Serum lipid changes and insulin resistance in familial Mediterranean fever

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Abstract
Objective: Inflammation is known to alter lipid profiles and to induce insulin resistance. This study was planned to test the hypothesis that familial Mediterranean fever (FMF) patients and their first-degree asymptomatic relatives may have lipid profile changes and/or insulin resistance, similar to other inflammatory diseases.

Material and Methods: We studied 72 FMF patients, 30 asymptomatic first-degree relatives, and 75 healthy controls. Fasting and 2-hour postprandial glucose, insulin, apolipoprotein (Apo) A1, Apo B, acute phase reactants, and lipid profiles of all subjects were studied. Insulin resistance was determined by the HOMA (Homeostasis Model Assessment) index.

Results: There was no difference between the groups with regard to sex, mean systolic and diastolic blood pressure, body mass index, smoking status, fasting and postprandial 2-hour glucose, insulin, acute phase reactants, and HOMA index levels. High-density lipoprotein cholesterol (HDL-C) levels were similar between FMF patients and FMF relatives (48.9±12.4 mg/dL vs 49.3±13.8 mg/dL; p=NS), and both were lower than controls (48.9±12.4 mg/dL vs 59.6±15.1 mg/dL; p<0.001 and 49.3±13.8 mg/dL vs 59.8±15.1 mg/dL; p=0.001, respectively). Apo A1 levels in FMF patients and asymptomatic first-degree FMF relatives were both lower than in controls, similar to the HDL-C levels (126.1±25.7 mg/dL vs 151.2±31.4 mg/dL; p<0.001 and 129.5±29.0 mg/dL vs 151.2±31.4 mg/dL; p=0.002, respectively). TG levels were significantly higher in FMF relatives as compared to controls (113.4±53.6 mg/dL vs 97.1±54.9 mg/dL; p=0.025).

Conclusion: Low HDL-C and low Apo A1 levels are found in FMF patients and their first-degree asymptomatic relatives. Low-grade inflammation caused by MEFV mutations may be responsible for these lipid profile changes.

Key words: Familial Mediterranean fever, inflammation, lipoprotein, MEFV, insulin resistance

Introduction
Familial Mediterranean fever (FMF) is an auto-inflammatory disease characterized by periodic attacks of fever and serositis. Mediterranean fever (MEFV) gene mutations are the cause of FMF. FMF has been thought to have an autosomal recessive inheritance though a single mutation that may cause symptoms in some cases (1, 2). It has been shown that low-grade inflammation continues during attack-free periods in FMF patients and also asymptomatic first-degree relatives of the patients (3). The mechanism of accelerated atherosclerosis in inflammatory rheumatic diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), include both insulin resistance and dyslipidemia (4). This study was planned to test the hypothesis that FMF patients (homozygotes or compound heterozygotes) and their first-degree asymptomatic relatives (heterozygotes) may have lipid profile changes and/or insulin resistance, similar to other inflammatory diseases.

Material and Methods
Familial Mediterranean fever patients were selected from consecutive patients at the rheumatology outpatient clinic of Hacettepe University Hospital. All FMF patients who were recruited into the study fulfilled the clinical criteria for FMF (5).

Familial Mediterranean fever patients were asked to invite their first-degree relatives to be enrolled into the study. Asymptomatic first-degree FMF relatives who were screened for the presence of FMF were also enrolled into the study. The study protocol was approved by the Hacettepe University Local Research Ethics Committee.

Participants 18 years old or older were enrolled. Conditions that can affect the lipid profile, such as endocrinopathies (diabetes mellitus (DM), hypothyroidism, Cushing syndrome, etc.), drugs (thiazides, β-blockers, steroids, anti-hyperlipidemic drugs, estrogen), alcohol, obesity (body mass index (BMI) >30), current active infectious disease, pregnancy, history of familial dyslipidemia, liver or kidney disease, and inflammatory dis-
ease (other than FMF), were exclusion criteria for all participants. FMF patients with amyloidosis were also excluded.

