# Familial Mediterranean fever may actually be a persistent inflammatory process on vascular endothelium all over the body

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## Abstract

Background: We tried to understand whether or not there is a persistent inflammatory process in Familial Mediterranean Fever (FMF).

Methods: Consecutive patients with the FMF and controls were studied.

Results: The study included 39 patients with the FMF (18 females) and 39 controls. Mean age of the FMF patients was 27.5 ± 11.9 (11-58) years. Although the body weight and body mass index (BMI) were retarded in the FMF patients (64.6 versus 71.7 kg and 24.1 versus 25.7 kg/m2, respectively), the differences were nonsignificant probably due to the small sample size of the study (p>0.05). The mean body heights were similar in both groups (163.4 versus 166.8 cm, p>0.05). As negative acute phase reactants (APR), low density lipoproteins (LDL) (99.0 versus 114.3 mg/dL) and high density lipoproteins (HDL) (37.5 versus 44.5 mg/dL) were suppressed whereas triglycerides (TG) increased (110.2 versus 105.1 mg/dL) as positive APR, but the differences were nonsignificant probably due to the small sample size of the study, again (p>0.05). On the other hand, systolic blood pressures (BP) (115.0 versus 124.8 mmHg, p= 0.047) and diastolic BP (79.2 versus 88.9 mmHg, p= 0.001) were suppressed parallel to the suppressed body weight and BMI, significantly.

Conclusion: Although the FMF is described as intermittent attacks of painful inflammation, probably there is a persistent vascular endothelial inflammation all over the body. The suppressed body weight, BMI, LDL, HDL, and systolic and diastolic BP and the increased TG levels probably play roles of positive and negative APR in the systemic inflammatory process.

Key words: Familial Mediterranean fever, chronic endotelial damage, atherosclerosis, metabolic syndrome, acute phase reactants, triglycerides, blood pressure.

## Introduction

Chronic endothelial damage may be the major underlying cause of aging and death by causing end-organ insufficiencies in human being (1, 2). Much higher blood pressures (BP) of the afferent vasculature may be the major accelerating factor by causing recurrent injuries on vascular endothelial cells. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the medical literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those eventually reduce blood supply to the terminal organs, and increase systolic BP further. Some of the well-known accelerating factors or indicators of the inflammatory process are physical inactivity, sedentary lifestyle, excess weight, animal-rich diet, smoking, alcohol, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, aging, and death (3, 4). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, and aging, endothelial changes can not be reversed completely due to their fibrotic natures. The accelerating factors and terminal consequences are researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the medical literature, extensively (5, 6). Although their normal limits could not been determined clearly yet, plasma triglycerides (TG) may be significant positive acute phase reactants (APR) of the metabolic syndrome (7). Due to the significant association between high plasma TG values and CHD, Adult Treatment Panel (ATP) III adopts lower cutpoints for TG abnormalities than did ATP II (8, 9). Although ATP II determined the normal upper limit of TG as 200 mg/dL in 1994, World Health Organisation in 1999 (10) and ATP III in 2001 reduced the normal upper limit as 150 mg/dL (9). Although these cutpoints are usually used to define borders of the metabolic syndrome, there are suspicions about the safest upper limit of the TG in the plasma. On the other hand, Familial Mediterranean fever (FMF) is the most frequent hereditary inflammatory disease characterized by self-limited recurrent attacks of fever and serositis. It affects certain ethnic groups mainly Jews, Turks, Arabs, and Armenians (11-14). It is characterized with intermittent attacks of painful inflammation, abdominal pain, fever, and arthritis (15, 16). Although the FMF is described as intermittent attacks of systemic inflammation, we tried to understand whether or not there is a persistent vascular endothelial inflammation all over the body in the FMF.

## Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University on consecutive patients with the FMF and routine check up cases between March 2007 and June 2016. The FMF is diagnosed with Tel-Hashomer clinical criteria (17). Two or more major or one major plus two minor criteria are required for the diagnosis. The major criteria include recurrent febrile episodes with serositis (peritonitis, synovitis or pleuritis), amyloidosis of AA type without a predisposing disease, and favorable response to regular colchicine treatment. The minor criteria include recurrent febrile episodes, erysipelas-like erythema, and FMF in a first-degree relative. Medical histories of the FMF patients were learnt. A complete physical examination was performed by the Same Internist. Body mass index (BMI) of each case was calculated by the measurements of the Same Internist instead of the verbal expressions. Weight in kilogram is divided by height in meter squared (9). Systolic and diastolic BP were checked after a 5-minute of rest in seated position by using the mercury sphygmomanometer (ERKA, Germany), and no smoking was permitted during the previous 2 hours. Cases with any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including fasting plasma glucose (FPG), low density lipoproteins (LDL), high density lipoproteins (HDL), and TG were performed. Eventually, the mean body weight, height, BMI, FPG, LDL, HDL, TG, and systolic and diastolic BP were detected in each group, and compared in between. Mann-Whitney U Test, Independent-Samples t Test, and comparison of proportions were used as the methods of statistical analyses.

## Results

The study included 39 patients with the FMF (18 females) and 39 age- and sex-matched control cases. Interestingly, 53.8% of the FMF patients were male. Mean age of the FMF patients was 27.5 ± 11.9 (11-58) years. Although the mean body weight and BMI were retarded in the FMF patients (64.6 versus 71.7 kg and 24.1 versus 25.7 kg/m2, respectively), the differences were nonsignificant probably due to the small sample size of the study cases ($p>0.05$). The mean body heights were similar in both groups (163.4 versus 166.8 cm, $p>0.05$). As some significant negative APR, LDL (99.0 versus 114.3 mg/dL) and HDL (37.5 versus 44.5 mg/dL) were suppressed whereas as a positive APR, TG increased (110.2 versus 105.1 mg/dL) in patients with the FMF, but the differences were nonsignificant probably due to the small sample size of the study cases, again ($p>0.05$). On the other hand, systolic BP (115.0 versus 124.8 mmHg, $p= 0.047$) and diastolic BP (79.2 versus 88.9 mmHg, $p= 0.001$) were suppressed parallel to the suppressed mean body weight and BMI the in the FMF patients, significantly (Table 1).

**Table 1: Characteristic features of the study cases**

| Variables | Patients with FMF* | *p*-value | Control cases |
|---|---|---|---|
| Number | 39 | | 39 |
| Mean age (year) | 27.5 ± 11.9 (11-58) | Ns† | 27.8 ± 8.8 (17-58) |
| Female ratio | 46.1% (18) | Ns | 46.1% (18) |
| *Weight (kg)* | *64.6 ± 16.6 (34-117)* | *Ns* | *71.7 ± 15.1 (46-105)* |
| Height (cm) | 163.4 ± 9.7 (140-187) | Ns | 166.8 ± 10.2 (150-188) |
| *BMI‡ (kg/m²)* | *24.1 ± 5.4 (14.7-41.9)* | *Ns* | *25.7 ± 5.3 (18.4-41.2)* |
| FPG§ (mg/dL) | 92.3 ± 9.7 (73-114) | Ns | 91.4 ± 8.8 (70-108) |
| LDL¶ (mg/dL) | 99.0 ± 33.4 (48-177) | Ns | 114.3 ± 30.5 (59-177) |
| HDL** (mg/dL) | 37.5 ± 12.8 (12-68) | Ns | 44.5 ± 11.0 (27-65) |
| TG*** (mg/dL) | 110.2 ± 52.8 (31-246) | Ns | 105.1 ± 50.4 (39-287) |
| *Systolic BP**** (mmHg)* | *115.0 ± 18.3 (90-170)* | *0.047* | *124.8 ± 20.5 (100-200)* |
| *Diastolic BP (mmHg)* | *79.2 ± 12.1 (60-110)* | *0.001* | *88.9 ± 9.8 (70-120)* |

