International Journal of Urology and Nephrology ISSN: 2091-1252 Vol. 3 (3), pp. 082-089, March, 2015.
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*Full Length Research Paper*

# Comparison of inflammation effects in the patients with familial mediterranean fever and dialysis patients

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Accepted 30 December, 2014

**We aimed to assess the presence and clinical effect of inflammation in the patients with familial mediterranean fever who follow-up treatment regularly. All the patients were measured with C-reactive proteine, homocysteine, fibrinogene levels and biochemical parameters; the presence of atherosclerotic plaque was investigated in the carotid intima artery. Leucocyte, C-reactive protein and fibrinogene levels were found to be significantly higher in the familial mediterranean fever group patients. Homocysteine levels and the presence of atherosclerotic plaque in the carotid intima artery were found to be significantly lower in the familial mediterranean fever group patients. Increasing the odds ratio for homocysteine was found to be related to dialysis treatments. The correlation between the presence of proteinuria, microalbuminuria, inflammation and the presence of atherosclerotic plaque in the carotid intima artery were not determinate to the familial mediterrian fever group of patients. We demonstrated that inflammation might be present continuously despite regular treatment in the patients with familial mediterrian fever and that this inflammation can be the main reasons or contributory factor to the complications of the disease.**

**Key words:** Familial mediterrian fever, hemodialysis, ınflammation, peritoneal dialysis.

## INTRODUCTION

Familial Mediterrian Fever (FMF) is a hereditary auto inflammatory disorder inherited in an autosomal recessive manner. Although, it is commonly encountered in the world, FMF is usually seen in non-Ashkenazi Jewish, Arabic, Turkish, and Armenian populations (Yamazaki K,2009).

Today, especially deficiency of complement inhibitory system (such as C5a, IL8 etc.) as well as the effect of disequilibrium of antioxidant/oxidant system in prevention of ınflammation are known in the development of FMF (Bashardoust B , Maleki N, 2014; Sahin A, 2014 ). FMF can be described as a recurrent attack and ınflammation of serosal membranes like peritoneal, pericardial, pleural, synovial and meningeal coverings. Fever, arthritis, abdominal and chest pain during recurrent attacks are the most important characteristic features ofthe disease (Yamazaki K,2009).

Although; it has been reported that solid tumors can accompany the patients with FMF in some cases, it is considered that frequency of malignity does not increase. Currently, it is known that amyloidosis or renal involvement are the most severe complications of FMF disease. The development of amyloidosis or proteinuria and microalbuminuria can contribute to increase of cardiovascular diseases risk (Twig G, et al, 2014;Canpolat U, et all,2012). In the patients with renal involvement with proteinuria especially not in nephrotic range, it has also been demonstrated that the disease may be accompanied by various glomerulonephritis (focal segmental glomerulosclerosis, membrano proliferative glomerulonephritis etc.) (Bashardoust B, Maleki N, 2014; Kukuy O et al., 2013).

In the diagnosis of FMF disease, a positive family history and the clinical picture of the patient is more important than the specific diagnostic tests in the diagnosis of the disease. In the course of the disease,

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increasing acute phase responses are important to support the diagnosis during attacks (Bashardoust B, Maleki N, 2014; Ben-Zvi I, Livneh A,2011). Since FMF disease is better described and it can be diagnosed and treated early, its amyloidosis complication is less frequently encountered. Also, description of genes of alpha/alpha genotype of the serum amyloid A or SAA1 which have been used for the determination of amyloidosis risk, could be attributed to the estimation and prevention of amyloidosis and other complications in the patients of FMF disease (Caglayan AO et al. 2010).

The levels of the acute-phase proteins, cytokines and ınflammation-induced proteins have been found to be higher, except for the existence of acute attacks in the FMF patients, this condition can be as a result of the presence of a subclinical ınflammation in these patients. Subclinical inflammation can be the cause of the different life-threatening complications like anemia, splenomegaly and heart disease (Ben-Zvi I , Livneh A, 2011).

It was demonstrated in the studies that the most critical cause of death in the patients with end-stage renal disease were cardiovascular diseases and the frequency of cardiovascular disease could be increased 20-40-fold compared to the normal population (Allon M, 2013). The effects of dialysis modalities on morbidity and mortality are controversial, but when the appropriate renal replacement therapies (dialysis) are applied in the appropriate patients in the long-term, there is a general confusion as to which is superior to the other (Suzuki K; et al., 2010).

