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Nonalcoholic Fatty Liver Disease and Familial Mediterranean Fever: Are They Related?

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SUMMARY

Introduction Familial Mediterranean fever (FMF) is a periodic febrile disease characterized by acute recurrent episodes of serositis. Liver disease is not considered a part of the spectrum of clinical manifestations of FMF.

Objective The purpose of this study was to characterize the nonalcoholic fatty liver disease (NAFLD) that could be associated with familial Mediterranean fever (FMF).

Methods Clinical findings and treatment information of the patients with FMF were obtained from outpatient files. Weight, height, hip and waist circumference, blood pressure, blood C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, glucose, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), creatinine, alanine aminotransferase (ALT), and insulin levels were determined in all subjects, and additionally liver ultrasonography was performed for signs of hepatosteatosis.

Results Fifty-two age and gender matched patients with FMF, and 30 healthy controls were included in the study. The prevalence of metabolic syndrome in the patient group was determined to be significantly higher in the patient group compared to the healthy group. When FMF patients with and without hepatosteatosis were compared, the prevalence of metabolic syndrome was determined to be 6 vs. 3, respectively ($p<0.001$). Eleven patients with FMF were found to have grade 1-2 hepatosteatosis, and only 6 of healthy subjects had grade 1 hepatoseatosis ($p=0.901$).

Conclusion When compared with healthy controls, we found the prevalence of NAFLD was not increased in patients with FMF.

Keywords: familial Mediterranean fever; nonalcoholic fatty liver diseases; metabolic syndrome

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent inflammatory febrile attacks of serosal and synovial membranes [1]. No study has shown association between FMF and nonamyloid liver disease; however several case reports have suggested such an association. Two cases of recurrent acute cryptogenic hepatitis were described in children with FMF. In a case report, generalized triglycerides storage examination by light microscopy showed no inflammation and fibrosis in the patient's biopsy sample [2, 3, 4]. In another case series, patients with FMF and cryptogenic cirrhosis were reported [5].

Nonalcoholic fatty liver disease (NAFLD) encompasses a wide spectrum of conditions associated with exceeding accumulation of fat in the liver ranging from simple steatosis to steatosis and signs of hepatocellular injury and inflammation (nonalcoholic steatohepatitis – NASH), and to cirrhosis. A growing body of evidence supports a central role of TNF-α and other inflammatory cytokines (e.g. IL-6) in the progression from fatty liver to NASH [6]. During the FMF attack serum IL-6 levels increase. Increased TNF-alpha levels were reported in FMF patients with or without acute attacks [7, 8].

We investigated the prevalence of ultrasonography (USG) findings and NAFLD in FMF occurring in association with chronic inflammation.

OBJECTIVE

The purpose of this study was to characterize the nonalcoholic fatty liver disease (NAFLD) that may be associated with familial Mediterranean fever (FMF).

METHODS

Fifty-two patients with FMF and 30 healthy subjects were enrolled in the study. The study

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involved patients under follow-up at the Rheumatology Outpatients' Clinic. Clinical findings and treatment information of the patients with FMF were obtained from their files. The control group included age and gender matched healthy subjects.

All the subjects completed a questionnaire that included questions detailing past medical history specially diabetes, hyperlipidemia, hypertension, liver disease and current medications. The patients were screened for viral (HCV) and metabolic diseases (Wilson disease) that can cause fatty liver disease; the subjects with positive results were excluded from the study.

Height was precisely measured without shoes by a stadiometer, and weight by an electronic scale to the nearest 0.1 kg with the participants clothed lightly. Waist circumference was measured from mid-point between the iliac crest site and the 10th rib, and hip circumference at the level of the greater trochanter. Blood pressure was measured on the right arm in the seated position using an automated sphygmomanometer, after a 5 min rest period. The mean systolic (SBP) and diastolic blood pressure (DBP) was calculated after three measurements. BMI was calculated by the mathematical formula with weight in kg/height m^2.

Blood samples were collected after overnight fasting to measure total cholesterol, LDL, HDL, TG, glucose, creatinine, ESR, CRP and insulin. Insulin levels were measured using the Immulite 2000 analyzer (DPC, Los Angeles, CA, USA) by the chemiluminescent immunometric assay and IR was determined by homeostatic model assessment of insulin resistance (HOMA-IR) index [serum insulin (mg/dl) plasma glucose (mg/dl)/405] [9].