*Familial Mediterranean fever †Nonsignificant (p>0.05) ‡Body mass index §Fasting plasma glucose ¶Low density lipoproteins **High density lipoproteins ***Triglycerides ****Blood pressures

## Discussion

FMF is an autosomal recessive hereditary disease commonly observed around the Mediterranean basin presenting as recurrent febrile episodes. But the fever may even be absent in some cases in the literature (18). Most patients with FMF have their first attack before the age of 20 years. Whereas more patients than expected may have late-onset FMF in Japan (19). They may have a milder form of the disease with less frequent peritonitis and pleuritis, and the response to colchicine therapy may also be better (19). FMF is associated with genetic mutations in the MEFV gene located on the short arm of Chromosome 16 encoding pyrin (20), and is characterized by recurrent, often stress-provoked attacks of fever and serositis, but sometimes also with chronic subclinical inflammation (21). This protein is expressed mainly in myeloid/monocytic cells and modulates IL-1 beta processing, NF-kappaB activation, and apoptosis (22). A mutated pyrin results in excessive production of proinflammatory cytokines thereby evoking inflammatory attacks. The most devastating complication of FMF is amyloidosis, leading to CRD (22). M694V homozygocity, male gender, and the alpha/alpha genotype of serum amyloid A1 gene are currently established risk factors for amyloidosis (22). Daily colchicine is the mainstay of the therapy for the disease, resulting in complete remission or marked reduction in the frequency and duration of attacks in most cases (22). It is also effective in preventing and arresting renal amyloidosis. Lifelong treatment with colchicine is required for homozygotes for the p.Met694Val mutation or compound heterozygotes for p.Met694Val and another disease-causing allele; this prevents the inflammatory attacks and the deposition of amyloid (23).

Cholesterol, TG, and phospholipids are the major lipids of the body. Cholesterol is an essential structural component of animal cell membrane, bile acids, adrenal and gonadal steroid hormones, and vitamin D. TG are fatty acid esters of glycerol, and they are the major lipids transported in the blood. The bulk of fat tissue deposited all over the body is in the form of TG. Phospholipids are TG that are covalently bound to a phosphate group. Phospholipids regulate membrane permeability, remove cholesterol from the body, provide signal transmission across the membranes, act as detergents, and help in solubilization of cholesterol. Cholesterol, TG, and phospholipids do not circulate freely in the plasma instead they are bound to proteins, and transported as lipoproteins. There are five major classes of lipoproteins including chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), LDL, and HDL in the plasma. Chylomicrons carry exogenous TG from intestine to liver via the thorasic duct. VLDL are produced in the liver, and carry endogenous TG from the liver to the peripheral organs. In the capillaries of adipose and muscle tissues, 90% of TG is removed by a specific group of lipases. So VLDL are converted into IDL by removal of TG. Then IDL are degraded into LDL by removal of more TG. So VLDL are the main sources of LDL in the plasma. LDL deliver cholesterol from the liver to other parts of the body. Although the liver removes majority of LDL from the circulation, a small amount is uptaken by scavenger receptors on macrophages those may migrate into arterial walls and become the foam cells of atherosclerotic plaques. HDL remove fats and cholesterol from cells, including within arterial wall atheroma, and carry the cholesterol back to the liver and steroidogenic organs including adrenals, ovaries, and testes for excretion, reutilization, and disposal. All of the carrier lipoproteins in the plasma are under dynamic control, and are readily affected by diet, illness, drug, body weight, and BMI. Thus lipid analysis should be performed during a steady state. But the metabolic syndrome alone is a low-grade inflammatory process on vascular endothelial cells all over the body. Thus the metabolic syndrome alone may be a cause of the abnormal lipoproteins levels in the plasma. On the other hand, although HDL are commonly called as 'the good cholesterol' due to their roles in removing excess cholesterol from the blood, and protecting the arterial