All patients underwent a detailed history and physical examination, including BMI. Clinical and laboratory assessment of FMF patients was performed during an attack-free period. The smoking status was noted as smoker or non-smoker. Family history of coronary heart disease was also noted. FMF patients who were unresponsive to colchicine therapy were defined as suffering from an attack at any typical site more than once within a 3-month period, despite regular use of 2 mg/day colchicine (6).

All blood samples were obtained after an overnight fast. Plasma glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) levels were studied by an autoanalyzer (Hitachi P800™, Roche Diagnostics, Manheim, Germany). C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were also studied in subjects by routine methods. Apolipoprotein (Apo) A1 and B levels were determined by immunonephelometric method using Beckman Apo A and B kits by an autoanalyzer (BECKMAN Immage®, immunotech SA, Prague, Czech Republic). Insulin was estimated by a commercially available radioimmune assay method (Immuno-tech®). Insulin resistance was determined by the HOMA (Homeostasis Model assessment) index as the product of fasting insulin (μU/L) and fasting plasma glucose (mmol/L) divided by 22.5 (7).

Statistical analysis
Statistical Package for Social Sciences (SPSS), version 11.0 was used for analysis. Distribution of data was assessed using one-sample Kolmogorov–Smirnov test. Values are expressed as mean±SD unless indicated otherwise. For comparison of categorical variables or percentages, chi-square test or Fisher’s exact test was used when appropriate. Differences between numerical variables were tested with student’s t-test or Mann-Whitney U-test. Correlation was tested using Spearman’s rank order or Pearson correlation coefficient. A significance level was set at p<0.05.

Results
We screened 104 FMF patients and 47 first-degree asymptomatic relatives. Among them, 32 FMF patients (9 with BMI >30.0 with concomitant ankylosing spondylitis (AS), 4 with amylodrosis, 2 with current pregnancy, 2 with DM, 1 with concomitant microscopic polyangiitis, 1 with Behçet’s disease, and 3 already on statin treatment) and 17 first-degree asymptomatic relatives were excluded. We studied 72 FMF patients, 30 first-degree asymptomatic relatives, and 75 healthy controls.

All FMF patients were Turkish. The mean age at onset of FMF and disease duration were 15.3±9.5 years and 14.8±8.3 years, respectively. Clinical manifestations of FMF were: fever (n=67, 93.1%), abdominal pain (n=67, 93.1%), pleuritis (n=16, 22.2%), arthritis (n=16, 22.2%), and erythromelalgia-like rash (n=1, 1.4%). Five patients (6.9%) had hepatomegaly, and 2 patients (2.8%) had splenomegaly. Forty-five (62.5%) had a family history of FMF. Mean current dosage of colchicine was 1.5±0.3 mg/day. Five patients (6.9%) were newly diagnosed, and 5 patients (6.9%) were considered colchine non-responders.

Mean age was similar between FMF patients and healthy controls (30.2±8.0 years vs 32.8±8.4 years; p=NS). FMF first-degree relatives were older then FMF patients (38.7±13.1 years vs 30.2±8.0 years; p<0.001) and healthy controls (38.7±13.1 vs 32.8±8.4 years; p=0.046). Characteristic features of the groups are shown in Table 1. There were no significant differences between the groups in terms of gender, BMI, smoking status, or blood pressure (p=NS for all). Mean waist/hip ratio was significantly higher in FMF first-degree relatives as compared to FMF patients (0.82±0.08 vs 0.79±0.06; p=0.017). Family history of coronary heart disease was higher in first-degree FMF relatives as compared to both FMF patients (40.0% vs 15.3%; p=0.006) and healthy controls (40.0% vs 17.3%; p=0.014).

