic index. The results of numerous studies indicate an increase in the frequency of dyslipidemia in this category of patients (up to 84%) [12]. In RA patients, several years before the clinical manifestation of the disease, there is an increase

in the level of cholesterol and a decrease in HDL cholesterol. In patients with early RA, an increase in the level of antibodies to oxidized LDL-C and a decrease in the activity of lipoprotein-associated phospholipase A_2, which are involved in the pathogenesis of both early RA and atherosclerosis, were noted [1, 16, 22].

Despite the extreme importance of the problem of dyslipidemia and its consequences (NAFLD, atherosclerosis, cardiovascular diseases) both from a theoretical and practical point of view, and the presence of a large number of studies devoted to the problem of the development of dyslipidemia and liver steatosis in RA, information about their mechanisms and prevalence of risk factors remains controversial, and still need further investigations.

The objective: to investigate serum lipids levels in RA patients with NAFLD and without signs of liver damage.

MATERIALS AND METHODS

A comprehensive clinical, laboratory and instrumental examination of 126 patients with RA and 30 people without autoimmune pathology as a control group was performed.

All RA patients met the following inclusion criteria: provided written patient consent to participate in the study; female and male patients aged 20 to 55 years old; the diagnosis of RA was established according to the criteria of ARA, 1987.

The control group consisted of patients who met the following inclusion criteria: provided written patient consent to participate in the study; female and male persons aged 20 to 55 years old; absence of any autoimmune pathology, inflammatory conditions and diseases; absence of any chronic diseases in the active phase.

According to the inclusion criteria, RA patients and people of the control group who had an increase in the level of ALT, AST three times or more from the upper limit of normal were not included in the study. All RA patients included in the study and people of the control group had negative results of hepatitis B (HBsAg, AB-HBcor), hepatitis C (HCV, AB-HCV) and markers of autoimmune hepatitis (напиши праивльно які атитіла).

The main data on the clinical and demographic characteristics of patients with RA and the control group are shown in Table 1.

In order to study the parameters of lipid metabolism the laboratory blood test was performed. There were determined the parameters of the lipid profile (total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglycerides (TG), atherogenic index (IA)). Determination of the level of cholesterol, HDL cholesterol and TG were carried out on an automatic biochemical analyzer OLYMPUS AU-400 (Japan) using «Beckman Counter» kits (USA) according to the manufacturer's method. In none of the RA patients and the control group included in the study did the TG level of blood serum exceed 4.5 mmol/l, which made it possible to use the calculation method according to the W. T. Friedwald's formula (1997) in mmol/l [25] to determine the content of LDL-C and VLDL-C in blood serum:

LDL-C = TC – HDL-C – (TG*0.45);

VLDL-C = TC – HDL-C – LDL-C.

The atherogenicity index was calculated according to the formula of A. N. Klimov (Stupnytska H. Ya., Fediv O. I., et al., 2015):

IA = (TC - LDL-C)/ HDL-C.

To characterize the state of the hepatobiliary system, an ultrasound examination of the liver was performed. All ultrasounds were performed by one doctor, the study was performed on the ULTIMA PRO-30 ultrasound machine, «RADMIR», Kharkiv, using the C2-5 MHz convex sensor.

Analysis and processing of statistical data of the conducted clinical studies was carried out on a personal computer using the STATISTICA 10.0 StatSoft for Windows and MS Excel XP application program package.

RESULTS AND DISCUSSION

Based on the ultrasound of the liver was found that 77 (61.1%) RA patients have an increase in the size of the liver and fatty infiltration of the liver (steatosis) of varying grades of severity, which are probable ultrasound criteria for fatty liver disease.

According to our study results, fatty liver infiltration of the first grade was observed in 30 (38.96%) RA patients, II grade – in 28 (36.36%) and III grade – in 19 (24.67%) RA patients. As for the control group, only 1 (3.33%) person had grade I steatosis and 1 (3.33%) person had grade II steatosis. Grade III fatty liver infiltration was not registered in the control group.

