

## Liver histology according to the presence of metabolic syndrome in nonalcoholic fatty liver disease cases

Hüseyin Saadettin Uslusoy, Selim Giray Nak, Macit Gülten, Zeynep Bıyıklı

Hüseyin Saadettin Uslusoy, Selim Giray Nak, Macit Gülten, Uludag University Medical School, Department of Gastroenterology, Bursa 16059, Turkey

Zeynep Bıyıklı, Ankara University School of Medicine, Department of Biostatistics, Ankara 06100, Turkey

**Author contributions:** Uslusoy HS performed research; Nak SG wrote and translated the manuscript; Gülten M designed research and performed revisions; Bıyıklı Z performed the analysis and interpretation of data.

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Correspondence to: Dr. Hüseyin Saadettin Uslusoy, Uludag University Medical School, Department of Gastroenterology, Bursa 16059, Turkey. [hulusoy.23@hotmail.com](mailto:hulusoy.23@hotmail.com)

Telephone: +90-354-2121070 Fax: +90-354-2120923

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### Abstract

**AIM:** To investigate the histologic features of the liver in nonalcoholic fatty liver disease (NAFLD) cases according to the presence of metabolic syndrome or its individual components.

**METHODS:** We enrolled 81 patients (40 male, 41 female) who were diagnosed with fatty liver by ultrasonographic scan and fulfilled the inclusion criteria. First anamnesis, anthropometric, clinical, laboratory and imaging features of all participants were recorded and then liver biopsy was performed after gaining consent from patients. Diagnosis of metabolic syndrome was dependent on patients having 3 or more out of 5 risk criteria defined by the WHO. Biopsy specimens were assessed according to Brunt *et al*'s classification.

**RESULTS:** Sixty-nine of the 81 patients had nonalcoholic steatohepatitis (NASH), 11 had simple fatty liver and 1 had cirrhosis according to histologic evaluation. Comparisons were made between two groups of NASH patients, those with and without metabolic syndrome. We did not detect statistically significant differences in liver histology between NASH patients with and without metabolic syndrome.

**CONCLUSION:** NASH can progress without metabolic risk factors or the presence of metabolic syndrome.

### INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is common and has a spectrum of liver pathologies beginning with simple fatty liver and progressing to steatohepatitis, cirrhosis and liver failure<sup>[1,2]</sup>. NAFLD is frequently present along with the components of metabolic syndrome and, hence, is generally regarded as a manifestation of metabolic syndrome<sup>[3]</sup>. As insulin resistance (IR) is a main mechanism in the pathogenesis of metabolic syndrome, it is also thought to be an initiating factor in the process of NAFLD<sup>[4,5]</sup>. Nevertheless, some NAFLD cases did not fulfill all criteria of metabolic syndrome and did not display IR at the onset of disease according to the literature<sup>[6]</sup>. Certain recent studies revealed that all patients with NAFLD did not also have metabolic syndrome or its separate symptoms, including IR<sup>[6]</sup>.

In the present study, differences in liver histology according to the presence of metabolic syndrome or its individual components were investigated. We also explored the effect of IR on the development of NAFLD. The features of patients with an NAFLD-like clinical course, accompanying diseases, laboratory findings and histologic aspects, are able to provide remarkable clues into the etiopathogenesis of the disease. Although there were many common points and reported issues supporting the presence of metabolic disorder and its components in the etiology of NAFLD, some studies revealed that NAFLD could also progress in lean people, nondiabetics, males, adolescents and children<sup>[7,8]</sup>.

Certain articles in the literature have disclosed striking findings; for example, the frequency of IR in NAFLD patients varies from 47%-98% without diabetes also being present. Likewise the prevalence of metabolic syndrome in NAFLD patients was as low as 36% in some studies<sup>[6]</sup>. Furthermore, in different populations the prevalence of metabolic syndrome is about 22% and in NAFLD patients there was a subgroup who did not have IR<sup>[6]</sup>. We aimed to reveal whether there is a group of NAFLD patients without metabolic syndrome and IR or not. Recently, increasing number of studies on this topic are being presented. But more investigations are needed to attain convincing outcomes.

