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Original Investigation

# 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 ferver (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-

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**Table 1.** Demographic characteristics of participants

| | FMF patients | First-degree relatives of FMF patients | Control group |
|---|---|---|---|
| Age | 30.2±8.0[a] | 38.7±13.1[b] | 32.8±8.4 |
| Female (%) | 72.2 | 66.7 | 65.3 |
| BMI (kg/m$^2$) | 22.5±3.5 | 24.2±3.4 | 22.9±3.4 |
| Waist/hip ratio | 0.79±0.06[c] | 0.82±0.08 | 0.80±0.07 |
| Family history of CHD (%) | 15.3[d] | 40[e] | 17.3 |
| Systolic BP (mm Hg) | 108.5±12.5 | 112.0±14.4 | 112.6±14.9 |
| Diastolic BP (mm Hg) | 69.8±9.4 | 71.1±11.1 | 70.5±10.5 |
| Smokers (%) | 23.6 | 20.0 | 21.3 |

Values are expressed as mean±SD; [a]FMF patients vs FMF first-degree relatives (p<0.001), [b]FMF first-degree relatives vs control group (p=0.046), [c]FMF vs FMF first-degree relatives (p=0.017), [d]FMF vs FMF first-degree relatives (p=0.006), [e]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

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, Praque, Czech Republic). Insulin was estimated by a commercially available radioimmune assay method (Immunotech®). 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 >30.10 with concomitant ankylosing spondylitis (AS), 4 with amyloidosis, 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 (6 with BMI >30.5 with DM, 1 with SLE, 1 with Behçet's disease, and 4 already on statin treatment) 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 eryzypel-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 colchicine 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), 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). 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), and both were lower than 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). The number of subjects whose HDL-C level was <40 mg/dL was higher in 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 2.** Serum lipid profile and acute phase reactant levels and other metabolic parameters of FMF patients, their first-degree relatives, and control subjects

| | FMF patients | First-degree relatives of FMF patients | Control group |
|---|---|---|---|
| Total cholesterol (mgr/dL) | 161.4±39.0 | 176.1±31 | 172.6±34.2 |
| LDL-cholesterol (mgr/dL) | 99.8±34.5 | 111.3±28.9 | 101.8±29.1 |
| HDL-cholesterol (mgr/dL) | 48.9,±12.4[a] | 49.3±13.8[b] | 59.8±15.1 |
| Triglycerides (mgr/dL) | 100.9±53.9 | 113.4±53.6[c] | 97.1±54.9 |
| Apo A1 (mg/dL) | 126.1±25.7[d] | 129.5±29.0[e] | 151.2±31.4 |
| Apo B (mg/dL) | 86.7±32.2 | 95.6±25.8 | 86.06±25.1 |
| CRP (mgr/dL) | 0.51 (0.1-5.8) | 0.33 (0.1-1.3) | 0.25 (0.1-0.9) |
| ESR (mm/hour) | 10 (1-53) | 10 (1-46) | 8 (1-21) |
| HOMA index | 1.1±0.7 | 1.0±0.4 | 1.0±0.5 |
| Insulin (mIU/mL) | 8.6±6.1 | 8.4±3.4 | 8.1±4.3 |
| FPG (mgr/dL) | 88.9±9.6 | 87.8±11.7 | 86.5±10.0 |
| PPG (mgr/dL) | 95.3±16.3 | 98.4±16.4 | 92.3±13.7 |

Values are expressed as mean±SD; for CRP and ESH mean, minimum and maximum levels are presented. [a]FMF patients vs control subjects (p<0.001), [b]FMF relatives vs control group (p=0.001), [c]FMF relatives vs controls (p=0.025), [d]FMF patient vs controls (p<0.001), [e]FMF relatives vs controls (p=0.002).
FMF: familial Mediterranean fever; LDL: low-density lipoprotein; HDL: high-density lipoprotein; ESR: erythrocyte sedimentation rate; CRP: c-reactive protein; Apo A1: apolipoprotein A1; ApoB: apolipoprotein B; HOMA: homeostasis model assessment; FPG: fasting plasma glucose; PPG: postprandial plasma glucose

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).

