

## ULTRASOUND DIAGNOSTICS OF THE LIVER AS AN EFFECTIVE METHOD OF CONTROLLING NON-ALCOHOLIC FATTY LIVER DISEASE THERAPY IN RHEUMATOID ARTHRITIS PATIENTS

**Iryna Klymas**

MD, Assistant Professor at the Department of Internal Diseases, Family Medicine, Hematology and Transfusiology, Shupyk National Healthcare University of Ukraine, Ukraine  
e-mail: gp-ira@bigmir.net, orcid.org/0000-0002-1142-5958

### Summary

Today, the method of ultrasound diagnostics is the most widespread method of internal organs and tissues visualization. In particular, the liver ultrasound is the safest and most informative method of diagnosing non-alcoholic fatty liver disease (NAFLD) and an effective method of monitoring the effectiveness of NAFLD treatment, namely its manifestation of liver steatosis. The aim of this paper was to investigate the changes in the state of the liver by ultrasound in rheumatoid arthritis (RA) patients with the use of additional combined therapy of atorvastatin and essential phospholipids. We were examined and treated 77 RA patients with NAFLD (64 women (83.1%) and 13 men (16.9%)), under the age of 55 years old. The patients were divided into 3 studied groups. The first group (n=25) received additional atorvastatin, the second group (n=26) – essential phospholipids, and the third group (n=26) – combination of atorvastatin and essential phospholipids for 6 months. Ultrasound assessment of steatosis was performed before treatment, after 3 and 6 months of treatment. In the III group, an improvement of the ultrasound images was observed already after 3 months of combined use of atorvastatin and essential phospholipids, which was not observed in the separate use of these medicines in the I and II groups. In 6 months of treatment with the studied medicines, positive dynamics of the liver parenchyma echogenicity was observed in all studied groups.

**Key words:** liver steatosis, autoimmune inflammation, dyslipidemia, non-invasive diagnostics, atorvastatin, essential phospholipids.

DOI <https://doi.org/10.23856/5928>

### 1. Introduction

One of the urgent problems of modern medical science is liver damage, with the development of non-alcoholic fatty liver disease (NAFLD), in patients with immunoinflammatory rheumatic diseases. The development of rheumatoid arthritis (RA) is manifested by generalized immunological (autoimmune) inflammation, which is accompanied by a wide range of damage to extra-articular organs, of which liver pathology is prominent, including NAFLD. Most often, NAFLD develops in RA patients with high clinical and immunological disease activity (Wendt M. M. N., de Oliveira M. C., et al., 2019).

The authors (Vassiliadis E., Oliveira C. P., et al., 2012) showed that in the liver of RA patients are observed the structural changes on which the functioning of this organ directly depends, namely: granular and fatty dystrophy, deposition of amyloid masses, less often – annular cirrhosis and necrosis of hepatocytes. Similar changes were found in the liver of RA patients by other researchers (Aithal G. P., 2011). Moreover, the works (Radovanović-Dinić B., Tešić-Rajković S., et al., 2018; Sellami M., Saidane O., et al., 2020)

demonstrated a correlation between structural and functional liver disorders and the activity of the rheumatoid process.

Non-invasive methods of diagnosing NAFLD are based on two different approaches: biological, which consists in the quantitative determination of serum biomarkers in the blood, and physical – measuring the stiffness of the liver, due to the determination of the internal physical activity of the liver parenchyma (*Castera L., Friedrich-Rust M., Loomba R., 2019; Zhou J. H., Cai J. J., She Z. G., Li H. L., 2019*). The use of non-invasive markers for the diagnosis of NAFLD, which develops against the background of RA, helps to: 1) identify, at the level of primary care, the possibility of developing NAFLD in persons with a high metabolic risk; 2) at the secondary and tertiary level of medical care, identify patients with severe non-alcoholic steatohepatitis (a worse prognosis is diagnosed); 3) assess disease progression; 4) predict the response of the patient's body to antirheumatic therapy and establish the effectiveness of the use of liver metabolic medicines, which will reduce the need for a liver biopsy. Today, non-invasive methods are used at all stages of NAFLD pathogenesis (*Castera L., Friedrich-Rust M., Loomba R., 2019; Zhou J. H., Cai J. J., She Z. G., Li H. L., 2019*).

