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Etiologic Factors of Nonalcoholic Hepatosteathosis in Malatya

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Abstract

Aim: Etiology of non-alcoholic fatty liver disease is not exactly understood. The aim of this study is to investigate the etiologic factors in patients with non-alcoholic fatty liver disease in and around Malatya, Turkey.

Material and Methods: In patients who applied to the Department of Gastroenterology, Inonu University, fatty liver was detected through hepatobiliary ultrasonography; these patients were evaluated retrospectively. Patients having over 20 gram alcohol/day in females and 30 gram alcohol/day in males were ruled out to exclude alcohol dependent fatty liver. Patients with normal liver enzyme levels and those with a two fold or higher increase were accepted as hepatosteatosis and steatohepatitis patients, respectively.

Results: A total of 112 patients 58 (51.8%) women, 54 (48.2%) men with the 43.8±11.3 years mean age were included in the study. The mean age of men was 41.8±11.3 years and the mean age of women was 45.4±11.3 years. In a total of 112 patients, we have detected hyperlipidemia in 97 (86.6%), obesity in 53 (47.3%), insulin resistance in 47 (42%), hyperlipidemia with insulin resistance in 16 (14.2%), hyperlipidemia with obesity in 27 (24.1%), obesity with insulin resistance in 35 (31.3%), and latent diabetes mellitus in 11 (31.3%).

Conclusion: Our results suggest that it is important to evaluate patients with the risk factors such as hyperlipidemia, obesity, insulin resistance regarding non-alcoholic fatty liver disease, which itself may lead to cirrhosis. Besides patients with non-alcoholic fatty liver disease should be evaluated in terms of latent diabetes.

Key Words: Non-Alcoholic Hepatosteathosis; Etiological Factors; Malatya.

Malatya ve Çevresinde Nonalkolik Karaciğer Yağlanması Olan Hastalarda Etiyolojik Faktörler

Özet

Amaç: Non alkolik karaciğer yağlanmasına neden olan faktörler tam olarak ortaya anlaşılamamıştır. Bu çalışmada Malatya ve çevresinde nonalkolik yağlı karaciğer hastalığı olan hastalarda etiyolojik faktörleri araştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmada İnönü Üniversitesi Tıp Fakültesi, Gastroenteroloji Polikliniğine başvuran ve hepatobilier ultrasonografide karaciğer yağlanması tespit edilen hastalar retrospektif olarak incelendi. Alkole bağlı karaciğer yağlanmasının dışlamak amacıyla kadınlarda 20 gram/gün, erkeklerde 30 gram/gün üzerindeki dozlar alkol alımı olarak kabul edildi ve çalışmanın dışında bırakıldı. Karaciğer enzim düzeyleri normal hastalar hepatosteatoz, enzim düzeyi normalin iki katı veya daha yüksek olanlar steatohepatit olarak değerlendirildi.

Bulgular: Toplam 112 hastanın 58'i (51,8%) kadın, 54'ü erkek (48,2%) ve tüm hastaların yaş ortalaması 43,8±11,3 yıl idi. Erkeklerin yaş ortalaması 41,8±11,3 yıl, kadınların ise 45,4±11,3 yıldı. Toplam 112 olgunun 97'sinde (%86,6) hiperlipidemi, 53'ünde (%47,3) obezite, 47'sinde (%42) insülin direnci, 16'sında (%14,2) hiperlipidemi ile birlikte insülin direnci, 27'sinde (%24,1) hiperlipidemi ile birlikte obezite, 35'inde (%31,3) obezite ile birlikte insülin direnci, 11 hastada (%9,8) latent diyabetes mellitus tesbit edildi.

Sonuç: Hiperlipidemi, obezite, insülin direnci gibi risk faktörlerine sahip bireylerin karaciğer sirozuna kadar ilerleyebilen nonalkolik karaciğer yağlanması açısından değerlendirilmesi önem arzetmektedir. Nonalkolik karaciğer yağlanması hastalığı olan hastalar latent diabet açısından araştırılmalıdır.

Anahtar Kelimeler: Nonalkolik Karaciğer Yağlanması; Etiyolojik Faktörler; Malatya.