In our study, we aimed to show the presence of subclinical ınflammation which upon evaluation contribute to the atherosckerosis and cardiovascular disease risk in patients with FMF. Hovewer; comparison of development risk of inflammation and atherosckerosis were made to the patients of the peritoneal dialysis, hemodialysis and FMF groups who follow-up treatment regularly.

## MATERIALS AND METHODS

A total number of 119 patients aged 18-77 years old were included in this study. Thirty patients undergo peritoneal dialysis (PD) therapies and forty-two patients received hemodialysis (HD) replacement therapies, while forty-seven patients had FMF disease. All of the subjects were followed-up in Nephrology and Rheumatology Clinic of Istanbul Bakirkoy and were attended to in Dr. SadiKonuk Training and Research Hospital.

Treatment durations of the patients for at least 1 year were taken into consideration. Dialysis adequacy was provided in hemodialysis and peritoneal dialysis patients. Patients with heart failure, cancer, existence of acute and chronic infection, collagen tissue disease and bedridden patients were excluded from the study. Patients with positive family history of amyloidosis and patients with amyloidosis or patients with FMF disease, who were determined to have proteinuria > 3,5 g/day in a 24-hour urines were excluded from the study. Also, patients who were not treatment compliant and unresponsive were excluded from the study.

Some patients with FMF were investigated regarding mutation type. Diagnosis of FMF disease was determined to have clinical characteristics (fever, abdominal pain, chest pain, arthritis) and/or a positive family history, in all the patients with FMF disease.

Following a fasting period of 12 hours, venous blood samples were simultaneously collected from all of the patients and biochemical parameters, C-reactive proteine (CRP), homocysteine and fibrinogene levels were measured. Also, all the patients with FMF disease were evaluated on renal functions. Urea and creatinine levels were measured from the venous blood samples. Urine volume was calculated by collecting 24-hour urines of the patients and microalbumin and protein levels of the 24-hour urines. The mean 24-hour urine volumes of hemodialysis and peritoneal dialysis group patients were calculated as less than 0,5 L/day and 24- hour urines were not included to the evaluation of the dialysis groups which residual renal function would not affect the results of this study.

Kinetics evaluations were carried out for dialysis adequacy. At the kinetics evaluation; Kt/V and URR were measured for hemodialysis patients. [URR= (postdialysis urea/predialysis urea)] formula was used to calculate URR values. Kt/V >1,4 and URR>70% were accepted as an adequate dialysis.

Peritoneal dialysis patients received continuous ambulatory peritoneal dialysis (CAPD). Change for a mean of 4 times were performed in CAPD patients. CAPD 2 stay safe peritoneal dialysis solutions of 2000/2500 mL were used in CAPD patients. Glucose (1,5% glucose, 2,3% glucose) and calcium content (1,25 mmol/L, 1,75 mmol/L) of the dialysis solutions were varied according to the patient.

At the Kt/V evaluation; peritoneal Kt was taken into consideration and Watson (V= 2.447- 0.009516 (age) + 0.1704 Height (cm) + 0.3362 Weight (kg) (in males), (V= 2.097 + 0.1069 Height (cm) + 0,2466 Weight (kg) (in females)) formula was used in calculation of the total body water. Kt/V >1,7 value was accepted as an adequate dialysis.

Blood samples were collected into the tubes by using vacutainer blood collection tubes: citrated tube for fibrinogen; gel vacuum tubes for lipid profile, urea, creatinine and CRP values and EDTA tube for homocysteine levels.

Blood samples taken into gel tubes and following it was allowed to stand 30 minutes for complete clotting prior to centrifugation and then it was centrifuged for 15 minutes at 4000 rpm.

Serum levels of lipid profile were measured by using an Abbott-Aeroset Auto-analyzer device (Abbott Aeroset System, Germany).

Serum CRP levels were measured in a Delta Seac Analyzer (Radim Reagent, Italy) by using a nephelometric method.

In order to determine the homocysteine levels, the blood samples were taken into EDTA tube then it was centrifuged for 15 minutes at 4000 rpm by obtaining the plazma samples after centrifugation were studied in an Immulite 1000 Analyzer (Siemens, U.S.A) by using chemiluminescent method.

Fibrinogene test was studied in Sysmex CA-1500 analyzer device (Dade Behring Thrombin Reagent, Germany) by using the plasma samples.

Turbidimetric method was used to evaluate the presence of protein and microalbumin in 24-hour urines and the evaluation device used was Abbott Aeroset Analyzer (Abbott Park, USA).