A diagnosis of metabolic syndrome was made if at least three of the proposed diagnostic criteria were met [blood pressure ≥130/85 mmHg or use of anti-hypertensive medication; fasting plasma glucose ≥110 mg/dl or use of anti-diabetic medication; fasting triglycerides >150 mg/dl; HDL <40 mg/dl (men) or <50 mg/dl (women); and waist circumference >102 cm (men) or >88 cm (women)] [10, 11].

We scanned the prevalence of NAFLD by ultrasonographic method. Hepatic ultrasonographic examinations were carried out by experienced radiologists who were blinded to the clinical and laboratory details of participants at the time of the procedure. Hepatic US (Acuson, Sequoia 512, Siemens, Mountain View, CA) was used to diagnose a fatty liver and assess its degree. Echogenic hepatic fat accumulation intensities were graded semi-quantitatively according to the criteria described as follows: normal echogenicity; mild, slight diffuse increase in bright homogenous echoes in the liver parenchyma, with normal visualization of the diaphragm and portal and hepatic vein borders, and normal hepatorenal contrast if echogenic; moderate, diffuse increase in bright echoes in the liver parenchyma with slightly impaired visualization of the peripheral portal and hepatic vein borders; and a severe, marked increase in bright echoes at a shallow depth with deep attenuation and impaired visualization of the diaphragm and marked vasculature.

All participants gave informed consent and the Ethics Committee of the Sivas Cumhuriyet Universty Medical School approved the study.

Data are described using mean and standard deviation (SD) or median and inter-quartile range (IQR) (25%-75%) or number and proportion. Baseline characteristics across groups were compared using the Mann–Whitney U-tests, chi-square test, where appropriate. A two-tailed p value of <0.05 was considered significant. Statistical analysis was performed using SSPS 13.0.

RESULTS

Fifty-two age and gender matched patients with FMF and 30 healthy controls were included in the study (age 30.17±9.59 vs. 33.03±7.74, p=0.065; gender 35 F/17 M vs. 18 F/ 12 M, p=0.505). The demographics and clinical characteristics and complaints of the patients with FMF are summarized in Table 1.

BMI, waist circumference, glucose, insulin, HOMA-IR, TG, HDL, LDL readings and prevalence of metabolic syndrome were found to be significantly higher in the patient group compared to the healthy group (Table 2).

When FMF patients with and without hepatosteatosis were compared, the prevalence of metabolic syndrome was determined to be 6 (54.5%) vs. 3 (7.3%), respectively (p=0.019). LDL, TG levels, waist circumference, BMI, DBP readings, body weight and age were observed to be significantly greater in FMF patients with NAFLD, compared to those without NAFLD. Age, weight, SBP, DBP, BMI and LDL levels were determined to be significantly higher in the participants with hepatosteasosis than in those without hepatosteatosis (Table 3).

While 11 (21.1%) of those with FMF were found to have grade 1-2 hepatosteatosis, only 6 (20%) of healthy subjects were determined to have 1 hepatoseatosis (p=0.901).

Table 1. Demographic and clinical characteristics of patients with FMF characteristics

Characteristics		Total (52)
Age, mean±SD (range), years		30.17 (±9.59)
Disease duration, median, IQR (25%-75%), years		13.00 (7.75-23.50)
Treatment duration, median, IQR (25%-75%), year		2.00 (0.50-4.00)
Symptoms during attacks, n (%)	Fever	39 (75)
	Abdominal pain	46 (95.8)
	Chest pain	35 (74.5)
	Arthralgia, myalgia	35 (74.5)
	Peripheral arthritis	30 (56.6)
	Erysipelas-like lesions	12 (25)
Amyloidosis, n (%)		0 (%0)
Concomitant disease, n (%)*		0(%0)

* Hypertension, diabetes mellitus and inflammatory bowel disease

Table 2. Baseline demographics, clinical and metabolic features of FMF and control subjects