No difference was observed in the TC or LDL-C levels between the groups (p=NS for all, Table 2). However, HDL-C levels were similar between FMF patients and FMF relatives (48.9±12.4 mg/dL vs 49.3±13.8 mg/dL; p=NS), but both were lower than controls (48.9±12.4 mg/dL vs 59.6±15.1 mg/dL; p<0.001 and 49.3±13.8 mg/dL vs 59.8±15.1 mg/dL; p=0.001, respectively). ApoA1 levels were not different between FMF patients and FMF relatives (126.1±25.7 mg/dL vs 129.5±29.0 mg/dL; p=NS), but both were lower than controls, similar to the HDL-C levels. TC or LDL-C levels between FMF patients and first-degree FMF relatives as compared to healthy controls (21/72 subjects vs 5/75 subjects; p<0.001 and 9/30 subjects vs 5/75 subjects; p=0.003, respectively). TG levels were higher in FMF first-degree relatives as compared to healthy controls (113.4±53.6 mg/dL vs 97.1±54.9 mg/dL; p=0.025). On the other hand, there were no differences between the groups regarding fasting glucose, postprandial glucose, fasting insulin, HOMA index, or acute phase reactant levels (p=NS for all, Table 2).

There was no correlation between HDL-C levels and disease duration or acute phase reactant levels in FMF patients (p=NS, for all). HDL-C levels were not different in colchicine-unresponsive or newly diagnosed FMF patients as compared to the rest of the FMF patients (57.5±17.2 mg/dL vs 48.3±11.9 mg/dL; p=NS and 49.0±12.5 mg/dL vs 48.4±10.0 mg/dL; p=NS).

Discussion
In this study, HDL-C levels were found to be similar between FMF patients and asymptomatic first-degree FMF relatives, and HDL-C levels in these 2 groups were lower than in healthy

### Table 1. Demographic characteristics of participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FMF patients</th>
<th>First-degree relatives of FMF patients</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.2±8.0</td>
<td>38.7±13.1</td>
<td>32.8±8.4</td>
</tr>
<tr>
<td>Female (%)</td>
<td>72.2</td>
<td>66.7</td>
<td>65.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.5±3.5</td>
<td>24.2±3.4</td>
<td>22.9±3.4</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.79±0.06</td>
<td>0.82±0.08</td>
<td>0.80±0.07</td>
</tr>
<tr>
<td>Family history of CHD (%)</td>
<td>15.3%</td>
<td>40%</td>
<td>17.3%</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>108.5±12.5</td>
<td>112.0±14.4</td>
<td>112.6±14.9</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>69.8±9.4</td>
<td>71.1±11.1</td>
<td>70.5±10.5</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>23.6</td>
<td>20.0</td>
<td>21.3</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD; *FMF patients vs FMF first-degree relatives (p<0.001), †FMF first-degree relatives vs control group (p=0.046), ‡FMF vs FMF first-degree relatives (p=0.017), §FMF vs FMF first-degree relatives (p=0.006), ¶FMF first-degree relatives vs control subjects (p=0.014).

BMI: body mass index; CHD: coronary heart disease; BP: blood pressure; FMF: familial Mediterranean fever.
controls so as the ApoA1 levels. TG levels of the asymptomatic first-degree FMF relatives were higher than in healthy controls. On the other hand, there were no differences between the groups in terms of TC, LDL-C, ApoB1, fasting glucose, postprandial glucose, fasting insulin levels, or HOMA index.

Serum lipid changes have already been shown in inflammatory diseases, such as SLE, RA, and AS (8, 9, 10). Low TC, LDL-C, and HDL-C levels and high TG levels are characteristic changes observed in inflammatory diseases (11). Among these changes, low HDL-C level is the most frequent one. Serum lipid changes are considered a risk factor for accelerated atherosclerosis in inflammatory diseases (3, 10). Dyslipidemia improves by controlling disease activity (12, 13).