## MATERIALS AND METHODS

### Patients

This study consisted of 81 patients who were referred to Uludag University Gastroenterology Division. All 81 patients were diagnosed with fatty liver by ultrasonographic scan. After this complete clinical, anthropometric and laboratory assessments and liver biopsy were performed. Exclusion criteria included: alcohol consumption of > 20 g/d, pregnancy, positive tests indicating the presence of hepatitis B or C virus, autoimmune liver disease, hemochromatosis, Wilson's disease,  $\alpha$ -1 antitrypsin deficiency, primary biliary cirrhosis, primary sclerosing cholangitis and toxic liver disease.

### Laboratory studies

After taking a medical history, all cases underwent liver examination by ultrasonography and then clinical, anthropometric, complete blood count and biochemical assessments were performed. Biochemical evaluation consisted of assessment of alanine aminotransferase (ALT), aspartate aminotransferase (AST),  $\gamma$ -glutamyltransferase (GGT), alkaline phosphatase (ALP), bilirubin, albumin, high density lipoprotein (HDL)-cholesterol, triglycerides, glucose, and insulin levels and an oral glucose tolerance test (OGTT). Anthropometric parameters measured were height, weight, body mass index (BMI), waist and hip circumferences and waist/hip ratio values. Assessment of obesity was dependent on WHO criteria<sup>[9]</sup>. American Diabetes Association (ADA) criteria were used to define type 2 diabetes, impaired glucose intolerance, and impaired fasting glycemia<sup>[10]</sup>. Patients receiving oral antidiabetics or insulin therapy were accepted as diabetics. Hypertension was considered to be present when resting blood pressure was  $\geq$  140/90 mmHg or patients were receiving antihypertensive drug therapy. The homeostasis model assessment of IR (HOMA-IR) method was used to measure IR and patients were classified as 'insulin resistant' when HOMA-IR value was > 2.70. ALT levels 1.5 or more times higher than upper normal values indicated an elevation in ALT. The diagnosis of metabolic syndrome was made according to WHO criteria<sup>[10,11]</sup> (BMI  $\geq$  30 kg/m<sup>2</sup>, waist/hip circumference ratio > 0.90 in men and > 0.85 in women, fasting blood glucose  $\geq$  1100 mg/L, overt diabetes, presence of impaired glucose tolerance and/or IR,

triglycerides  $\geq$  1500 mg/L, HDL-cholesterol < 400 mg/L in men and < 500 mg/L in women, arterial blood pressure  $\geq$  140/90 mmHg and presence of microalbuminuria). Patients should have at least three of these criteria to be diagnosed with metabolic syndrome. The study was approved by the hospital ethics committee.

### Pathology

Liver biopsies were performed in 81 patients according to the severity of the clinical disease after the patients had given consent. All liver biopsy specimens were examined by a liver pathologist. Scoring of necroinflammation and fibrosis was performed using criteria devised by Brunt *et al*<sup>[12,13]</sup>. Nonalcoholic steatohepatitis (NASH) was diagnosed according to liver histology indicating steatosis (mild: < 33% of lobules, moderate: 33%-66% of lobules and severe: > 66% of lobules) with (1) ballooning degeneration of hepatocytes/mallory bodies; (2) necroinflammation (lobular or portal); (3) fibrosis (perisinusoidal, periportal and/or bridging) or cirrhosis.

### Statistical analysis

Due to the number of patients being small, statistical evaluation and *P* values were not available, as shown in all tables. Hence, features of patients were evaluated according to their percentage values.