We did not find any differences between groups with regard to HOMA index. The anti-inflammatory effect of colchicine treatment may have underestimated our results by improving the dyslipidemic changes and also the effect of inflammation on insulin resistance in our study population. The HOMA index is considered to be a less sensitive method to test for the presence of insulin resistance as compared to other methods (21). Therefore, the HOMA index may not be an accurate method of testing insulin resistance in these groups of subjects.

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 HLD-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.

**Author contributions:** Concept - A.A., İ.E., Z.C.; Design - A.A., İ.E., Z.C.; Supervision - M.Ç., Ş.B., S.K.; Resource - A.A., Ö.K., U.K.; Materials - Z.C., A.A., U.K.; Data Collection&/or Processing - Z.C., A.Ş.,Ö.K; Analysis&/or Interpretation - A.A., Z.C., U.K.; Literature Search - A.A., Z.C., U.K.; Writing - A.A., Z.C., U.K.; Critical Reviews - İ.E., U.K., M.Ç.

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## References

1. Touitou I. The spectrum of Familial Mediterranean Fever (FMF) mutations. Eur J Hum Genet 2001; 97: 473-83. [CrossRef]
2. Livneh A, Aksentijevich I, Langevitz P, Torosyan Y, G-Shoham N, Shinar Y, et al. A single mutated MEFV allele in Israeli patients suffering from familial Mediterranean fever and Behcet's disease (FMF-BD). Eur J Hum Genet 2001; 9: 191-6. [CrossRef]
3. Tunca M, Kirkali G, Soyturk M, Akar S, Pepys MB, Hawkins PN. Acute phase response and evolution of familial Mediterranean fever. Lancet 1999; 353: 1415. [CrossRef]
4. Haskard DO. Accelerated atherosclerosis in inflammatory rheumatic diseases. Scand J Rheumatol 2004; 33: 281-92. [CrossRef]
5. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997; 40: 1879-85. [CrossRef]
6. Lidar M, Scherrmann JM, Shinar Y, Chetrit A, Niel E, Gershoni-Baruch R, et al. Colchicine nonresponsiveness in familial Mediterranean fever: clinical, genetic, pharmacokinetic, and socioeconomic characterization. Semin Arthritis Rheum 2004; 33: 273-82. [CrossRef]
7. Ikeda Y, Suehiro T, Nakamura T, Kumon Y, Hashimoto K. Clinical significance of the insülin resistance index as assessed by Homeostasis Model Assesment. Endocrine Journal 2001; 48: 81-6. [CrossRef]
8. Borba EF, Bonfa E. Dyslipoproteinemias in systemic lupus erythematosus:influence of disease, activity, and anticardiolipin antibodies. Lupus 1997; 6: 533-9. [CrossRef]
9. van Halm VP, Nielen MM, Nurmohamed MT, van Schaardenburg D, Reesink HW, Voskuyl AE, et al. Lipids and inflammation: serial measurements of the lipid profile of blood donors who later developed rheumatoid arthritis. Ann Rheum Dis 2007; 66: 184-8. [CrossRef]
10. Van Halm VP, Van Denderen JC, Peters MJ, Twisk JW, van der Paardt M, van der Horst-Bruinsma IE, et al. Increased disease activity is associated with a deteriorated lipid profile in patients with ankylosing spondylitis Ann Rheum Dis 2006; 65: 1473-7. [CrossRef]
11. Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation 2003; 108: 2957-63. [CrossRef]
12. Spanakis E, Sidiropoulos P, Papadakis J, Ganotakis E, Katsikas G, Karvounaris S, et al. Modest but sustained increase of serum high density lipoprotein cholesterol levels in patients with inflammatory arthritides treated with infliximab. J Rheumatol 2006; 33: 2440-6.
