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Ultrasonic evaluation MAFLD in screening severity metabolic disorders

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Abstract

Metabolic dysfunction associated fatty liver disease (MAFLD) is a new proposed term for non-alcoholic fatty liver disease (NAFLD). a liver steatosis associated with Type 2 diabetes mellitus or increased physical weight/thickness, or with two or more metabolic disorders. This indicates metabolic abnormalities that result in fat accumulation in hepatocytes without the presence of alcoholic liver disease or other causes that would lead to hepatocyte abnormalities. Our goal was determine the correlation between certain stages of fatty liver disease determined by ultrasonography with increased body weight/obesity, diabetes mellitus and other metabolic disorders and with the values of biochemical parameters of liver enzymes. A prospective study was conducted at the public health institution Zivinice Health Center from August 2022 until January 2024 on a random sample of 101 patients. Observing the entire examined group, a difference in the gender distribution of hepatic steatosis is noticed, and graphically it is shown that men have hepatic steatosis more often than women. In fatty liver disease (MAFLD), stage G2 was most prevalent in 32% of patients.

Ultrasonography, along with clinical and biochemical indicators, should be an integral part of screening and monitoring of metabolic disorders as it is a non-invasive and easily accessible imaging method and allows timely therapeutic action and prevention of hepatic and extrahepatic complications.

Keywords: MAFLD; BMI; Diabetes mellitus; Ultrasonography liver

1. Introduction

Metabolic associated fatty liver disease (MAFLD) is a new term proposed in 2020 by international experts of 22 countries with the aim of associating fatty liver disease with other metabolic disorders, regardless of other causes of chronic liver disease, in order to more accurately define the pathogenesis of the disease and avoid the risk of adverse outcomes that accompany metabolic syndrome in all organs, including the liver [1]. MAFLD implies liver steatosis assessed by imaging or other diagnostic methods that are associated with diabetes mellitus type 2, by increased weight, or with at least 2 metabolic abnormalities; increased waist circumference, prediabetes, elevated blood pressure and dyslipidemia. This includes evidence that 6-20% of patients with MAFLD, who are of normal BMI and without a diagnosed diabetes mellitus, have metabolic dysregulation (most commonly visceral fat distribution) and an increased risk of complications. [2]. These metabolic abnormalities result in fat accumulation in hepatocytes without the presence of alcoholic liver disease or other known causes that would lead to hepatocyte abnormalities (viral hepatitis, total parenteral nutrition, drug-induced hepatitis, autoimmune hepatitis, etc.) [3].

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1.1. Etiology and prevalence of MAFLD

The etiology of the disease itself is still unknown, but there are well-known risk factors such as: central obesity, type 2 diabetes, i.e. insulin resistance, people older than 45, and sudden weight loss [4]. The pathology is not yet fully understood, but the most widely accepted theory is the "two-stroke" theory. The "first strike" implies the accumulation of fats primarily triglycerides and fatty acids as a result of insulin resistance; whereas β oxidation of fatty acids with the expression of pro-inflammatory cytokines leads to apoptosis or necrosis of hepatocytes followed by inflammation and consequently with fibrosis is considered a "second strike" [5]. Most patients are clinically free of problems and problems are detected accidentally during general medical systematic examinations or visits to the doctor for other reasons. A small number of patients experience nonspecific symptoms such as fatigue, malaise and pain under the right rib arch. Hepatomegaly can be observed in patients during physical examination, and the appearance of splenomegaly is often the first sign of portal hypertension and advanced liver disease [6].

Fatty disease is the most common liver disorder in the world, with increasing prevalence in young people. The prevalence of MAFLD in the general population is high-about 25% with a tendency to increase in Europe, and this prevalence in DM type 2 and obesity ranges from 50-60%, while in obese people goes up to 80%. The latest meta-analyses show that more than one third of the global population is affected by MAFLD, and that the global prevalence is around 50%, slightly higher in men than in women (59% vs. 47.5%) [7].