walls against atherosclerosis (24), recent studies did not show similar results, and low plasma HDL levels may alert clinicians about searching of additional metabolic or inflammatory pathologies in the body (25, 26). Normally, HDL may show various anti-atherogenic properties including reverse cholesterol transport and anti-oxidative and anti-inflammatory properties (26). However, HDL may become 'dysfunctional' in pathological conditions which means that relative compositions of lipids and proteins, as well as the enzymatic activities of HDL are altered (25). For instance, properties of HDL are compromised in patients with DM due to the oxidative modification and glycation as well as the transformation of HDL proteomes into proinflammatory proteins. Additionally, the highly effective agents of increasing HDL levels such as niacin, fibrates, and cholesteryl ester transfer protein inhibitors did not reduce all cause mortality, CHD mortality, myocardial infarction, or stroke (27). While higher HDL levels are correlated with cardiovascular health, medications used to increase HDL did not improve the health (27). In other words, while high HDL levels may correlate with better cardiovascular health, specifically increasing one's HDL values may not increase cardiovascular health (27). So they may just be some indicators instead of being the main actors of the process. Beside that, HDL particles that bear apolipoprotein C3 are associated with increased risk of CHD (28). Similarly, BMI, FPG, DM, and CHD were the lowest between the HDL values of 40 and 46 mg/dL, and the prevalence DM was only 3.1% between these values against 22.2% of outside of these limits (29). In another definition, the moderate HDL values may also be the results instead of the causes of the better health parameters. The lower mean body weight, BMI, LDL, HDL, and systolic and diastolic BP and the higher mean TG values in patients with the FMF can be explained by definition of the metabolic syndrome in the present study (30, 31).

Probably excess weight may be the most common cause of vasculitis, worldwide, and the leading cause of major health problems in this century. It leads to structural and functional abnormalities in many organ systems of the body (32). Adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines, all of those behave as APR in the plasma (33). Excess weight induced chronic low-grade vascular endothelial inflammation may play a significant role in the pathophysiology of disseminated atherosclerosis all over the body (1, 2). On the other hand, excess weight may cause an increased blood volume as well as an increased cardiac output thought to be the result of an increased oxygen need of the excessive fat tissue. The prolonged increase in the blood volume may lead to myocardial hypertrophy, terminating with a decreased cardiac compliance. FPG and total cholesterol (TC) values increased parallel to the increased BMI values in the literature (34). Combination of these cardiovascular risk factors will eventually terminate with an increased left ventricular stroke work and higher risks of arrhythmias, cardiac failure, and sudden death. Additionally, the prevalences of CHD and stroke increased parallel to the increased BMI values in another study (35), and risk of death from all causes including cancers increased throughout the range of moderate to severe excess weight in all age groups (36). The relationships between excess weight, increased BP, and higher plasma TG values were described in the metabolic syndrome, extensively (37), and clinical manifestations of the syndrome include obesity, hypertriglyceridemia, hyperbetalipoproteinemia, HT, insulin resistance, and proinflammatory and prothrombotic states (37). Similarly, prevalences of smoking (42.2% versus 28.4%, $p<0.01$), excess weight (83.6% versus 70.6%, $p<0.01$), DM (16.3% versus 10.3%, $p<0.05$), and HT (23.2% versus 11.2%, $p<0.001$) were all higher in the hypertriglyceridemia group in another study (38). On the other hand, the prevalences of hyperbetalipoproteinemia were similar both in the hypertriglyceridemia (200 mg/dL and higher) and control groups (18.9% versus 16.3%, $p>0.05$, respectively) in the above study (38). Similarly, plasma LDL values increased just up to the plasma TG value of 200 mg/dL but no more in another study (39). Beside that, the mean BMI values increased just up to the plasma TG value of 150 mg/dL, significantly ($p<0.05$ for each step) (39). On the other hand, the greatest number of deteriorations in the metabolic parameters was observed just above the plasma TG value of 60 mg/dL (39). According to our opinion, although excess weight does not affect each individual with the same severity, overweight, obesity, severe obesity, and morbid obesity histories of years should be added into the calendar age with various degrees during calculation of physiological age of the individuals.