Therefore, the NAFLD detected in the early stages of development – at the stage of steatosis, in RA patients is considered within the framework of the liver component of metabolic syndrome, and may be associated with

Table 1

Clinical and demographic characteristics of RA patients and control group individuals

Indicator	Distribution feature	RA patients, n=126		Control group, n=30	
		n	%	n	%
Gender	Women	102	80.95	25	83.33
	Men	24	19.05	5	16.67
Age	Young	53	42.06	13	43.33
	Average	73	57.94	17	56.67
Grade of RA activity	I, DAS28≤3.2	7	5.56	-	-
	II, 3.2<DAS28≤5.1	79	62.7	-	-
	III, DAS28>5.1	40	31.75	-	-

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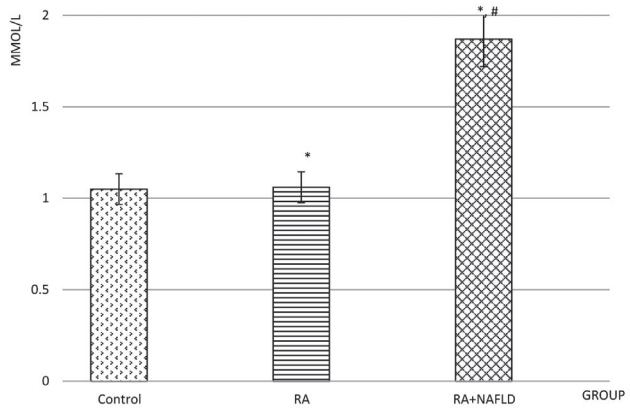

Fig. 1. Serum triglycerides in study patients groups

Notes: * – the difference to the control group is significant, p<0.05; # – the difference to the RA group is significant, p<0.05.

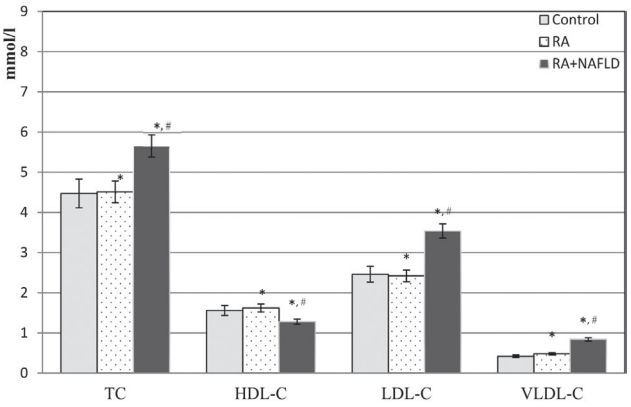

Fig. 2. Serum total cholesterol and lipoproteins in studied patients groups

Notes: * – the difference to the control group is significant, p<0,05, # – the difference to the RA group is significant, p<0.05.

abdominal-visceral obesity, peripheral insulin resistance, dyslipidemia, and arterial hypertension [13, 15]. The basis of the pathogenesis of NAFLD at the stage of steatosis may be an increase in the synthesis of fats in the liver, which will be expressed by dyslipidemia. Destructive changes in the liver with NAFLD, including at the stage of steatosis, can lead to changes in metabolic processes in this organ, in particular, lipid metabolism, which will be expressed by dyslipidemia. In order to verify this assumption, we determined the indicators of lipid metabolism in blood serum.

Table 2 presents the results of the serum lipids tests in RA patients with NAFLD and without NAFLD (RA group) and in the control group.

The results of the studies showed that in patients with RA and steatosis, there is an increase in the level of TG in the blood serum is 1.8 times higher than in RA group (without NAFLD) and the control group (Fig. 1, tabl. 2).

Hypertriglyceridemia is one of the causes of the development of NAFLD and can be the cause of the development of atherosclerosis in NAFLD, which can be explained by two pathogenetic mechanisms (Younossi Z. M., 2019): 1) some lipoproteins that are rich in TG can penetrate the artery wall, where they accumulate over time, showing an atherogenic effect; 2) the metabolism of TG is closely related to the metabolism of atherogenic LDL-C.

Thus, hypertriglyceridemia is associated with the risk of developing atherosclerosis in NAFLD, but this relationship is not as important as in hypercholesterolemia. Therefore, the next step was to determine the level of total cholesterol and its fractions in blood serum.

The results of the studies showed that RA patients with NAFLD have an increase in total cholesterol, which is 1.3 times higher than that of RA patients without NAFLD (Fig. 2).