1.2. MAFALD diagnostics

The diagnosis of NAFLD is based on the exclusion principle. After excluding alcohol and drugs as a possible cause of liver steatosis, chronic liver damage caused by HBV and HCV must be ruled out by serology [8]. In case of negative results, one should think of rarer and unusual causes of liver damage such as: autoimmune liver diseases (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis) and metabolic diseases (Wilson's disease, hemochromatosis, alpha 1-antitrypsin deficiency); as well as the possibility of NAFLD in pregnancy and starvation. During monitoring of NAFLD, sequential monitoring of aminotransferases over a period of more than six months with an AST:ALT ratio of less than 1 is most often used. In some cases there may also be an increase in alkaline phosphatase and gamma-glutamyl transpeptidase. NAFLD also requires periodic monitoring of arterial pressure, lipograms, serum creatinine, albuminuria, and glucose and HbA1c values for the treatment of associated metabolic diseases [9].

1.3. Goals

In our research we wanted determine the correlation between certain stages of fatty liver disease detected by ultrasonography with increased body weight/obesity, arterial blood pressure, diabetes mellitus and other metabolic disorders and with the values of biochemical parameters of liver enzymes.

- Also, we wanted to determine the prevalence of fatty liver disease, as well as its stages, detected by ultrasonography in the overall patient sample and by gender.
- To determine the correlation of individual stages of liver steatosis with blood glucose level, increased body weight/fat and other metabolic disorders in the total sample and according to gender.
- Determine the correlation between individual stages of MAFLD and the value of biochemical parameters of liver enzymes as markers of liver damage.

2. Material and Methods

A prospective study was conducted at the public health institution Zivinice Health Center in the period August 2022 until January 2024 on a randomly selected sample of 101 patients who were referred for ultrasound examination of the abdomen for nonspecific abdominal pain, between ages of 34 to 84 years. In the group of patients, 55 patients were female and 46 were male. Patients have confirmed in writing that they voluntarily agree to participate in the study.

All patients were measured body mass in kilograms, waist circumference in centimeters, body height in meters, on a mechanical body scale for adults (for professional medical use) with an altimeter of up to 210 cm. Body mass index (BMI) is calculated using the formula that is mass/height^2. Waist circumference was measured with a medical tape in centimeters, with a graduation of 1 mm, in the area above the umbilicus (the thinnest part of the waist). On the basis of BMI, obesity was classified as overweight. The blood pressure of the patients was measured on the left upper arm with a mercury sphygmomanometer three times, and the mean value was taken as the result. Laboratory analyses were performed from peripheral venous blood, in the morning after 10 hours of fasting with standard biochemical tests

All patients were examined with conventional ultrasonography in B mode, on an ultrasound machine made by Esaote MyLabX6 with an abdominal convex probe 3.5mHz. Evaluation of hepatic steatosis was carried out using criteria for the degree of hepatic steatosis; a) brightness-echogenicity of parenchyma b) liver-kidney contrast c) deep attenuation of the ultrasound beam d) definition of the vessel wall and intrahepatic conduits, e) definition of the gallbladder wall

On the basis of these five criteria, the main finding that classified hepatic steatosis was:

- Grade G0 - no steatosis;
- Grade G1 mild steatosis;
- Grade G2 moderately severe steatosis;
- Grade G3 severe steatosis of the liver.

The study did not include patients with excessive alcohol intake, chronic liver disease of other known etiology, with malignant diseases and acute diseases.