If NAFLD is suspected, which develops as a concomitant disease in RA patients it is necessary to confirm the presence of steatosis. Steatogenesis affects the risk of developing cardiovascular pathologies, diabetes and hypertension. The cause of liver dysfunction is autoimmune processes on the one hand, and the influence of medicines on the other. Hepatotoxic reactions that occur during the use of RA basic therapy depend on the duration of the disease, the timing of administration and the dose of medicines (*Karlsson Sundbaum J., Eriksson N., et al., 2019*).

As a result of the progression of the pathological process in RA, successive stages of NAFLD develop in the liver – steatosis, steatohepatitis, fibrosis, for the diagnosis of which various methods have been used in recent years. Today, in clinical practice, determining the amount of fat is of interest as an indicator of the effectiveness of treatment. The hepatobiliary system includes the liver, gallbladder, and bile ducts. To assess the macrostructure of the liver, gall bladder and biliary tract, the ultrasound method is used. Today, the ultrasound method is the most widespread method of visualization of internal organs and tissues. Its advantages include safety, high informativeness, non-invasiveness and relatively low cost. The listed properties and the possibility of conducting studies in dynamics make the ultrasound method especially valuable in the examination of various groups of patients, including RA patients. Modern ultrasound equipment allows you to accurately differentiate the structure of the liver and gallbladder. According to authors (*Mitkov V.V., Bryukhovetsky Yu.A., 1996; Batskov S.S., 2004*) the ultrasound method is the most informative, which makes it possible to determine changes in the organ even when other examination methods do not yet indicate deviations from the norm (*Wheeler, P. G., Theodossi, A., et al., 1979*).

Three ultrasonographic grades of liver steatosis are used to detect liver steatosis by ultrasound (*Batskov S.S., 1996; Brooks M., 1998; PalMentieri B. et al., 2006; Panchyshyn Yu. M., 2008*).

Grade I – normal liver size or moderate hepatomegaly, liver contours and edges are even, weakly expressed increased echogenicity of liver parenchyma, echo structure is heterogeneous, compacted, vascular pattern is preserved, visualization of hepatic veins is unchanged, hepatic veins and bile ducts, portal vein are not dilated, distal there is no weakening of the ultrasound signal.

Grade II – moderate hepatomegaly, the contours and edges of the liver are smooth, moderately expressed increased echogenicity of the liver parenchyma, the echo structure is heterogeneous, compacted, the vascular pattern is partially preserved, the visualization of the hepatic

veins is slightly changed, the hepatic veins and bile ducts, the portal vein are not dilated, there may be distal attenuation ultrasound signal.

Grade III – hepatomegaly, the contours and edges of the liver are smooth, the increased echogenicity of the liver parenchyma is significantly pronounced, the echo structure is heterogeneous, compacted, the vascular pattern is lost, the visualization of the hepatic veins is complicated, the hepatic veins and bile ducts, the portal vein are not dilated, there is a distal weakening of the ultrasound signal.

**The aim of the study** was to study the changes in the state of the liver by the method of ultrasound diagnostics in RA patients NAFLD whose using additional combined therapy of atorvastatin and essential phospholipids.

## 2. Materials and methods

For the study we selected 77 RA patients who had signs of liver fatty infiltration according to ultrasound; under the age of 55 years old; who signed the patient's consent to participate in the study. RA was diagnosed according to ARA criteria (1987); patients with hepatitis, alcohol abuse, >55 years old were not included. There were used a comprehensive assessment of the clinical results, biochemical blood analysis and an ultrasound research method of imaging the liver.

To assess the state of the hepatobiliary system, an ultrasound examination of the liver and gallbladder was performed. All ultrasounds were performed by one doctor; the study was performed on an ULTIMA PRO-30 ultrasound machine, "RADMIR", Kharkiv, using a C2-5 MHz convex sensor. The following sequence of ultrasound examination of hepatobiliary system in RA patients was used: first, visualization of the liver and its examination, then the gallbladder and bile ducts.