		FMF	Healthy controls	p
Age (years)		30.17 (±9.59)	33.03 (±7.75)	0.065
Sex	Male	17 (32.7%)	12 (40%)	0.505
	Female	35 (67.3%)	18 (60%)	
Fibrinogen (gr/L)		255.91 (±62.97)	248.10 (±76.13)	0.696
SBP (mmHg)		113.35 (±13.62)	108.26 (±9.36)	0.234
BMI (kg/m^2)		24.95 (±5.87)	22.16 (±2.45)	0.016
Waist (cm)		103.25 (±11.83)	79.26 (±7.22)	<0.001
Glucose (mg/dl)		91.2 (±8.5)	85.53 (±4.28)	0.001
HDL (mg /dl)		39.61 (±9.27)	48.99 (± 12.60)	<0.001
LDL (mg /dl)		98.55 (±32.56)	113.67 (±28.48)	0.041
Insulin‡ (IU/ml)		8.19 (4.93-10.87)	5.88 (4.32-6.77)	0.026
HOMA-R‡		1.87 (1.16-2.49)	1.23 (0.98-1.40)	0.009
TG‡ (mg/dl)		93.0 (65.0-150.0)	53.0 (33.75-101.0)	<0.001
ESR‡ (mm/h)		14.0 (6.25-18.0)	13.0 (8.75-23.0)	0.378
Metabolic syndrome		9 (17.3%)	0 (0%)	0.016

SBP – systolic blood pressure; BMI – Body Mass Index; HDL – high-density lipoprotein; LDL – low-density lipoprotein; HOMA-R – insulin resistance index; TG – triglycerides; ESR – erythrocyte sedimentation rate
‡ These parameters are expressed as median and IQR (25%-75%).

DISCUSSION

This study is the first to investigate NAFLD prevalence in FMF patients, where healthy subjects were enrolled as controls. We found NAFLD in 11 patients with FMF and in 6 healthy controls. A significantly increased prevalence of metabolic syndrome was observed in subjects with FMF compared to controls. LDL and HDL levels in patients with FMF were determined to be lower compared to the control group.

Two previous studies have described liver disease that is associated with FMF. First study by Tweezer et al. reported nine patients with cryptogenic cirrhosis in FMF. In this case series, cryptogenic cirrhosis was reported to be more prevalent in FMF patients compared to the general population. In liver biopsies of patients, only one patient (20%) was reported to have fatty changes accompanied by cirrhotic findings [5]. In the second study, Rimar et al. [12] results indicated that NAFLD was diagnosed based on a biopsy (74%) in 20 patients out of 27 with chronic liver disease but metabolic syndrome frequency had not increased when compared to the control group. This similar frequency of metabolic syndrome in the control group suggests that NAFLD has a different pathogenic path in patients with FMF. Proinflammatory cytokines that are

Table 3. Comparison of demographic characteristics, biochemical readings, prevalence of metabolic syndrome of FMF patients with and without NAFLD, and of all subjects in the study