This phenomenon is probably related to the intensification of lipogenesis processes with the participation of glycerol-3-phosphate dehydrogenase, which is involved in the formation of glycerol-3-phosphate and diacylglycerol acyltransferase, an enzyme that catalyzes the formation of triglycerides [11]. In addition to lipogenesis enzymes, HMG-CoA (3-hydroxy-3-methylglutaryl

Table 2

Serum lipids in RA patients with NAFLD and without NAFLD and in the control group, M±SD

Indicator	RA patients with NAFLD (n=77)	RA patients (n=49)	Control group (n = 30)
TC, mmol/l	5.66±0.59*, #	4.51±0.67*	4.47±0.03
HDL-C. mmol/l	1.28±0.20*, #	1.62±0.16*	1.56±0.08
LDL-C, mmol/l	3.54±0.68*, #	2.42±0.80*	2.46±0.02
VLDL-C, mmol/l	0.84±0.14*, #	0.48±0.08*	0.42±0.06
TG, mmol/l	1.87±0.32*, #	1.06±0.18*	1.05±0.03
IA	3.57±1.02*, #	1.86±0.74*	1.84±0.06

Notes: * – the difference to the control group is significant, p<0.05; # – the difference to the RA group is significant, p<0.05.

coenzyme A) reductase, which participates in cholesterol synthesis, is also activated. The strengthening of these processes can be activated by cytokines, which are formed in the body of RA patients. An increase in the concentration of total cholesterol in blood serum in the pathology under study can occur due to an increase in the content of high or low-density lipoproteins since cholesterol is their component (Zhang T., Bai X., Mao X., 2013).

It is known that TC in the peripheral blood exists mainly in bound form. To a greater or lesser extent, cholesterol is included in all classes of blood lipoproteins, but 43% of it is contained in LDL-C, and 18% in HDL-C. For these reasons, LDL-C is considered an atherogenic class, while the only non-atherogenic class of lipoproteins is HDL-C (Weyand C.M., Zeisbrich M., Goronzy J.J., 2017).

The analysis of HDL cholesterol content showed that in RA patients with NAFLD, level of HDL-C decreased by 18.00% compared to the control group and by 21.01% to the group of RA patients without NAFLD (Fig. 2). A decrease in HDL-C in the blood has a negative meaning, since their role in the body is determined, first of all,

by their participation in the homeostasis of cholesterol in blood plasma and tissues of various organs due to the processes of involvement in the so-called reverse transport of cholesterol in the liver [21]. Moreover, HDL-C takes an active part in the removal of cholesterol from cells by its esterification. This facilitates the delivery of TC to the liver, from where it is excreted as part of bile, first into the intestines, and then removed from the body.

A decrease in the level of HDL-C may be caused by a pathological process in the body, which is observed in RA. It has been shown that cytokines, the level of which increases especially against the background of RA, can disrupt the composition of HDL-C particles, as well as the activity of lecithin-cholesterol acyltransferase and lipid-transfer protein, which causes a significant decrease in their amount in the body [23].

On the contrary, all other lipoproteins transport cholesterol into tissue cells. Determination of LDL-C in RA patients with NAFLD showed its increased level (Fig. 2), which indicates the increased cardiovascular risk in this group of patients. The increase in the level of LDL-C is due to its inhibitory utilization by the receptor-mediated mechanism, as well as the prolonged time of circulation in the blood, during which they can undergo chemical modifications, which significantly affects their capture by cells of peripheral tissues and removal from the bloodstream.

Since LDL-C contains phospholipids, free cholesterol, and apoprotein B-100, which can be oxidized like the components of the cell membrane (Zhao S., Mysler E., Moots R.J., 2018), active forms of oxygen, the amount of which increases in RA, interacting with fatty acids or proteins causes their oxidative modification [18]. As a result of such modifications, the structure and functions of lipoproteins are disturbed. Oxidized LDL-C accumulate in the blood due to impaired receptor-mediated utilization or are captured by macrophages, which produce even more active forms of oxygen. Oxidized LDL-C changes their properties in two directions: first, their interaction with liver receptors increases, and then they become active for monocytes. Activated monocytes penetrate into the subendothelial space of blood vessels and turn into macrophages that phagocytose modified LDL-C, after which they turn into foam cells (cells that are full of cholesterol esters). The foam cells and activated macrophages release biologically active substances: adhesion molecules, growth factors and pro-inflammatory cytokines. As a result, atherosclerotic plaques are formed, which leads to the narrowing of the vessel and the formation of an intravascular thrombus (Riccio A., Postiglione L. et al., 2018).