Although the obvious consequences of excess weight on health, nearly three-quarterss of cases above the age of 30 years have excess weight (40). The prevalence of excess weight increases by decades, particularly after the third decade, up to the eighth decade of life (40). So 30th and 70th years of age may be the breaking points of life for body weight, and aging may be the major determining factor of excess weight. Relatively decreased physical and mental stresses after the age of 30 years, and debility and comorbid disorders induced restrictions after the age of 70 years may be the major causes for the changes of BMI at these ages. Interestingly, the mean age and BMI increased just up to the plasma TG values of 200 mg/dL and 150 mg/dL in the above study, respectively (39). So smoking remained as the major underlying factor for the hypertriglyceridemia above the plasma TG value of 200 mg/dL. Beside that, the mean BMI values were 24.6, 27.1, 29.4, 29.9, and 30.0 kg/m2 in the five study groups, respectively (39). In other words, only cases with the plasma TG values lower than 60 mg/dL had a normal mean BMI value (39). On the other hand, the mean age and TG value of the first group were 35.6 years and 51.0 mg/dL, respectively (39). They were 43.6 years and 78.3 mg/dL in the second, 47.7 years and 122.2 mg/dL in the third, and 51.2 years and 174.1 mg/dL in the fourth groups, respectively (39). In another definition, TG values increased about 7.8 mg/dL for each year of aging up to 200 mg/dL in the plasma (39). So aging alone may be another risk factor for chronic low-grade inflammation on vascular endothelium all over the body.

Although ATP III reduced the normal upper limit of plasma TG as 150 mg/dL in 2001 (9), whether or not much lower limits provide some additional benefits for human body remains unclear (41). Similar to the recent study (42), prevalence of smoking was the highest in the highest TG having group in the above study (39) that may also indicate inflammatory role of smoking on vascular endothelium in the metabolic syndrome, since TG may behave as positive APR in the plasma. BMI, FPG, HT, DM, COPD, and CRD increased parallel to the increased plasma TG values from the first up to the fifth groups, continuously in the above study (39). Just as an opinion of us, significantly increased mean age by the increased plasma TG values may be secondary to aging induced decreased physical and mental stresses, which eventually terminates with excess weight and its consequences. Interestingly, although the mean age increased from the lowest TG having group up to TG value of 200 mg/dL, then it decreased (39). The similar trend was also seen with the mean LDL values (39). These trends may be due to the fact that although the borderline high TG values (150-199 mg/dL) is seen together with physical inactivity and overweight, the high TG (200-499 mg/dL) and very high TG values (500 mg/dL or higher) may be secondary to genetic factors, smoking, and terminal consequences of the metabolic syndrome including obesity, DM, HT, COPD, cirrhosis, CRD, PAD, CHD, and stroke (9). But although the underlying causes of the high and very high plasma TG values may be a little bit different, probably risks of the terminal endpoints of the metabolic syndrome do not change in them. For example, prevalences of HT, DM, and COPD were the highest in the highest TG having group in the above study (39). Eventually, although some authors reported that lipid assessment can be simplified by measurements of TC (43), most of the others indicated a causal relationship between higher TG values and irreversible end-points of the metabolic syndrome (44).

As a conclusion, although the FMF is described as intermittent attacks of painful inflammation, probably there is a persistent vascular endothelial inflammation all over the body. The suppressed body weight, BMI, LDL, HDL, and systolic and diastolic BP and the increased TG levels probably play roles of positive and negative APR in the systemic inflammatory process.

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