	FMF patients			All subjects		
NAFLD	Absent (41)	Present (11)	p	Absent (65)	Present (17)	p
Age (years)	26.46 (±7.37)	39.0 (± 9.34)	0.001	29.38 (±8.35)	37.24 (±8.39)	0.001
Male/ Female	9/26 (26/74) *	8/9 (47/53) *	0.124	21/38 (±35/65)	8/15 (35/65) *	0.945
Weight (kg)	65.68 (±13.52)	86.27 (±22.19)	0.013	64.90 (±11.59)	80.12 (±20.41)	<0.001
SBP (mmHg)	110.93 (±9.42)	121.67 (± 18.37)	0.133	91.03 (±17.88)	105.80 (±24.76)	0.018
DBP(mmHg)	71.00 (±10.39)	81.11 (±10.54)	0.035	71.00 (±10.39)	81.11 (±10.54)	0.032
BMI(kg/m^2)	22.90 (±3.49)	30.72 (±7.08)	<0.001	22.32 (±2.99)	28.35 (±6.65)	<0.001
Waist (cm)	87.10 (±14.04)	104.36 (±12.77)	0.002	82.84 (±11.89)	96.47 (±15.38)	0.115
Glucose (mg/dl)	90.04 (±8.77)	95.73 (±10.10)	0,120	87.88 (±7.39)	92.35 (±9.59)	0.181
HDL (mg/dl)	38.38 (±7.24)	40.82 (±10.20)	0.485	44.01 (±11.76)	42.76 (±11.00)	0.704
LDL (mg/dl)	87.4 8 (±32.35)	117.36 (± 28.82)	0.012	97.76 (±30.21)	123.41 (±32.02)	0.004
Fibrinogen(gr/L)	258.75 (±57.98)	271.38 (±63.32)	0.684	249.56 (± 66.14)	264.14 (±81.15)	0.524
AST(IU/L)	21.56 (±7.06)	25.73 (± 6.48)	0.095	20.50 (±6.30)	23.81 (±8.10)	0.228
ALT¶ (IU/L)	18.0 (13.0-24.0)	24.0 (19.0-13.0)	0.061	16.0 (13.0-21.75)	23.0 (18.0-27.0)	0.019
GGT (IU/L)	17.0 (12.0-23.0)	15.0 (12.0-30.0)	0.538	14.5 (12.0-22.25)	15.0 (11.5-21.5)	0.420
CRP¶ (mg/dl)	3.28 (1.31-9.94)	5.56 (2.62-12.3)	0.195	1.10 (0.7-4.29)	2.62 (0.5-9.21)	0.152
ESR¶ (mm/h)	12.0 (5.75-17.2)	16.5 (7.75-23.0)	0.145	12.5 (8.0-18.25)	16.5 (7.25-29.0)	0.152
Insulin¶(IU/ml)	9.16 (5.11-11.6)	6.24 (4.3-9.08)	0.287	6.19 (4.85-10.12)	6.12 (4.83-7.86)	0.757
HOMA-R¶	2.01 (1.16-2.53)	1.44 (1.10-2.18)	0.482	1.35 (1.12-2.20)	1.35 (1.13-1.95)	1.000
TG (mg/dl)¶	85.0 (64.2-121.0)	184.0 93.0-237.0)	0.006	74.0 (54.0-107.5)	93.0 (43.5-222.0)	0.367
Metabolic syndrome	3 (7.3) *	6 (54.5) *	0.019	3 (4.6) *	6 (35.2) *	0.019

SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; HDL – high-density lipoprotein; LDL – low-density lipoprotein; AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-gluthamil transferase; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; HOMA-R – insulin resistance index; TG – triglycerides
* Numbers in parenthesis indicate percentages.
¶ Parameters are given as median and IQR (25%-75%).

elevated in FMF patients may play a role in the transformation of simple steatosis to NASH. Even though in our FMF positive study group there were more patients with metabolic syndrome, when compared to the healthy control group the co-occurrence of NAFLD and FMF had not increased significantly. The reason for this dissimilarity may have been caused by the different ways the studies were designed and by the different population groups included in the study.

NAFLD is also found in non-obese patients. Although a variety of causes like drugs, hereditary, and bowel diseases have been associated with steatohepatitis, the etiology of NAFLD in non-obese patients often remains unclear [13]. Specifically, patients with chronic inflammatory bowel disease usually are not obese and do not suffer from any components of the metabolic syndrome. NAFLD occurs in 15%-80% of patients with inflammatory bowel disease IBD [14]. IBD was present in 0.5% of FMF patients, compared to <%0.1 in the general population [15]. Moreover, MEFV gene mutation is known to modify the clinical manifestation of Crohn's disease [16]. In the literature, the frequency of homozygous MEFV mutation was found in (70%-71%) FMF patients with cryptogenic cirrhosis [5, 12] may be an additional factor to help explain the relation of FMF with NAFLD. Due to increased concomitance of these two diseases and to potential contribution of MEFV gene mutation, persons with FMF may have a high risk for NAFLD. However, there was no clinical finding in our patients suggesting inflammatory intestinal disease.

Sonsuz et al. [17] reported hyperinsulinemia and hyperglycemia as common in non-diabetic non-obese patients with NASH. We found increased insulin and glucose levels in our FMF patients compared to the healthy controls; however, there was no more pronounced insulin and glucose elevation in the FMF patients determined to have NAFLD than in those without NAFLD. Similarly, no difference was observed with regard to insulin and glucose levels when we compared individuals with NAFLD with individuals without NAFLD (Table 3). Colchicine inhibits the release of insulin from pancreatic B cell [18]. For this reason, it might be possible that we could not find insulin resistance despite the increased prevalence of metabolic syndrome. In addition, steatosis found in our patients may only be a simple steatosis. In another study by Gholam et al. [19] supporting this finding, reported that subjects with NASH had more severe insulin resistance when compared to those with simple fatty liver. Due to normal ALT levels and to noninvasive scanning for hepatosteatosis, we might have faced a simple hepatosteatosis. However, ALT levels did not predict the extent of histological severity of liver disease [20]; in a previous series of NAFLD, aminotransferase levels did not differ in relation to the severity of steatosis, necroinflammatory infiltration and fibrosis [21].