Along with this, the level of VLDL-C increased in the blood serum of RA patients with NAFLD (Fig. 2). Large VLDL-C is not actually atherogenic, but high concentrations of these large TG-rich lipoproteins can complicate the course of NAFLD [9]. The established changes indicate that patients with NAFLD may experience atherogenic shifts in the lipid spectrum of the blood, as the atherogenic factor increases in RA patients with NAFLD (Fig. 3).

One of the reasons for the development and progression of steatosis in RA can be an imbalance of adipocytokines, which leads to the occurrence and progression of disorders of lipid metabolism, as well as the development and formation of components of metabolic syndrome. The obtained data indicate the influence of lipid metabolism disorders on the progression of metabolic disorders in the liver in RA, since excessive amounts of fats and carbohydrates enter the liver, which are converted into fatty acids, which are a substrate for TG synthesis and accumulate in hepatocytes [6, 15].

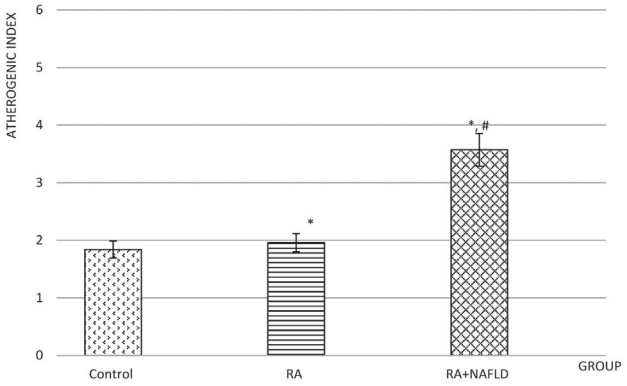

Fig. 3. Atherogenic index in patients with rheumatoid arthritis and non-alcoholic fatty liver disease

Notes: * – the difference to the control group is significant, p<0,05; # – the difference to the RA group is significant, p<0,05.

Therefore, the presence of NAFLD in RA patients is associated with lipid metabolism disorders, which is confirmed by the correlation analysis between the presence of liver steatosis and lipid metabolism disorders. The conducted correlation analysis showed a very high positive correlation of liver steatosis with the level of TG and VLDL-C ($r=0.89$, $p<0.05$), an average positive correlation was found with the level of total cholesterol and IA ($r=0.55$, $p<0.05$), a moderate positive correlation with LDL-C ($r=0.44$, $p<0.05$), and a moderate negative correlation with HDL-C ($r=-0.48$, $p<0.05$).

Therefore, increasing the synthesis or inhibition of the oxidation of fatty acids in mitochondria under conditions of RA contributes to an increase in TG production, as well as a violation of the removal of TG from hepatocytes. In them, VLDL-C are formed, which are successively transformed into highly atherogenic intermediate density lipoproteins (IMDL), which, accordingly, transform into LDL-C. It can be predicted that any factor that promotes the formation of LDL-C also increases the synthesis of IMDL-C and LDL-C. The rate of formation of VLDL-C in the liver is regulated by the concentration of insulin in the blood plasma and the presence of substrates – free fatty acids and glucose [15].

It follows from this that the lipid metabolism disorders we identified are strongly interconnected and underlie the development of metabolic disorders in RA patients and, especially, in RA patients with NAFLD. Therefore, the treatment of such disorders should be comprehensive and aimed at eliminating all existing biochemical changes and normalizing all types of metabolism, which should lead to the elimination of complications and accompanying diseases.

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CONCLUSIONS

1. In 77 (61.10%) included RA patients, liver changes were detected by ultrasound examination, which were interpreted as liver steatosis of various grades. In the comorbidity of RA with NAFLD, more prominent lipid metabolism disorders were observed compared to RA patients without NAFLD. Hepatosteatosis connected to significant increase in TG, total cholesterol and VLDL-C level, decrease of HDL-C and higher level of LDL-C and atherogenc index.

2. Standard examination of RA patients should include ultrasound and laboratory liver evaluation and lipid metabolism tests and further use of non-pharmacologic and pharmacologic algorithms for their correction.

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