All patients were divided into three groups. All patients continued to receive RA anti-rheumatic therapy. The first group consisted of 25 RA patients with NAFLD (21 women (84%) and 4 men (16%)), who additionally received atorvastatin in a daily dose of 10 mg in the evening for 6 months. The second group consisted of 26 RA patients with NAFLD (22 women (84.6%) and 4 men (15.4%)), who additionally received essential phospholipids at a dose of 600 mg (two capsules) three times a day for 6 months. The third group consisted of 26 RA patients with NAFLD (21 women (80.8%) and 5 men (19.2%)), who, in addition to RA anti-rheumatic therapy, received essential phospholipids at a dose of 600 mg (two capsules) three times a day and atorvastatin at a daily dose of 10 mg for 6 months.

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. The reliability of differences was defined at  $p < 0.05$ .

## 3. Results and discussion

One of the selection criteria for the study was the presence the signs of liver fatty infiltration according to ultrasound in RA patients. 77 RA patients were selected, in whom, according to the results of an ultrasound of the liver, liver changes were registered in the form of hepatomegaly, with increased liver parenchyma echogenicity of various grades of intensity, a heterogeneous echostructure with even contours and edges, which may be a manifestation of liver steatosis of varying grades of severity. According to the results of the liver ultrasound and steatosis criteria, grade I – 30 (38.96%), grade II – 28 (36.36%), grade I – 28 (36.36%) of liver steatosis were found in RA patients (Table 1).

Table 1

**Characteristics of RA patients in the studied groups depending on the liver steatosis grade**

Grade of steatosis according to ultrasound	I group (n=25)		II group (n=26)		III group (n=26)		Total (n=77)	
	n	%	n	%	n	%	n	%
Grade I	9	36.00	10	38.46	11	42.30*	30	38.96
Grade II	10	40.00	9	34.62	9	34.62	28	36.36
Grade III	6	24.00	7	26.92	6	23.10	19	24.67

\* – statistically significant difference compared to the indicators of the I group,  $p < 0.05$

Steatosis of the first and second grades was most often observed in all studied groups. In RA patients of the I group, steatosis of the grade I met in 9 (36.00%) and steatosis of the grade II in 10 (40.00%) RA patients, in the II group – 10 (38.46%) and 9 (34.62%) respectively, in the III group – 11 (42.30%) and 9 (34.62%) respectively. Grade III of steatosis was registered in 6 (24.00%) RA patients group I, in 7 (26.92%) RA patients group II, and in 6 (23.10%) RA patients group III. The difference in indicators of steatosis grades of the studied groups is not statistically significant ( $p > 0.05$ ).

Therefore, the analysis of patients of groups I, II and III showed that they are comparable in age, gender, degree of RA activity and of liver steatosis grade, which allows monitoring of the studied groups of patients according to the effectiveness of the proposed treatment regimens and their impact on ultrasound signs of liver condition.

The criteria for the effectiveness of the complex use the atorvastatin and essential phospholipids in RA patients with NAFLD of the III group can be considered positive clinical dynamics, since after 3 months of treatment, a decrease in fatigue, a feeling of discomfort in the right hypochondrium, and an improvement in appetite were noted. Along with this, there was a positive trend in the detection of the grade of steatosis during ultrasound control of the liver (Table 2).

Thus, in RA patients of the III group, a normal ultrasound image of the liver was achieved after 3 months in 9 (34.62%) patients and in 11 (42.31%) patients after 6 months (Table 2). Whereas in RA patients of the I and II groups, normal ultrasound characteristics of the liver were achieved after 6 months: in 7 (28%) RA patients of the I group and in 5 (19.23%) RA patients of the II group (Table 2).

Positive ultrasound dynamics were noted in all groups, which indicates a positive effect of the studied medicines on the state of the liver (Table 3).

The research results showed that in 17 (65.4%) RA patients of the III group, hepatomegaly decreased already after 3 months of combined use of atorvastatin and essential phospholipids, which was statistically significantly different from the I and II groups ( $p < 0.05$ ) (Table 3).