INTRODUCTION

Alcoholic fatty liver is a fattened liver disease due to alcohol consumption. Non-alcoholic fatty liver disease (NAFLD), on the other hand, is the fattening of the liver as a result of reasons that are not related with alcohol. NAFLD is the name of an entire set of clinical manifestations with a broad spectrum ranging from simple hepatic steatosis, inflammation and hepatocyte necrosis to cirrhosis by characterised steatohepatitis (1). Although fatty liver is observed in non-alcoholic of hepatic steatosis (NAHS) patients, there is no inflammatory infiltration. In NASH, however, along with manifestations that are also found in alcoholic liver disease such as in ballooning in hepatocytes, inflammatory infiltration, mallory bodies, megamitochondria and fibrosis, fattening of the liver is also present (2). Broadly speaking, "steatosis" refers to lubrication while "steatohepatitis" means inflammation caused by fat accumulation in the liver. Fatty liver is either defined as the amount of fat in the liver, particularly of triglycerides, exceeding 5% of liver weight or noting more than 5% of hepatocytes being filled with

fat vacuoles through an histological analysis (3). In Turkey, fatty liver frequency is 17-33% while NASH frequency varies between 5.7% and 17% (4). People with obesity, hyperlipidemia, diabetes mellitus; those whose impaired glucose tolerance test is positive; people over the age of 45; and individuals who are exposed to rapid weight loss people are at high risk for NAFLD development (5).

The NAFLD frequency has beed reported to be 60-95% in patients with (BMI)> 30 kg/m2 body mass index and over; 28-55% in patients with Type 2 diabetes; and 20-92% in hyperlipidemia patients (6). Insulin resistance is a risk factor for the development of NAFLD and NASH. Approximately 80% of overweight people also have fatty liver. In addition to this, 75% of Type 2 diabetes patients, 50% of lipid metabolism disorder patients, and 33% of people with NASH share coronary heart diseases that requires treatment. Although NASH is known as a benign disease, it may progress to an end-stage liver disease (7).

MATERIAL AND METHODS

The study has been conducted on Inonu University, Faculty of Medicine, Gastroenterology clinic patients with fatty liver detected through hepatobiliary ultrasound. Various clinical findings in the files and laboratory tests of the patients have retrospectively been analysed. All cases were examined for clinical and laboratory findings in order to exclude other possible liver diseases. 20 grams/day in females and 30 grams/day in males was considered overdose to exclude alcohol intake. Those who have exceeded alcohol intake dose of 20 grams/day for 2 years; those with diabetes mellitus, inflammatory bowel diseases or similar serious systemic and malignant diseases; those with drug use histories (of tamoxifen, amiodarone, glucocorticoids, diltiazem and nifedipine of long periods of time); and those who had bowel resection surgery were excluded from the study.

Patients with fatty liver and, after the tests performed prior to the study, newly diagnosed diabetes were included in the study. To exclude autoimmune hepatitis, anti-smooth muscle antibody (ASMA), anti-nuclear antibody (ANA), anti liver/kidney antibody markers (ALKM) were examined. More to the point, to rule out viral hepatitis, hepatitis B (HBsAg, antiHBs, antiHBc IgM) and hepatitis C (anti-HCV) microelisa serologies were examined. Patients with positive markers were excluded from the study. Patients with abnormal laboratory findings like hypoalbuminemia, prolonged prothrombin time, and hyperbilirubinemia and those patients with developed ascites and portal hypertension symptoms were assessed as cirrhotic liver cases and were excluded from the study alike. Body mass indexes (BMI) of all our patients were calculated by the weight (kg) / height (m^2) formula. Patients' insulin resistance, meanwhile, were calculated by the homeostasis model of insulin resistance assement (HOMA-IR) formula (fasting insulin μU/ml X fasting glucose mmol/L/22.5). Patients with HOMA-IR values higher than 2.5 were evaluated as insulin resistant cases. Following the hepatobiliary ultrasonography carried out by using a Siemens Acuson Antares-color doppler ultrasound device, patients who had minimal diffuse increase in terms of hepatic echogenicity and a normal view of diaphragm and intrahepatic vessel borders were assessed as Grade I hepatic steatosis patients; patients with moderate diffuse increase in their hepatic echogenicity and slightly deteriorated images in diaphragm and intrahepatic vessels were considered Grade II hepatic steatosis patients; while patients who had conspicuous increase in their echogenicity, in whose case it was difficult visualise liver's right lobe posterior segment, and with indistinct or invisible intrahepatic vascular structures and diaphragm boundaries were assessed as Grade III hepatic steatosis patients.

Patients with normal liver enzyme levels were considered hepatic steatosis, while those with enzyme levels greater than twice of the normal level were evaluated as steatohepatitis. Mean values and standard deviations of all values were calculated. $P<0.05$ value was regarded significant. During the statistical analysis of the study, tests like chi-square, Pearson's correlation test, independent sample T test, and Mann-Whitney U test were used.