## RESULTS

### Anthropometric, clinical and laboratory results

Eighty-one patients (40 male, 41 female) who were diagnosed as having fatty liver by ultrasonographic examination participated in this study at the Uludag University Gastroenterology Division. Only 8% of patients had slight and dull abdominal pain. The prevalence of hepatomegaly was 16% and 4% in NASH and simple fatty liver groups, respectively. All 81 patients underwent liver biopsy; 69 (35 male, 34 female) were diagnosed with NASH, 11 (4 male, 7 female) were diagnosed with simple fatty liver and 1 (male) was diagnosed with cirrhosis. First, we compared all cases with NASH and simple fatty liver to each other according to anthropometrical, clinical and laboratory data, including presence of IR and metabolic syndrome, but we did not find any significant difference between the 2 groups. For instance, numbers and proportions of IR and metabolic syndrome in NASH patients were 30 (43.4%) and 46 (66.7%) respectively and in simple fatty liver patients were 6 (54.5%), and 9 (81.8%) respectively. Then, the features of liver histology were examined in detail with regard to individual components of metabolic syndrome. As shown in Table 1, liver steatosis and necro-inflammation were evaluated with respect to individual parameters of metabolic syndrome. Because the numbers of cases in each section of Table 1 were too small, statistical assessments were not available and data analysis and interpretation were performed using percentage values. It seemed that the presence of individual risk factors did not affect the severity of steatosis and necroinflammation. Similarly, in Table 2 progression of liver fibrosis was

**Table 1** Presence of metabolic risk factors and liver histology (steatosis/necroinflammation) in NASH cases

	NASH patients (n = 69)					
	Fatty infiltration			Necroinflammation		
	Mild (%)	Moderate (%)	Severe (%)	Mild (%)	Moderate (%)	Severe (%)
Gender						
Male	37.1	40.0	22.9	31.4	62.9	5.7
Female	41.2	35.3	23.5	20.6	64.7	14.7
Hepatomegaly						
(+) <sup>1</sup>	31.3	37.5	31.2	25.0	62.5	12.5
(-) <sup>1</sup>	38.5	38.5	23.0	27.0	61.5	11.5
Body mass index						
18.5-24.9	0	66.6	33.4	33.4	33.3	33.3
25-29.9	35.3	41.2	23.5	26.5	64.7	8.8
30-39.9	46.5	25.0	28.5	28.6	57.1	14.3
> 40	25.0	75.0	0	25.0	75.0	0
Central obesity						
(+)	38.8	40.8	20.4	26.5	63.3	10.2
(-)	35.0	30.0	35.0	30.0	55.0	15.0
Hypertension						
(+)	33.4	33.3	33.3	19.0	62.0	19.0
(-)	39.6	39.6	20.8	33.3	58.3	8.4
Diabetes						
(+)	40.0	35.0	25.0	33.4	57.1	9.5
(-)	38.7	38.7	22.6	30.7	59.1	10.2
Hypertriglyceridemia						
(+)	36.2	34.0	29.8	21.4	63.8	14.8
(-)	41.0	54.5	4.5	41.0	54.5	4.5
Insulin resistance						
(+)	33.3	36.7	30.0	13.3	73.4	13.3
(-)	43.5	34.7	21.8	47.8	43.5	8.7

<sup>1</sup>(+): Present; (-): Absent. Presence of hypertriglyceridemia and insulin resistance seemed to increase the severity of steatosis and necroinflammation but these findings were not significant.

evaluated with respect to individual parameters of metabolic syndrome and again it seemed that individual metabolic risk factors did not initiate or advance liver fibrosis. In Table 3, dual combinations of risk factors were compared to grading and staging values of liver histology and there was no remarkable outcome. Finally, in Table 4 detailed histological parameters were evaluated according to the presence of metabolic syndrome. However, we did not determine any correlation between histological severity and the presence of metabolic syndrome.

When the distribution of risk factors and metabolic syndrome was examined in 11 simple fatty liver patients, the following results were found: central obesity 57%, hypertension 53%, diabetes 18.1%, hypertriglyceridemia 58%, low HDL level 57%. While 9 of these 11 patients had metabolic syndrome, the remaining 2 patients had only 2 risk factors for metabolic syndrome. The single cirrhotic patient was a 55-year-old male with metabolic syndrome who had obesity (also central obesity), diabetes and a low-HDL level.