Hyperlipidemia is a coexisting condition frequently associated with nonalcoholic fatty liver disease. Hypertriglyceridemia rather than hypercholesterolemia may increase the risk of nonalcoholic fatty liver disease [22]. We found significantly higher triglyceride levels in our patients compared to the healthy controls. In the study by Ugurlu et al. [23], serum cholesterol levels (total, HDL and LDL) in FMF patients were found to be low compared to healthy controls as was in our study. Low lipid levels in FMF can also be explained by the lipid lowering and perhaps anti-atherogenic effect of colchicine, which has been reported in several studies in the past [24-30]. Possible mechanisms were defined as an interference with the enterohepatic cycle of bile acids and lipids and hydroxymethyl-glutaryl-CoA reductase (HMG CoA) inhibition.

The short examination time required and noninvasiveness make abdominal ultrasonography the best screening method of NAFLD in the general population. Previous studies demonstrated that ultrasonography had a relatively high sensitivity (82–94%) and specificity (66–95%) in detecting fatty liver [31-35]. Ultrasonographic changes appear when steatosis is more than 15–20% of the liver [36]. Abdominal ultrasonography has been shown to have an acceptable level of sensitivity for detecting fatty liver, though it does not provide reliable quantitative information [37]. This method, despite its limitations mentioned above, is the leading imaging method for fatty liver examination. We investigated NAFLD in our patients by ultrasonography.

The limitations of our study are that it was cross-sectional, that the patients who were found to have NAFLD were not subjected to advanced diagnostic examinations and that the healthy controls did not precisely reflect the rates seen in the general population.

CONCLUSION

In one of case reports in the literature, reporting of simple steatosis in a FMF patient [4], and the presence of cryptogenic cirrhosis case series in FMF patients [5] indicates that NAFLD should be considered in FMF patients. Although we determined in our study that the prevalence of NAFLD did not increase, we found, on the other hand, that the prevalence of metabolic syndrome, the most important risk factor for NAFLD, was increased compared to healthy controls. Further studies are needed to evaluate the prevalence of NAFLD in FMF that follows an episodic course causing elevations in IL-1, IL-6 and TNF-alpha.

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Неалкохолна болест масне јетре и породична медитеранска грозница: постоји ли повезаност?

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КРАТАК САДРЖАЈ

Увод Породична медитеранска грозница (ПМГ) је наследно обољење с периодичном фебрилношћу коју одликују акутне појаве серозитиса које се понављају. Болест јетре се не сматра саставним делом клиничке слике ПМГ.

Циљ рада Испитивање је урађено да би се описала неалкохолна болест масне јетре (НБМЈ), која се понекад јавља удружено са ПМГ.

Методе рада Податке о клиничким налазима и лечењу болесника са ПМГ преузети су из амбулантне картотеке. Код свих болесника одређивани су: телесна тежина, обим карлице и струка, крвни притисак, ниво *C*-реактивног протеина (*CRP*) у крви, вредности седиментације еритроцита, фибриногена, гликемије, липопротеина мале густине (*LDL*), липопротеина велике густине (*HDL*), триглицерида, креатинина, аланин-аминотрансферазе (*ALT*) и инсулина, а додатно је урађен ултразвучни преглед јетре ради утврђивања знакова хепатостеатозе.

Резултати Испитивањем је обухваћена група од 52 болесника са ПМГ, одговарајуће старости и пола, и 30 здравих особа, које су чиниле контролну групу. Утврђено је да је учесталост метаболичког синдрома била значајно повишена у групи болесника у односу на контролну групу. Поређењем испитаника оболелих од ПМГ са хепатостеатозом и без ње установљено је да је учесталост метаболичког синдрома била 6, односно 3 ($p<0,001$). Једанаест болесника са ПМГ имало је хепатостеатозу првог, другог и трећег степена, а само шест особа из контролне групе хепатостеатозу првог степена ($p=0,901$).

Закључак Упоређивањем с контролном групом утврђено је да учесталост НБМЈ није била повишена код болесника са ПМГ.

Кључне речи: породична медитеранска грозница; неалкохолна болест масне јетре; метаболички синдром

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