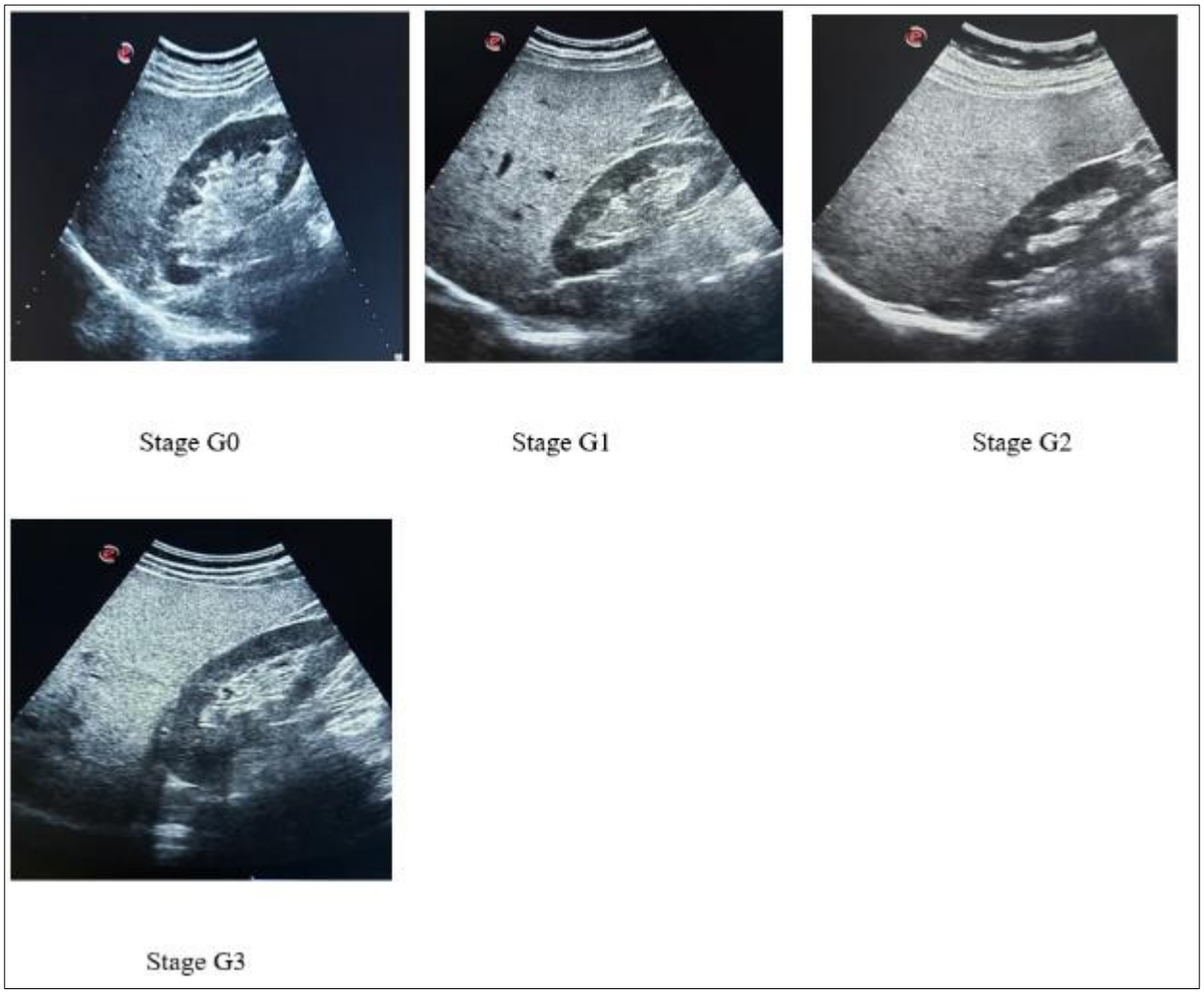

Figure 1 Degrees of hepatic steatosis based on ultrasound (G0, G1, G2, G3)

The study did not include patients with excessive alcohol intake, chronic liver disease of other known etiology, with malignant diseases and acute diseases.

3. Results

A total of 101 patients were included in the trial, of which there were 46 male and 65 female patients. This difference in the incidence of male and female respondents is also statistically significant in favor of female respondents (.χ^2=11.025; df=1; p=0.001) (Figure 2.).