This study was approved by the Ethics Committee of Bakirkoy Training and Research Hospital and conducted in accordance with the principles of the Declaration of Helsinki. All participants were given all the necessary information about this study and patient consent was given prior to participation in this study.

**Statistical Evaluations**

NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) program was used for the statistical analysis. During the evaluation of the study data, regarding the comparisons of descriptive statistical methods (mean, standard deviation, median, frequency, rate, minimum, maximum) as well as quantitative data, One-way ANOVA test was used for the intergroup comparisons of three or more groups with normal distribution and Tukey HSD test was used for determination of group causing difference. Kruskal Wallis test was used for the intergroup comparisons of three or more groups without normal distribution and Mann Whitney U test was used for the determination of group causing difference. Pearson Chi-Square test was used for the comparison of qualitative data. Spearman's Correlation Analysis was used for evaluation of the correlations between the parameters. Significance was evaluated at the levels of $p<0,01$ and $p<0,05$.

**RESULTS**

The study involved 119 patients in Nephrology Clinic and Rheumatology Clinic of Bakirkoy and Dr SadiKonuk Training and Research Hospital. The ages of the patients ranged between 18 and 77 years and the mean age found 41,14±16,93 years. Fourty-eight point seven percent of the patients (n=58) were females and 51,3% of them (n=61) were males. (Table 1).

Mean glomerular filtration rate, mean proteinuria value and mean microalbuminuria value of FMF group patients were measured and the results were 82,32±37,90 ml/min 1,73 $m^2$, 935,94±1841,13 mg/day and 457,32±106,86 mg/day, respectively.

A statistically significant difference was determine between groups regarding the ages of the patients (p: 0,001; p<0,01). It was determine that the mean age of FMF group patients was statistically significantly less than the mean ages of HD and PD group patients (p: 0,001; p: 0,001; p<0,01; respectively). No statistically significant differences were determine between HD and PD group patients regarding the mean ages (p>0,05) (Table1).

A statistically significant differences were determine between groups regarding the body mass index (BMI) values of the patients (p: 0,001; p<0,01). It was determine that the mean BMI values of FMF group patients were statistically significantly higher than the mean BMI values of HD and PD group patients (p: 0,001; p: 0,002; p<0,01; respectively). No statistically significant differences were found between HD and PD group patients regarding the mean BMI values (p>0,05) (Table 1).

It was determine that a statistically significant differences were between the groups, regarding values of leucocyte (p: 0,001; p<0,01). It was found that the leucocyte values of FMF group patients were statistically significantly higher than the leucocyte values of HD and PD group patients (p: 0,001; p: 0,001; p<0,01; respectively). No statistically significant difference was found to that between HD and PD group patients, regarding leucocyte values (p>0,05) (Table 2).

When we compared the CRP values of the patient groups, there were statistically significant differences between the groups (p: 0,001; p<0,01).

While the CRP values of FMF group patients were found to be statistically significantly higher than the mean CRP values of HD and PD group patients (p:0,001; p:0,001; p<0,01; respectively) and between the mean CRP values of HD and PD group patients were determined to be statistically significant difference (p>0,05) (Table 2) (Figure 1).

When the mean fibrinogene values of the patients were evaluated, a statistically significant differences were determined between groups (p: 0,001; p<0,01). It was determine that the mean fibrinogene values of FMF group patients were statistically significantly higher than the mean fibrinogene values of HD and PD group patients (p: 0,001; p: 0,001; p<0,01; respectively). It was determined that the fibrinogene values of HD group patients were statistically significantly higher than the fibrinogene values of PD group patients (p: 0,006; p<0,01) (Table 2) (Figure 2).

**Table 1.** Comparison of demographic characteristics and clinical definitions according to groups.

| | **Allcases (n= 119)** **Median±ss** | **[1]FMF Group (n=47) Median ±ss** | **[2]HD Group (n=42) Median±ss** | **[3]PD Group (n=30) Median± ss** | **[a]p** | **[b]Post-hoc** |
|---|---|---|---|---|---|---|
| Age | 41,14 ± 16,93 | 30,83 ± 8,83 | 49,64 ± 18,51 | 45,40 ± 16,21 | 0,001** | 1<2,3 |
| BMI ($kg/m^2$) | 24,05 ± 3,19 | 25,87 ± 1,92 | 22,43 ± 2,86 | 23,53 ± 3,81 | 0,001** | 1>2,3 |
| | n (%) | n (%) | n (%) | n (%) | [c]p | |
| Female Gender | 58 (48,7) | 23 (48,9) | 17 (40,5) | 18 (60,0) | 0,263 | - |
| Male | 61 (51,3) | 24 (51,1) | 25 (59,5) | 12 (40,0) | | |