### Histopathology

The important highlights of liver histology belonging to our 81 cases were investigated. Since the numbers of patients in each of the subgroups were too small, statistical assessments were not available and interpretations of histological findings in all tables were dependent on

**Table 2** Presence of metabolic risk factors and liver histology (stage) in NASH cases

	NASH patients (n = 70) <sup>1</sup>				
	Fibrosis				Cirrhosis (%)
	Absent (%)	Perisinusoidal/ Pericellular (%)	Periportal (%)	Bridging (%)	
Gender					
Male	51.4	23.0	14.3	8.60	2.70
Female	38.2	47.0	5.9	8.90	-
Hepatomegaly					
(+) <sup>2</sup>	44.1	31.2	6.3	12.5	5.90
(-) <sup>2</sup>	44.3	36.5	13.5	7.70	-
Body mass index					
18.5-24.9	33.3	0	33.3	33.3	-
25-29.9	38.2	44.1	11.7	5.8	-
30-39.9	46.4	25.0	14.2	10.7	3.12
> 40	25.0	75.0	0	0	-
Central obesity					
(+)	46.9	30.6	16.3	6.1	2.04
(-)	65.0	20.0	10.0	5	-
Hypertension					
(+)	47.8	42.8	4.7	4.7	-
(-)	58.4	24.4	12.7	4.5	2.04
Diabetes					
(+)	28.5	38.0	14.2	14.2	4.76
(-)	53.1	25.5	12.7	8.5	-
Hypertriglyceridemia					
(+)	50.0	25.0	15.6	9.3	-
(-)	59.3	31.2	6.2	3.1	4.34
Insulin resistance					
(+)	53.3	36.6	13.3	3.3	3.33
(-)	65.7	18.4	10.5	2.6	-

<sup>1</sup>69 patients with NASH and 1 cirrhotic patient; <sup>2</sup>(+): Present; (-): Absent. Presence of diabetes and insulin resistance seemed to increase the severity of fibrosis, but these findings were not significant.

percentage values. As shown in Table 1, liver steatosis and necroinflammation were evaluated in detail according to the individual presence of metabolic risk factors and there was no significant difference in the two groups. Similarly Table 2 showed that when liver fibrosis was studied with respect to the presence of individual risk factors there was no significant difference. In Tables 3 and 4, the presence of dual combinations of risk factors and the presence of defined metabolic syndrome, respectively, were compared to liver histology. Neither the presence of a dual combination of risk factors nor the presence of defined metabolic syndrome were found to be closely related with the severity of steatosis, necroinflammation and fibrosis. Interestingly, among 11 patients with simple fatty liver each patient had at least two metabolic risk factors. In the simple fatty liver group, the prevalence of defined metabolic syndrome was 81.8% which was higher than that in the NASH group. Finally, 1 patient who was diagnosed with cirrhosis according to liver histology had metabolic syndrome.

### DISCUSSION

The relationship between NAFLD and metabolic

**Table 3** Dual combinations of risk factors and liver histology in NASH cases

Liver histology	NASH cases		
	Ob + DM (n = 6)	Ob + Htg (n = 8)	DM + Htg (n = 2)
Grade			
1	3	2	0
2	2	6	1
3	1	0	1
Stage			
0	1	3	0
1	4	4	1
2	1	0	0
3	0	1	1
4	0	0	0

Ob: Obesity; DM: Diabetes mellitus; Htg: Hypertriglyceridemia. Dual combination of risk factors did not seem to effect liver histology.

syndrome is well known. Certain metabolic disorders like obesity, diabetes, hypertriglyceridemia and hypertension frequently associate with NAFLD and are also components of metabolic syndrome<sup>[3,4,14]</sup>. Insulin resistance was thought to be a shared and basic metabolic disturbance in both these groups of diseases<sup>[15]</sup>. In the general population, the prevalence of NAFLD is 10%-24% while the prevalence of NASH is about 1%-5%<sup>[16]</sup>.

The association between NAFLD and metabolic syndrome gave rise to many studies on this subject. The prevalence of metabolic syndrome in NASH and simple fatty liver cases is 22.8%-88% according to the literature<sup>[14,17-20]</sup>. This suggests the relationship between NAFLD and metabolic syndrome is not a stable and constant feature. Moreover, the presence of IR was suggested to be a common and frequent finding in both NAFLD and metabolic syndrome in various studies<sup>[5,14,15,21]</sup>. Marchesini *et al*<sup>[17]</sup> revealed the prevalence of IR in NAFLD was 61%; but in certain recent studies, a low prevalence of IR in NAFLD was found<sup>[6,22,23]</sup>.