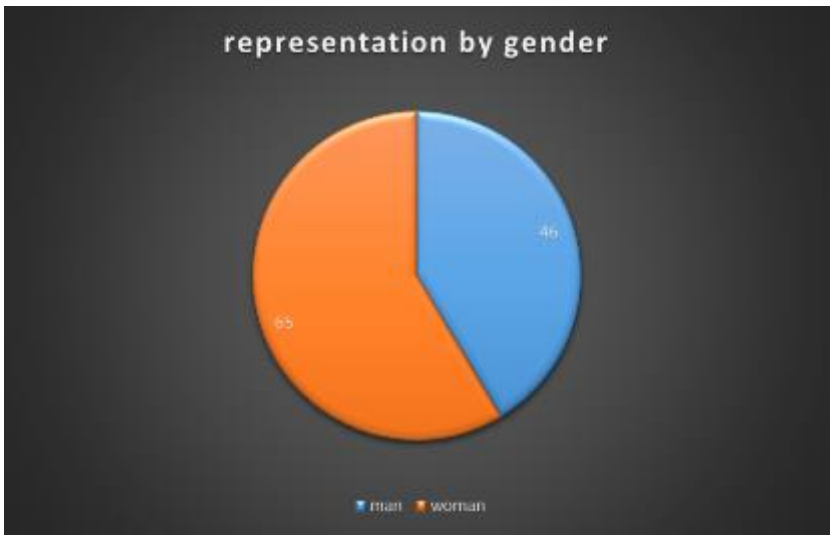

Figure 2 Representation by gender

Observing the entire examined group, a difference in the gender distribution of hepatic steatosis is noticed, and graphically it is shown that men have hepatic steatosis more often than women. Stages G2 and G3 of hepatic steatosis are most common in men (G2 = 31.68%, G3 0-23.76%) in a significantly higher ratio, which is also statistically significant (t = 19.428; df = 31; p<0.001) (Figure 3.).

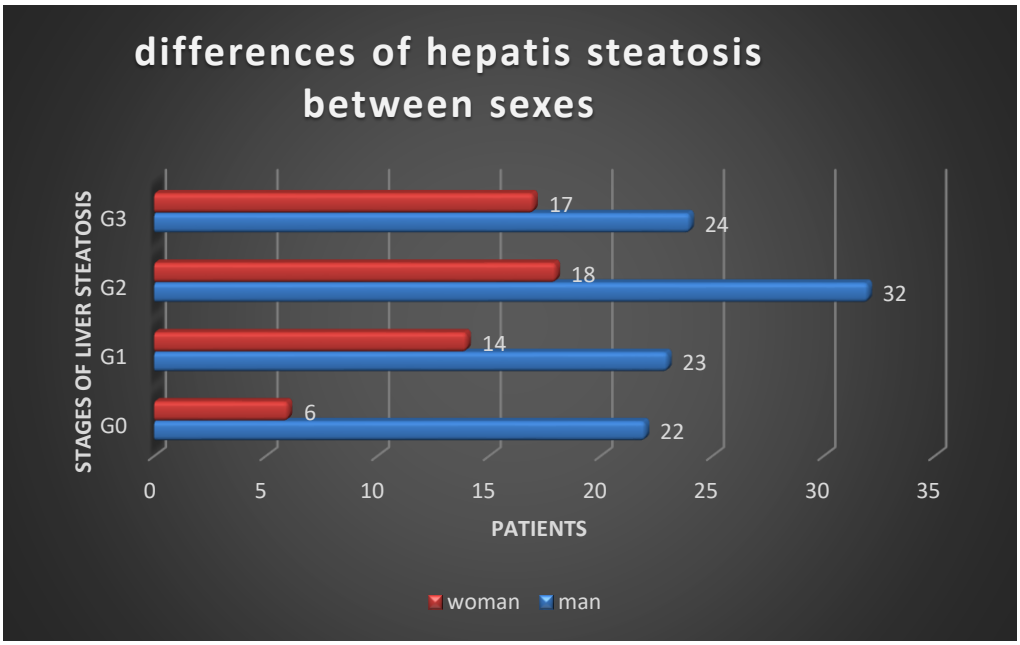

Figure 3 Presents liver steatosis between genders

By testing the correlation between BMI, SBP, DBP, WC and blood glucose levels, there was unidirectional correlation (Pearson's r = 0.179 p = 0.038) and a significant statistical difference in patients who have elevated BMI, which is correlated with elevated SBP and DBP. BMI and WC correlates with the T test, which is statistically significant in patients of both genders (χ^2 = 33.531; df = 5; p <0.0015) (Figure 4).