RESULTS

A total of 112 patients were enrolled in the study. Of these 112, 54 (48.2%) were male and 58 (51.8%) were female patients. The mean age of all patients was 43.8±11.3. The average age was 41.8±11.3 for males and 45.4±11.3 for females, respectively. The number of patients with hepatic steatosis were 60 (53%) while 52 (47%) patients had steatohepatitis. The mean age of patients with hepatic steatosis was 46.2±11.5 years; those who had steatohepatitis had an average age of 41±10.6 years. The mean BMI of the patients with hepatic steatosis was calculated 32.4±6.4 kg/m^2; the average BMI of steatohepatitis patients was calculated 30.2±6.21 kg/m^2. The statistical difference between hepatic steatosis patients and steatohepatitis patients in terms of age, gender, AST, ALT, ALP, GGT, total bilirubin, and albumin values was noteworthy ($p<0.01$). The comparison between the patients with hepatic steatosis and steatohepatitis with respect to demographic and laboratory characteristics is given in Table 1. The values and reference ranges of all patients in the study regarding their mean fasting blood glucose, total cholesterol level, triglyceride level, HDL, VLDL, insulin levels, AST, ALT, ALP, GGT, HOMA-IR are provided in Table 2.

After an etiological examining of all 112 patients in the study, it has been found out that 7 (6.2%) of patients with hepatic steatosis didn't show any risk factors. Oral glucose tolerance test (OGTT), that was performed on all patients in terms of latent diabetes, manifested that 11 of 112 patients (9.8%) had latent diabetes (newly diagnosed Type 2 diabetes mellitus). In the study, 58 were non-obese patients (BMI <30kg/m^2), and 54 patients were obese (BMI>30 kg/m^2).The mean HOMA-

IR values were 1.3±0.46 and 1.62±0.48 for non-obese patients and obese patients, respectively.
In ultrasonography-based classification of the patients in the study, it has been concluded that 30 (26.7%) patents had Grade I, 63 (56%) had Grade II, and 19 (17.3%) had Grade III hepatic steatosis. The demographic and laboratory data of the patients according to the degree of hepatic steatosis are given in Table 3.

Table 1. The comparison between demographic and laboratory characteristics of the patients with hepatic steatosis and steatohepatitis

Variables	Hepatic steatosis (n =60)		Steatohepatitis (n=52)		p
	Mean ± SD	Reference Value	Mean ± SD	Reference Value	
Age (years)	46.2±11.5	22-73	41±10.6	20-61	<0,01
Gender (n, F/M)	41/19		7/35		<0,01
Triglycerides (mg/dl)	189.0±100.7	28-504	213.5±104.1	67-504	0.2
Total cholesterol (mg/dl)	230.3±34.5	97-291	215.1±38	128-291	0.08
LDL (mg/dl)	124.2±28.1	11-185	126.7±39.0	11-184	0.69
HDL (mg/dl)	43.0±8.8	26-80	43.2±10.3	28-80	0.9
VLDL (mg/dl)	37.5±19.8	5-95	40.4±17.2	13-95	0.4
AST (U/L)	20.5±6.5	10-135	50.0±22.3	17-135	<0.01
ALT (U/L)	26.6±12.5	9-266	86.3±37.0	50-266	<0.01
ALP (U/L)	74.0±27.6	16-167	89.5±25.7	48-165	<0.01
GGT (U/L)	32.8±24.2	1-281	67.8±44.4	30-281	<0.01
Total Bilirubin (mg/dl)	0.54±0.22	0.2-4	0.79±0.60	0.3-4	<0.01
Indirect Bilirubin (mg/dl)	0.31±0.17	0.1-1.5	0.42±0.29	0.1-1.5	0.02
Direct Blirubin (mg/dl)	0.23±0.11	0.1-0.6	0.28±0.11	0.1-0.6	0.02
Total Protein (mg/dl)	7.46±0.49	5-8	7.54±0.36	7-8.3	0.38
Albumin (mg/dl)	4.98±0.49	2.6-6.1	5.19±0.29	4.7-6.	0.01
Globulin (mg/dl)	2.43± 0.29	1.7-3.1	2.36 ±0.34	1.7-3.1	0.31
Fasting Blood Glucose (mg/dl)	102.5±23.6	62-219	106.4±26.9	72-19	0.4
HOMA-IR	2.85 ±1.90	0.3-15	3.39 ±3.04	0.3-15.7	0.25
Body Mass Index (kg/m2)	32.4± 6.4	21-53	30.2 ±6.2	22-53.8	0.07