The influence of individual risk factors and defined metabolic syndrome on liver histology have become considerable and have inspired comprehensive studies. Marchesini *et al*<sup>[17]</sup> and Angelico *et al*<sup>[24]</sup> found a correlation between various degrees of liver steatosis (mild, moderate and severe) and BMI. According to studies by Willner *et al*<sup>[21]</sup>, Angulo *et al*<sup>[25]</sup> and Ratziu *et al*<sup>[26]</sup> advanced obesity may be a risk factor for the development of liver fibrosis. But Xanthakos *et al*<sup>[27]</sup> stressed that in morbidly obese adolescents, severe NASH was uncommon and the presence of metabolic syndrome did not distinguish NASH from steatosis. We did not observe any connection between increased BMI and liver histology (steatosis and necroinflammation/fibrosis) in our NASH cases (Tables 1 and 2). Camilo Boza *et al*<sup>[28]</sup> did not find a significant association between BMI and histological changes; but in their study, high HOMA-IR values and ALT levels were the only independent predictors of NASH. Among our 69 cases with NASH, only 3 (4.34%) had normal body weight and among our simple fatty liver group (n = 11) only 1 (9.09%)

**Table 4** Liver histology according to the presence of metabolic syndrome in NASH cases (%)

Liver histology	Patients with NASH (n = 69)	
	With metabolic syndrome (n = 46, 66.6%)	Without metabolic syndrome (n = 23, 33.4%)
Fatty infiltration		
Mild	20 (43.4)	11 (47.8)
Moderate	19 (41.3)	6 (26.1)
Severe	7 (15.3)	6 (26.1)
Necroinflammation		
Absent	0 (0)	0 (0)
Mild	13 (28.3)	9 (39.1)
Moderate	28 (60.9)	13 (56.5)
Severe	5 (10.8)	1 (4.40)
Fibrosis		
Absent	20 (43.4)	9 (39.1)
Perisinusoidal/pericellular	16 (34.7)	9 (39.1)
Periportal	7 (15.4)	2 (8.60)
Bridging	3 (6.50)	3 (13.2)
Cirrhosis	1 (2.12)	0 (0)

Evaluations were performed using percentage values. Presence of metabolic syndrome seemed to increase the severity of steatosis, necroinflammation and fibrosis in liver, but these results were not significant as well.

patient had normal body weight; there was no significant difference between these two groups. Diabetes and dyslipidemia (especially hypertriglyceridemia and low HDL level) were also considered to affect liver histology<sup>[29-31]</sup>. Risk factors for metabolic syndrome and defined metabolic syndrome was strongly considered to affect liver histology according to Marceau *et al*<sup>[32]</sup>.

But, still there are important and controversial points in the natural course of NAFLD. Which one has a precedence: liver steatosis or IR? Recently it was noticed that NAFLD could occur in nonobese, nondiabetic persons and even in infants and adolescents<sup>[7]</sup>. Some patients with NAFLD may not have metabolic risk factors initially and the components of metabolic syndrome may emerge during the course of the disease<sup>[24]</sup>. In these patients, after diagnosis of NAFLD the required time for genesis of metabolic disorders like hyperglycemia, hypertension and hyperlipidemia is not well known. Furthermore, not all NAFLD patients fulfill the criteria of metabolic syndrome according to the literature. Recently, certain studies showed that there have been lower prevalences of metabolic syndrome among NAFLD patients. For instance Moon *et al*<sup>[33]</sup> performed research to identify metabolic risk factors and clinical features for each stage of liver fibrosis in NAFLD patients and in their 25 study cases with NAFLD, only 14 patients (56%) had metabolic syndrome. They found no difference in the prevalence of metabolic syndrome between the simple steatosis and the NASH subgroups (5/10, 50% *vs* 9/15, 60%). In addition, there were no significant differences in the histological features of two separate NASH groups which were constituted according to the presence or absence of metabolic syndrome. Similarly, we detected some cases which did not have metabolic syndrome,



but had NASH (23 cases = 33.4% of all NASH cases). Conversely, some cases had metabolic syndrome, but were not diagnosed with NASH. The latter only had simple fatty liver (9 cases = 81.8% of all simple fatty liver cases). In our study, approximately 2/3 of the 69 NASH cases (66.6%) fit the criteria of metabolic syndrome and the remaining patients (33.4%) did not fit the full criteria of metabolic syndrome. These results suggest different causes of NASH other than metabolic syndrome should be searched for or that these NASH cases may represent patients in the early stages of metabolic syndrome. However, Kang *et al.*<sup>34]</sup> stated that a low proportion, 34% (31 of 91 patients), of NAFLD patients had metabolic syndrome, but these patients also had higher scores for steatosis and NASH activity.