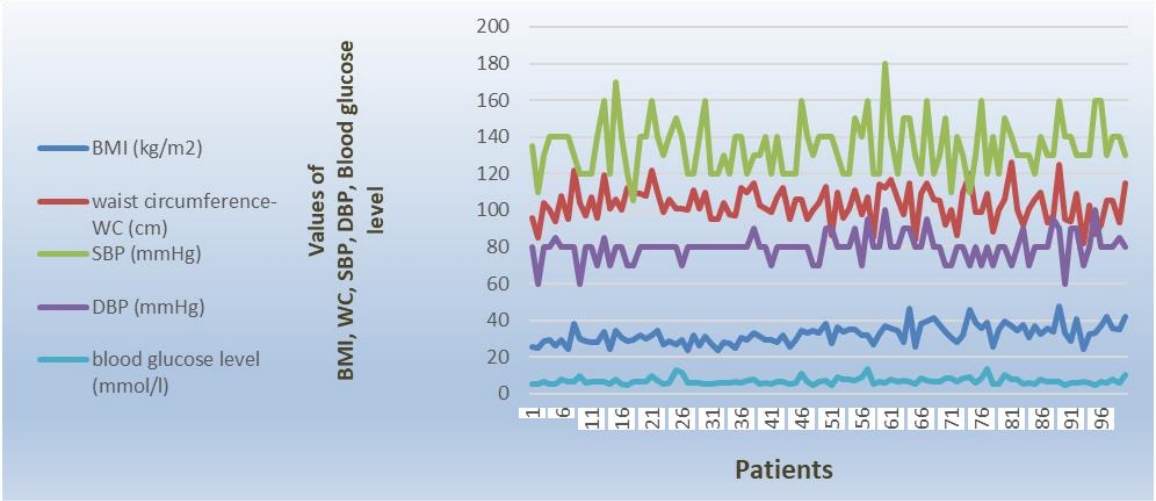

Figure 4 The influence of BMI on WC, SBP and DBP

As part of fatty liver disease (MAFLD), 22% of patients had stage G0 changes in the liver as part of steatosis on ultrasound examination, while 23% of patients had G1 changes, stage G2 was present in 32% and stage G3 in 24% of patients. According to the Kruskal-Wallis test, this difference is statistically significant (.χ^2= 18.6; df = 3; p = 0.001) (Figure 4.).