HOMA-IR: Homeostasis model of assessment - insulin resistance

Table 2. Mean values and reference differences of all the patients included in the study

Variables	Reference Difference	Reference Difference
Age (years)	43.8±11.39	-
Gender (n; F/M)	112.58/54	-
Height (cm)	165± 9	-
Weight (kilograms)	85.7±14.49	-
Triglycerides (mg/dl)	200.4±102.5	0–150
Total cholesterol (mg/dl)	208.8±36.5	0–200
LDL (mg/dl)	125.3±33.5	0–100
HDL (mg/dl)	43.1±9.56	50–90
VLDL (mg/dl)	38.8±18.6	10–130
AST (U/L)	34.2±21.6	5–34
ALT (U/L)	54.3±40.1	0–55
ALP (U/L)	81.2±27.7	30–120
GGT (U/L)	49.1±39.05	9–36
Total bilirubin (mg/dl)	0.66±0.45	0.2–1.2
Indirect bilirubin (mg/dl)	0.36±0.24	0.2–0.7
Direct bilirubin (mg/dl)	0.25±0.11	0–0.5
Total protein (gr/dl)	7.49±0.44	6–8.3
Albumin (gr/dl)	5.1±0.43	3–4.5
Globulin (gr/dl)	2.4±0.31	2–4
Fasting blood glucose (mg/dl)	104.3±25.18	70–105
Body Mass Index (kg/m^2)	31.4±6.38	-
HOMA-IR	3.1±2.50	<2.5

HOMA-IR: homeostasis model assement of insulin resistance

Table 3. Mean demographic and laboratory values according to the patients' hepatic steatosis grading classifications

Variables	Grade I HS.	Grade II HS.	Grade III HS.
	Mean±SD	Mean±SD	Mean±SD
Age (years)	43.6 ±14.4	44.2±10.4	42.8±9.2
Gender (n, F/M)	18/12	36/17	2/16
Triglycerides (mg/dl)	173.6±86.6	203.7±102.4	231.5±119.8
Total cholesterol (mg/dl)	204.3±31.8	208.0±38.9	218.8±35.0
LDL (mg/dl)	126.7±27.3	123.1±35.7	130.8±35.7
HDL (mg/dl)	43.9±11.2	43.0±8.2	42.1±11.1
VLDL (mg/dl)	33.8±15.8	39.5±19.1	44.6±20.0
AST (U/L)	23.0±8.7	35.5±20.5	47.6±30.2
ALT (U/L)	34.9±21.6	56.0±37.9	79.6±53
ALP (U/L)	75.8±28.7	83.7±29.7	81.4±17.3
GGT (U/L)	34.7±19.3	51.0±43.3	67.8±44.4
Total bilirubin (mg/dl)	0.59±0.28	0.70±0.50	0.60±0.22
Indirect bilirubin (mg/dl)	İ0.35±0.23	0.37±0.27	0.37±0.16
Direct bilirubin (mg/dl)	0.24±0.09	0.27±0.13	0.22±0.07
Total protein (mg/dl)	7.34±0.53	7.54±0.38	7.64±0.37
Albumin (mg/dl)	4.87±0.59	5.16±0.32	5.15±0.24
Globulin (mg/dl)	2.36± 0.28	2.40 ±0.31	2.46±0.38
Fasting blood glucose (mg/dl)	93.23±10.9	104.3±23.7	122.0±35.1
HOMA-IR	2.09 ±1.15	3.10±2.15	4.74±3.98
Body Mass Index (kg/m^2)	28.8± 4.2	32.3 ±6.8	31.4±6.4

HOMA-IR: Homeostasis model assement of insulin resistance

DISCUSSION

It has been shown that NAFLD in men is as common as in women (7). Non-alcoholic fatty liver, is more frequent in women in the literature (8). More common in females in general terms, this pathologic change is now assumed be connected more with the greater obesity levels in females (9). According to our findings, although non-alcoholic fatty liver disease is more common in obese females, it is more common in males with steatohepatitis than it is in females ($p<0.01$). Our study showed no statistically significant difference between males and females in relation to NAFLD though the reason behind this may be the limited number of patients at hand.