The analysis of the obtained results of ultrasound examination of the liver in examined RA patients of the III group compared to the I and II groups showed a statistically significant difference between the frequency of occurrence of echographic changes of the liver mainly after 3 months of use of atorvastatin and essential phospholipids. So, if in patients of the I and II groups, increased echogenicity was registered in 23 (92%) and 26 (100%) patients, respectively, then in patients of the III group – in 17 (65.4%) patients at  $p < 0.05$  (Table 3). After 6 months of separate and combined use of atorvastatin and essential phospholipids, no difference in echogenicity between the studied groups was found ( $p > 0.05$ ) (Table 3). Liver contours and edges were equal in all studied groups at all stages of patient examination.

Table 2

**Characteristics of rheumatoid arthritis patients depending  
on the liver steatosis grade before and after treatment**

Group	Treatment term		The steatosis grade according to ultrasound data			
			I	II	III	absent
<b>I group</b> (n=25)	Before treatment	n	9	10	6	-
		%	36	40	24	-
	After 3 months	n	9	10	6	-
		%	36	40	24	-
	After 6 months	n	9	6	3	7
		%	36	24	12	28
<b>II group</b> (n=26)	Before treatment	n	10	9	7	-
		%	38.46	34.62	26.92	-
	After 3 months	n	12	9	6	-
		%	46.15*	34.62*	23.08	-
	After 6 months	n	10	6	3	7
		%	38.46	23.01	11.23	26.9
<b>III group</b> (n=26)	Before treatment	n	11	9	6	-
		%	42.31	34.62	23.08	-
	After 3 months	n	7	5	4	9
		%	26.92*,#	19.23*,#	15.38*,#	34.62*,#
	After 6 months	n	9	4	2	11
		%	34.62	15.38*,#	7.69*,#	42.31*,#

\* – statistically significant difference compared to the indicators of the I group patients,  $p < 0.05$ ;

# – statistically significant difference compared to the indicators of the II group patients,  $p < 0.05$ .

During the study of the size of the left and right of the liver lobes, it was found that the patients of all studied groups had an enlarged right lobe of the liver, the decrease in the size of which was observed mainly in RA patients of the III group – in 9 (34.6%) patients after 3 months whose were used combined of atorvastatin and essential phospholipids (Table 3).

After 6 months, there was no difference in the size of the right and left liver lobes between the studied groups ( $p > 0.05$ ) (Table 3). At the same time, a decrease in liver density was observed only in the III group RA patients with NAFLD (Table 3).

Thus, in patients of the III group, an improvement of the ultrasound images was observed already after 3 months of combined use of atorvastatin and essential phospholipids, which cannot be observed with the separate use of these medicines. In 6 months after the start of treatment with the studied medicines, a positive dynamic of liver parenchyma echogenicity was observed in all studied groups.

Therefore, the corrective effect of atorvastatin and essential phospholipids that we discovered when they are used separately and, especially, when combined, on the indicators of the echostructure and echogenicity of the liver parenchyma, testify to their hepatoprotective effect on the liver. The main mechanism of action of these medicines is the reduction of fatty infiltration and the correction of metabolic disorders. Based on the obtained results, it is clear that essential phospholipids have not only a hepatoprotective effect, but also a cholesterol-lowering effect, which makes their use justified in RA patients with NAFLD. As for atorvastatin, in addition to the effect on lipid metabolism, this drug has other effects that enhance

its anti-atherosclerotic effect. It inhibits the synthesis of isoprenoids – substances that act as growth factors on the proliferation of vascular smooth muscle cells, reduces the activity of some coagulation and aggregation factors, and reduces blood plasma viscosity. Thanks to this action, it improves hemodynamics and contributes to the normalization of blood coagulation processes. In addition, HMG-CoA reductase inhibitors affect the metabolism of macrophages and thus suppress their activation, which reduces the risk of rupture of atherosclerotic plaques. All these properties of atorvastatin and essential phospholipids allow them to be used in combination with each other, in particular, in the treatment of steatosis in RA patients with NAFLD.