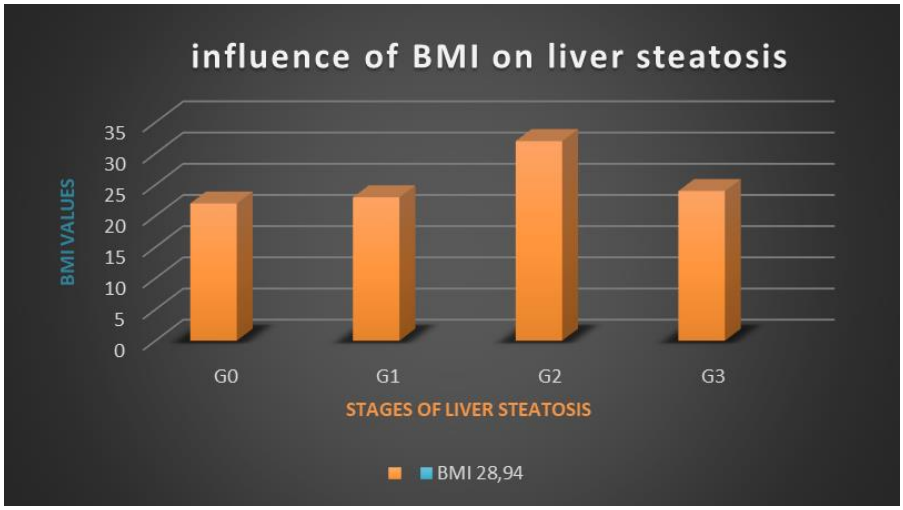

Figure 5 The influence of BMI on liver steatosis

The Kruskal-Wallis test for the test groups also showed a statistically significant difference between the non-steatosis hepatic (G0) and the hepatic steatosis (G1, G2, G3) groups (χ^2 = 30.446; df = 2; p <0.001). The group of patients with metabolic syndrome have a mean rank and the highest median, suggesting that this difference is most conditioned by WC values in these groups (Table 1.).

Table 1 Differences between individual groups in WC values

	Mann-Whitney U	**Significance level**	**Difference in favor of the group:**
Normal liver G0	Z=-4.92	p<0.001	Untreated
Liver steatosis G1	Z=-2.88	p=0.003	Treated with hypolipemics
Liver steatosis G2	Z=-3.79	p<0.001	Treated with hypolipemics
Liver steatosis G3	Z=-3.32	p<0.001	Treated with hypolipemic and antihypertensives

(χ^2 = 28.742; df = 2; p <0.001)

Mean systolic and diastolic arterial blood pressure in the I study group, as well as their highest and lowest values, were presented in **Table 2**. By testing the correlation between BMI and systolic and diastolic blood pressure values it was found that there was a one-way correlation (Pearson's r = 0.136; p = 0.043) (Table 2.).

Table 2 Values of systolic and diastolic blood pressure

		N	Average value	Standard deviation	Lowest value	Highest value
Systolic pressure	Normal liver	22	123.63	24.635	80	120
	Liver steatosis G1	23	134.88	27.885	70	130
	Liver steatosis G2	32	162.75	15.189	90	150
	Liver steatosis G3	24	164.53	9.182	85	160
	Total	101	146.44	35.593	81.25	140
Diastolic pressure	Normal liver	22	82.10	10.488	60	90
	Liver steatosis G1	23	87.00	12.547	70	90
	Liver steatosis G2	32	91.18	9.223	70	100
	Liver steatosis G3	24	93.75	7.808	80	90
	Total	101	89.50	14.475	70	92.5

F (3.452) = 103.034; p<0.001; eta squared = 0.67 (systolic blood pressure; F (3.764) = 59.291; p<0.001; eta squared = 0.51 (diastolic blood pressure

Table 3 The influence of dyslipidemia on liver enzymes and blood glucose level

	Value of AST enzyme	Value of ALT enzyme	Incidence of dyslipidemia	Blood glucose level
Male patients with G2 steatosis level	22.4	24.7	2	6.4
Female patients with G2 steatosis level	24.1	23.5	4	6.9
Male patients with G3 steatosis level	27.3	25.3	5	6.7
Female patients with G3 steatosis level	25.2	24.8	4	7.7
Total			15	27.7

14.85% of changes per type of dyslipidemia were observed as part of hepatic steatosis. According to the Kruskal-Wallis test, this difference is statistically significant (.χ^2=29.759; df=8; p<0.001). In female patients with stage 3 liver steatosis, a higher blood glucose level was observed (χ^2=19.321; df=4; p<0.003), which is also statistically significant (Table 3).

4. Discussion

In the study, we found that patients with severe hepatic steatosis (G2, G3) had 2 or more criteria for metabolic syndrome. All patients with a history of diabetes had severe steatosis, especially in obese patients with increased waist circumference. Arterial hypertension was not an independent correlation factor with degrees of hepatic steatosis, but was associated with other metabolic disorders, such as elevated glucose and dyslipidemia. Female patients on average had a higher degree of liver steatosis as well as a higher BMI and WC, the prevalence of hyperglycemia was higher in women compared to men.