The association between fatty liver and obesity is well known. There are even data that put forward the idea that obesity proves to be a greater risk than alcohol for fatty liver (10). In our study, the frequency rate of fatty liver patients with obesity (BMI> 30 kg/m2) was 47.3%. Hyperlipidemia is a recurrent abnormality in NAHS patients. 97 of our 112 patients (86.6%) had hyperlipidemia. The number of patients whose etiology had hyperlipidemia only was 34 (30.3%). The data obtained in several studies support the idea that hypertriglyceridemia has an important role in pathogenesis. Studying 86 obese patients with normal glucose tolerance according to their BMI, insulin and HOMA-IR values, Ventura et al. have discerned a positive correlation between HOMA-IR and BMI and have found insulin levels ($p=0.007$) and HOMA-IR ($p=0.02$) significantly higher (11). In our study, among a total of 112 patients without known diabetes, 47 (41.6%) had insulin resistance alone in their etiologies (HOMA-IR>2.5). While this rate was 40% in patients with simple fatty liver, the rate of insulin resistance was 46% in steatohepatitis patients. Steatohepatitis patients had a slightly higher rate of insulin resistance. Still, this difference was statistically significant ($p<0.01$).

Classifying all hepatic steatosis patients with regards to their liver fattening through ultrasonography, it has been found out that Grade I hepatic steatosis patients shared a HOMA-IR value of 2.0±4.1; Grade II hepatic steatosis patents had 3.1±2.1; and Grade III hepatic steatosis patients had a HOMA-IR value of 4.7±2.5, respectively. It has been observed that the greater the degree of hepatic steatosis is, the higher insulin resistance level increases. In our study, 85% (92) of the patients were afflicted by insulin resistance alone or with other risk factors in their etiologies. The frequency of being afflicted by insulin resistance is higher in NAFLD patients than in diabetes patients. This association may explain the risk of diabetes developing high in NAFLD. Evaluating the newly diagnosed case rate in our study (9.8%), the follow-up of patients is valuable because of the high risk of diabetes, albeit belatedly, after the development of NAFLD.

The prevalence rate of NAFLD in Type 2 diabetes is 28-55% (6). There were no patients with diabetes in our study. All NAFLD patients underwent OGTT and in 11 of the patients (9.8%) latent (newly diagnosed Type 2 diabetes mellitus) was detected. Throughout our story, we have also determined a statistically significant correlation ($p<0.01$) between obese and non obese patients and insulin resistance (HOMA-IR).

In Turkey, according to Turkish Diabetes Epidemiology Research Project (TURDEP) study data, the incidence rate of new type 2 diabetes and corrupted OGTT in 40-60 age group is approximately 15% (12). The fact that around 10% of the NAFLD patients had newly diagnosed type 2 diabetes in our study supports the necessity of OGTT for NAFLD patients with diabetes in the family history. Considering the overt possibility of diabetes progression in patients with impaired glucose tolerance, it may be thought that NAFLD may be a marker of diabetes.In the literature, ALT elevation is

dominant in the laboratory findings of NAFLD patients and the most frequently expected abnormalities are 2-3 times increased levels of AST and ALT. Nonalcoholic steatohepatitis cases usually show AST/ALT<1 ratio. Their ALP and GGT levels, meanwhile, can increase 2-3 times more than the normal values in 50% of the cases in the literature (13).

Examining all patients in our study without detaching them as simple fatty liver (hepatic steatosis) and steatohepatitis patients, we have calculated an average of 34.2±21.6 U/L for AST, 54.3±40.1 U/L for ALT, 81.2±27.7 U/L for ALP, and 49.1±39.0 U/L for GGT values, respectively. The AST/ALT ratio of all patients was less than 1.The AST and ALT levels were within normal limits in 60 of the patients (53%). The number of patients with high levels of AST and ALT was 52 (47%). In a total of 112 patients in the study, 30 (26.7%) showed AST and ALT two times higher than normal values, while 14 (12.5%) had 3 times higher AST and ALT values. This has indicated that the transaminase levels in the diagnosis of NASH was not a really significant parameter (14).

The restrictive aspects of our work were that the study had a retrospective nature and that the patients, whom we have diagnosed to be fatty liver patients following the ultrasound, did not undergo a liver biopsy.

As a result, the clinical conditions responsible for the etiology of NAFLD are hyperlipidemia, obesity, insulin resistance, latent diabetes or a combinations of all these mentioned conditions, respectively. It is important to evaluate such individuals with risk factors of nonalcoholic fatty liver that may end up in liver cirrhosis. Although our study excluded patients with diabetes, one tenth of the patients were diagnosed with newly diagnosed diabetes. Therefore, it may be beneficial to inspect patients with hepatic steatosis for latent diabetes.

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