13. Georgiadis AN, Papavasiliou EC, Lourida ES, Alamanos Y, Kostara C, Tselepis AD, et al. Atherogenic lipid profile is a feature characteristic of patients with early rheumatoid arthritis: effect of early treatment--a prospective, controlled study. Arthritis Res Ther 2006; 8: R82. [CrossRef]
14. Olofsson SO, Wiklund O, Borén J. Apolipoproteins A-I and B: biosynthesis, role in the development of atherosclerosis and targets for intervention against cardiovascular disease. Vasc Health Risk Manag 2007; 3: 491-502.
15. Akdogan A, Calguneri M, Yavuz B, Arslan EB, Kalyoncu U, Sahiner L, et al. Are familial Mediterranean fever (FMF) patients at increased risk foratherosclerosis? Impaired endothelial function and increased intima media thickness are found in FMF. J Am Coll Cardiol 2006; 48: 2351-3. [CrossRef]
16. Peru H, Altun B, Doğan M, Kara F, Elmaci AM, Oran B. The evaluation of carotid intima-media thickness in children with familial Mediterranean fever. Clin Rheumatol 2008; 27: 689-94. [CrossRef]
17. Sari I, Karaoglu O, Can G, Akar S, Gulcu A, Birlik M, et al. Early ultrasonographic markers of atherosclerosis in patients with familial Mediterranean fever. Clin Rheumatol 2007; 26: 1467-73. [CrossRef]
18. Işlek I, Simsek T, Baskin E, Simşek B, Küçüködük S, Bedir A, et al. Low serum apolipoprotein A1 levels in amyloidosis related to familial Mediterranean fever Pediatr Nephrol 2003; 18: 1005-8. [CrossRef]
19. Bilginer Y, Ozaltin F, Basaran C, Duzova A, Besbas N, Topaloglu R, et al. Evaluation of intima media thickness of the common and internal carotid arteries with inflammatory markers in familial Mediterranean fever as possible predictors for atherosclerosis. Rheumatol Int 2008; 28: 1211-16. [CrossRef]
20. Ugurlu S, Seyahi E, Çetinkaya F, Ozbakir F, Balci H, Ozdogan H, et al. Intima media thickening in patients with familial Mediterranean fever Rheumatology (Oxford) 2009; 48: 911-5. [CrossRef]
21. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab 2008; 294: E15-26. [CrossRef]
22. Kalyoncu U, Kalan I, Bitik B et al. The influence of MEFV mutations on serum lipid profile Ann Rheum Dis 2009; 68: 326.
23. Bersot TP, Vega GL, Grundy SM, Palaoglu KE, Atagündüz P, Ozbayrakçi S, et al. Elevated hepatic lipase activity and low levels of high density lipoprotein in a normotriglyceridemic, nonobese Turkish population. J Lipid Res 1999; 40: 432-8.
24. Mahley RW, Pépin J, Palaoğlu KE, Malloy MJ, Kane JP, Bersot TP. Low levels of high density lipoproteins in Turks, a population with elevated hepatic lipase. High density lipoprotein characterization and gender-specific effects of apolipoprotein e genotype. J Lipid Res 2000; 41: 1290-301.
25. Hodoğlugil U, Williamson DW, Huang Y, Mahley RW. Common polymorphisms of ATP binding cassette transporter A1, including a functional promoter polymorphism, associated with plasma high density lipoprotein cholesterol levels in Turks. Atherosclerosis 2005; 183: 199-212. [CrossRef]
26. Yilmaz E, Ozen S, Balcı B, Duzova A, Topaloglu R, Besbas N, et al. Mutation frequency of Familial Mediterranean Fever and evidence for a high carrier rate in the Turkish population. Eur J Hum Genet 2001; 9: 553-5. [CrossRef]
27. Langevitz P, Livneh A, Neumann L, Buskila D, Shemer J, Amolsky D, et al. Prevalence of ischemic heart disease in patients with familial Mediterranean fever. Isr Med Assoc J 2001; 3: 9-12.
28. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report, Circulation 2002; 106; 3143-421.