Several studies have shown that the definition of MAFLD is more practical in identifying patients at higher risk of progression of fatty liver disease. Huang et al. showed that patients diagnosed with MAFLD, had both a more severe degree of liver fibrosis compared to NAFLD, and a higher number of complications [10] **.** In retrospect analysis ITA.LI.CA the databases showed that there was no increase in incidence of infection with hepatitis B and C viruses from 2012 to 2019, actually it tends to decline. On the other hand, the incidence of MAFLD caused by hepatocellular carcinoma 3.6 was significantly increased% [11]**.** It has been observed that MAFLD is not only a risk of progression of liver disease, but also of extrahepatic events, especially cardiovascular events and extrahepatic malignancies such as colorectal cancer in men and breast cancer in women, but also many other metabolic disorders [12].

A major meta-analysis from 2015 has shown that the presence of steatosis in more than 33% of hepatocytes on liver biopsy becomes optimal for detection of steatosis using imaging methods, while none of the imaging methods can distinguish NASH from NAFL. The same meta-analysis also showed the unreliability of imaging methods if the degree of steatosis is less than 30 %. The same meta-analysis also showed the unreliability of imaging methods if the degree of steatosis is less than 30 % [13].

Newer research by Bulum's collaborators indicates that MAFALD can actively contribute to the development of chronic kidney disease by releasing a series of mediators from the liver into the circulation, which worsens systemic insulin resistance and causes atherogenic dyslipidemia [14].

There is evidence that progressive MAFLD-a-steatohepatitis may act as an independent risk factor, supporting atherogenic dyslipidemia, a pro-inflammatory, profibrogenic and procoagulant systemic environment. This suggests that assessing the extent of MAFLD is a good prognostic factor for extrahepatic adverse events **(3).** This connection between MAFLD and metabolic disorders is "two-way", that is, all of them separately, especially diabetes mellitus type 2, increase the risk of development and progression of MAFLD [15]**.**

On the basis of the proposed criteria by the consensus opinions of international experts 2020 the diagnosis of MAFLD is determined by histopathological (biopsy), imaging or blood biomarker evidence with the presence of the previously mentioned metabolic disorders. There are currently a large number of non-invasive scoring systems (Biopsy free scoring system-BFSS) for MAFLD screening and risk assessment for further progression to fibrosis and cirrhosis [16]**.** Their disadvantages are insufficient specificity for accurate diagnostic assessment, and less availability for wider use. Biopsy, on the other hand, is an invasive diagnostic procedure with the possibility of complications. For this reason, a combination of imaging and biochemical tests is needed in order to obtain an earlier and more accurate diagnostic assessment, for timely therapeutic intervention [17].

Numerous studies have shown the unreliability of imaging methods in the detection of grade and fibrosis. The" gold standard " for NASH diagnostics is still a liver biopsy. Liver biopsy although an invasive method allows for pathohistological grading of NASH and later liver fibrosis [18].

A meta-analysis performed by Pereira and colleagues in 2015 on more than 400 patients showed that patients suffering from MAFALD can develop progressive liver fibrosis [19].

5. Conclusion

Analyzing 101 patients with non-specific abdominal complaints, it can be concluded that higher body mass and waist circumference is an independent risk factor for the occurrence of liver steatosis and metabolic disorders. Hepatic steatosis worsens with a longer duration of metabolic disorders and it can serve as an indicator of the length and severity of metabolic disorders, and thus a greater possibility of complications. The evaluation of hepatic steatosis by ultrasonography alone cannot be an indicator of further progression of MAFLD into steatohepatitis and fibrosis, but the more severe degree of steatosis is a signal for further diagnostic treatment with more sensitive methods and evaluation of complications. This implies therapeutic action aimed at risk factors such as lifestyle changes, better regulation of diabetes and other measures while the liver disorder is still reversible. The emphasis is on the easy availability and non-invasive diagnostic technique that can be a predictor for further damage that produces a metabolic disorder in the entire organism, and above all cardiovascular complications.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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