In our study, HDL-C levels were lower in FMF patients than in controls, compatible with other inflammatory diseases. Moreover, asymptomatic first-degree FMF relatives also had low HDL-C levels. Changes in ApoA1 levels were also similar to the changes in HDL-C levels. As ApoA1 levels are highly correlated with HDL-C levels, we thought that changes in ApoA1 levels strongly reflect the changes in HDL-C levels (14). Although FMF patients are symptom-free between the attacks, subclinical inflammation continues during attack-free periods. Elevated CRP levels were reported not only in attack-free FMF patients but also in MEFV mutation carriers (3). Therefore, the impact of low-grade inflammation on serum lipid levels in FMF patients and asymptomatic first-degree FMF relatives could be the cause of the low HDL-C levels in our study. However, although median acute phase reactant levels in these groups were higher than in healthy controls, they did not differ significantly between the 3 groups, and there was no correlation between HDL-C and acute phase reactant levels in FMF patients in our study.

To the best of our knowledge there are limited data about serum lipid levels in large groups of FMF patients. In one of our previous studies, we found low HDL-C levels in FMF patients (15). On the other hand, in most of the small sample size studies there were no differences in serum lipid levels between FMF patients and healthy controls (16-19). In all of these studies, most of the FMF patients were on colchicine treatment, which may be the cause of these results. In a previous study that focused on apolipoprotein levels as a risk factor for the development of amyloidosis in FMF, ApoA1 levels were found to be lower in FMF patients than in healthy controls. However, in the same study, although HDL-C levels tended to be lower in FMF patients, there was no statistical significance between FMF patients and healthy controls (18). In this study, we did not have a diseased control with another inflammatory disease, but in a recently published study, HDL-C levels were reported to be lower in FMF patients, as in SLE patients, when compared to healthy controls, also supporting our findings (20).

Our study has a limited number of subjects. Therefore, our results should be considered carefully. As we did not perform a genetic analysis, we can not comment on the effect of certain mutations on serum lipid levels of FMF patients based on the results of this study, which have been shown to determine the clinical course of the disease, such as M694V (1). Recently, by a retrospective analysis of subjects with known MEFV mutations performed in our clinic, we have shown that mutations carriers have similar low HDL-C levels as compared to controls, and subjects with homozygous M694V mutations have lower HDL-C levels than the rest of the mutation carriers (22).

Low levels of HDL-C were reported in the Turkish population (23). The researchers tried to explain their findings by the excess number of smokers in the Turkish population, hepatic lipase activity, or polymorphisms of ATP-binding cassette transporter A1 by further investigations (23-25). The carrier rate of MEFV mutations reaches about 20% in Turks (26). Thus, MEFV mutations may be one of the causes of low HDL-C levels in the Turkish population. Clinical outcomes and the rate of inflammation differ in inflammatory diseases. There are no data about the frequency of atherosclerotic disease, except one study that showed no increase in atherosclerotic heart disease in FMF patients and their relatives (27). On the other hand, there are a number of studies reporting the presence of early markers of atherosclerosis, such as impaired endothelial function, higher intima-media thickness of carotid arteries, or decreased coronary flow reserve, in FMF patients (15-17). Low serum HDL-C levels were found in both FMF patients and first-degree FMF relatives in this study. Furthermore, there were a considerable number of patients who were at risk for atherosclerosis, according to the ATP III report, based on serum HDL-C level, which was lower than 40 mg/dL (28). Low-grade inflammation caused by MEFV mutations may be responsible for these lipid profile changes. These findings suggest that FMF patients and asymptomatic first-degree
FMF relatives may be at increased risk for atherosclerosis. Therefore, serum lipid profiles and the effect of colchicine should be investigated in a larger number of FMF patients and MEFV mutation carriers.

Ethics Committee Approval: Ethics committee approval was received for this study from Hacettepe University Local Research Ethics Committee.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.


Conflict of Interest: No conflict of interest was declared by the authors.

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References

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