Table 3

**Results of ultrasound examination of the liver in rheumatoid arthritis patients under the effects of atorvastatin and essential phospholipids**

Parameters	I group (n=25)			II group (n=26)			III group (n=26)			
	Before treatment	3 months	6 months	Before treatment	3 months	6 months	Before treatment	3 months	6 months	
<b>Hepatomegaly</b>	n	25	23	16	26	26	17	26	17	15
	%	100	92	64	100	100	65.4	100	65.4*.#	57.7
<b>Echogenicity decreased</b>	n	0	2	9	0	0	9	0	9	11
	%	-	8	36	-	-	34.6	-	34.6*.#	42.3
<i>increased</i>	n	25	23	16	26	26	17	26	17	15
	%	100	92	64	100	100	65.4	100	65.4*.#	57.7
<b>Echostructures monogeneous</b>	n	0	2	9	0	0	9	0	9	11
	%	-	8	36	-	-	34.6	-	34.6*.#	42.3
<i>heterogeneous</i>	n	25	23	16	26	26	17	26	17	15
	%	100	92	64	100	100	65.4	100	65.4*.#	57.7
<b>Contours and edges equal</b>	n	25	25	25	26	26	26	26	26	20
	%	100	100	100	100	100	100	100	100	100
<i>unequal</i>	n	-	-	-	-	-	-	-	-	-
	%	-	-	-	-	-	-	-	-	-
<b>Dimensions of the right lobe increased</b>	n	25	24	16	26	26	17	26	17	15
	%	100	96	64	100	100	65.4	100	65.4*.#	57.7
<i>not increased</i>	n	0	1	9	0	0	9	0	9	11
	%	-	4	36	-	-	34.6	-	34.6*	42.3
<b>Dimensions of the left lobe increased</b>	n	25	23	14	26	22	15	17	16	14
	%	100	92	56	100	84.6	57.7	65.4*.#	61.5*.#	53.8
<i>not increased</i>	n	0	2	11	0	4	11	9	10	12
	%	-	8	44	-	15.4	42.3	34.6*.#	38.5*.#	46.2
<b>Density compacted</b>	n	16	13	9	16	9	8	15	10	6
	%	64	52	36	61.5	34.6*	30.8	57.7	38.5*	23.1*.#
<i>uncompacted</i>	n	9	12	16	10	17	18	11	16	20
	%	36	48	64	38,5	65.4*	69.2	42.3	61.5*	76.9*.#

\* – statistically significant difference compared to the indicators of the I group patients, p<0.05; # – statistically significant difference compared to the indicators of the II group patients, p<0.05.

#### 4. Conclusions

1. Comprehensive examination of RA patients with the aim of analyzing the hepatobiliary system by using ultrasound and laboratory research allows detecting the pathology of the hepatobiliary system in the early stages.

2. The initial development of NAFLD, manifested by steatosis, in RA patients significantly limits the possibilities of adequate, long-term antirheumatic and hypolipidemic therapy, which is associated with the development of hepatotoxicity and an increase in cardiovascular risk.

3. Treatment of RA patients with NAFLD should consider aspects of not only the pathogenetic, but also the prognostic effect of medicines, as well as take into account the most significant mechanisms of the formation of the systemic pathological process.

4. In addition to antirheumatic therapy in RA patients with NAFLD, the use of essential phospholipids at a dose of 600 mg three times a day and atorvastatin at a daily dose of 10 mg for 6 months allows to reduce the severity of hepatotoxic reactions, avoid stopping or canceling antirheumatic therapy, and reduce the grade of liver steatosis.