Recent studies claimed that not only metabolic risk factors, but IR also could influence liver histology. Dixon *et al.*<sup>22]</sup> reported that HOMA-IR, ALT and arterial hypertension were independent predictors for NASH; but, they also found that 7.8% of their study patients had NASH even though they had normal AST and HOMA-IR values. Bahrami *et al.*<sup>35]</sup> found the rate of IR was only 54.7% in 53 patients with NASH. Similarly, Guidorizzi de Siqueira *et al.*<sup>23]</sup> determined the frequency of IR among NAFLD patients and described IR according to metabolic risk factors and histological findings. In their study, IR was detected in only 33% of NAFLD patients; but, there was a high frequency of IR in patients with advanced fibrosis, suggesting that IR may influence the prognosis of NAFLD. Sakurai *et al.*<sup>36]</sup> found that only steatosis was significantly and independently associated with elevated HOMA values; but there was no similar association with the grade or stage of NASH. However, we did not detect any connection between the presence of IR and liver histology. An interesting observation was expressed by Machado *et al.*<sup>6]</sup> who found that rates of IR in NAFLD patients ranged from 47% to 98% and only 36% of patients with NAFLD fulfilled three criteria of metabolic syndrome. The authors of this study designed it so that certain patients did not have IR at the onset of the study. The results of the study have been attributed to different factors. For instance, liver disease may precede IR or there may be a lack in sensitivity in the HOMA method.

In our study, NAFLD did not change histologically according to the presence of metabolic syndrome and its individual components. At the onset of NAFLD, metabolic disturbances may not be present, so patients with simple fatty liver should be followed for progression of metabolic disorders in the future.

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## COMMENTS

### Background

Obesity, diabetes and hyperlipidemia are components of metabolic syndrome

and are frequently associated with nonalcoholic fatty liver disease (NAFLD). NAFLD consists of simple fatty liver and nonalcoholic steatohepatitis (NASH). The prognosis of NAFLD may worsen when there is an association with risk factors or metabolic syndrome. Insulin resistance (IR) is considered the common pathogenetic factor in both metabolic syndrome and NAFLD. We aimed to emphasize that NAFLD and NASH could progress not only in patients with metabolic risk factors, but also in nonobese healthy persons. Hence we investigated the histologic features of liver in NAFLD cases according to the presence of metabolic syndrome or its individual components.

### Research frontiers

In certain patients with NAFLD and NASH, the prevalence of metabolic syndrome was low and the influence of risk factors or metabolic syndrome on liver histology was not significant when compared to those without metabolic syndrome.

### Innovations and breakthroughs

It is important to be aware that it is not just NAFLD or NASH patients with metabolic syndrome who are at risk of advanced liver disease, but other NAFLD and NASH cases without metabolic syndrome may have severe liver disease. A new approach for these patients should be designed.

### Applications

For general public health, individuals diagnosed by ultrasonography scan as having fatty liver with or without risk factors and metabolic syndrome should be followed up closely for further serious complications and outcomes.

### Terminology

NAFLD and NASH may progress and worsen without metabolic syndrome (obesity, diabetes and hyperlipidemia) being present. In contrast to general opinion, the approach to individuals diagnosed with fatty liver by ultrasonographic examination should not be limited to the presence of metabolic syndrome. All patients with fatty liver should be advised about the hazardous outcomes of NAFLD.

### Peer review

This article is consistent and factual, and meets the aims of introducing NAFLD and NASH, advising patients to avoid their likely noxious outcomes and recommending clinical staff make the requisite inspections if there has been a diagnosis of NAFLD or NASH.

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