#### References

1. Aithal G. P. (2011). *Hepatotoxicity related to antirheumatic drugs*. *Nature reviews. Rheumatology*, 7(3), 139–150. <https://doi.org/10.1038/nrrheum.2010.214>
2. Alkhoury, N., & Feldstein, A. E. (2016). *Noninvasive diagnosis of nonalcoholic fatty liver disease: Are we there yet?*. *Metabolism: clinical and experimental*, 65(8), 1087–1095. <https://doi.org/10.1016/j.metabol.2016.01.013>
3. Castera, L., Friedrich-Rust, M., & Loomba, R. (2019). *Noninvasive Assessment of Liver Disease in Patients With Nonalcoholic Fatty Liver Disease*. *Gastroenterology*, 156(5), 1264–1281. <https://doi.org/10.1053/j.gastro.2018.12.036>
4. Karlsson Sundbaum, J., Eriksson, N., Hallberg, P., Lehto, N., Wadelius, M., & Baecklund, E. (2019). *Methotrexate treatment in rheumatoid arthritis and elevated liver enzymes: A long-term follow-up of predictors, surveillance, and outcome in clinical practice*. *International journal of rheumatic diseases*, 22(7), 1226–1232. <https://doi.org/10.1111/1756-185X.13576>
5. Papatheodoridi, M., & Cholongitas, E. (2018). *Diagnosis of Non-alcoholic Fatty Liver Disease (NAFLD): Current Concepts*. *Current pharmaceutical design*, 24(38), 4574–4586. <https://doi.org/10.2174/1381612825666190117102111>
6. Pennisi, G., Celsa, C., Giammanco, A., Spatola, F., & Petta, S. (2020). *The Relevance of Noninvasive Tools To Assess Fibrosis in Non-Alcoholic Fatty Liver Disease*. *Current pharmaceutical design*, 26(32), 3928–3938. <https://doi.org/10.2174/1381612826666200521133307>
7. Radovanović-Dinić, B., Tešić-Rajković, S., Zivkovic, V., & Grgov, S. (2018). *Clinical connection between rheumatoid arthritis and liver damage*. *Rheumatology international*, 38(5), 715–724. <https://doi.org/10.1007/s00296-018-4021-5>
8. Sellami, M., Saidane, O., Mahmoud, I., Tekaya, A. B., Tekaya, R., & Abdelmoula, L. (2020). *Etiological Features of Liver Involvement in Rheumatoid Arthritis*. *Current rheumatology reviews*, 16(4), 332–336. <https://doi.org/10.2174/1573397115666191007121605>
9. Vassiliadis, E., Oliveira, C. P., Alvares-da-Silva, M. R., Zhang, C., Carrilho, F. J., Stefano, J. T., Rabelo, F., Pereira, L., Kappel, C. R., Henriksen, K., Veidal, S. S., Vainer, B., Duffin, K. L., Christiansen, C., Leeming, D. J., & Karsdal, M. (2012). *Circulating levels of citrullinated and*

*MMP-degraded vimentin (VICM) in liver fibrosis related pathology. American journal of translational research*, 4(4), 403–414.

10. Wendt, M. M. N., de Oliveira, M. C., Franco-Salla, G. B., Castro, L. S., Parizotto, Á. V., Souza Silva, F. M., Natali, M. R. M., Bersani-Amado, C. A., Bracht, A., & Comar, J. F. (2019). Fatty acids uptake and oxidation are increased in the liver of rats with adjuvant-induced arthritis. *Biochimica et biophysica acta. Molecular basis of disease*, 1865(3), 696–707. <https://doi.org/10.1016/j.bbadis.2018.12.019>

11. Wheeler, P. G., Theodossi, A., Pickford, R., Laws, J., Knill-Jones, R. P., & Williams, R. (1979). Non-invasive techniques in the diagnosis of jaundice--ultrasound and computer. *Gut*, 20(3), 196–199. <https://doi.org/10.1136/gut.20.3.196>

12. Zamani, M., Alizadeh-Tabari, S., Chitkara, P., Singh, S., & Loomba, R. (2023). Prevalence of Nonalcoholic Fatty Liver Disease in Patients With Rheumatoid Arthritis: A Systematic Review and Meta-analysis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*, 21(11), 2789–2796. <https://doi.org/10.1016/j.cgh.2023.02.021>

13. Zhou, J. H., Cai, J. J., She, Z. G., & Li, H. L. (2019). Noninvasive evaluation of nonalcoholic fatty liver disease: Current evidence and practice. *World journal of gastroenterology*, 25(11), 1307–1326. <https://doi.org/10.3748/wjg.v25.i11.1307>