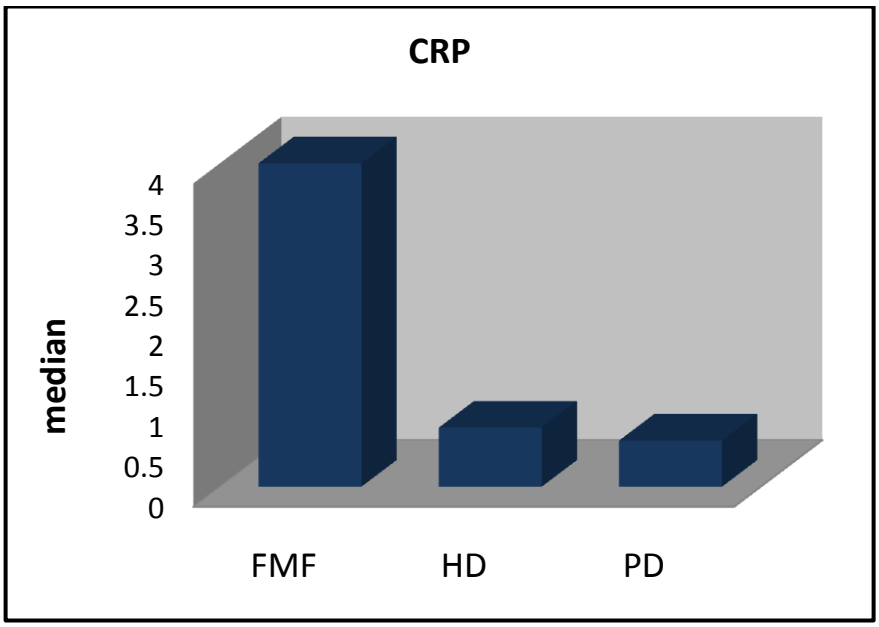
FMF: Familial Mediterrian Fever, HD: Hemodialysis, PD: Peritoneal Dialysis, BMI:Body mass ındex [a]One-way analysis of variance [b]Tukey HSD test [c]Pearsonki-kare test **p<0,01.

**Table 2**. According to groups comparison of biochemical parameters and atheroscklerosis risk factors.

| | **Allcases** (n= 119) **Median±ss** | **[1]FMF Groups** (n=47) **Median±ss** | **[2]HD Groups**(n=42) **Median±ss** | **[3]PD Groups** (n= 30) **Median±ss** | **[a]p** | **[d]Post-hoc** |
|---|---|---|---|---|---|---|
| Leucocyte | 4664,05±4047,89 (5000) | 7808,51±2794,70 (8000) | 2599,42±3227,2 (9,90) | 2628,23±3615,60 (9,45) | [d]0,001** | 1>2>3 |
| C-reactive proteine (mg/dL)) | 3,46±4,90 (2,00) | 7,09±6,08 (4,00) | 1,04±0,91 (0,73) | 1,18±1,60 (0,57) | [d]0,001** | [e]1>2>3 |
| Fibrinogene (IU/ mL) | 315,75±140,20 (250,50) | 450,77±137,15 (450,00) | 233,65±23,86 (235,80) | 219,18±19,81 (220,60) | [d]0,001** | [e]1>2>3 |
| Homocysteine (IU/ mL) | 18,94±11,50 (13,50) | 11,18±1,76 (11,20) | 21,64±12,35 (18,45) | 27,31±11,69 (24,75) | [d]0,001** | [e]1>2>3 |
| LDL-cholesterole (mg/dL) | 108,85±40,47 | 112,06±41,24 | 95,14±39,06 | 123,00±36,25 | 0,011* | [e]1>2>3 |
| HDL-cholesterole (mg/dL) | 38,66±10,00 | 41,23±9,27 | 35,98±10,72 | 38,40±9,32 | 0,045* | [e]1>2>3 |
| Triglyseride (mg/dL) | 150,82±83,11 (132,50) | 143,15±76,67 (123,50) | 164,81±99,17 (146,50) | 143,00±66,37 (122,00) | [d]0,514 | - |
| Plaque existence | 27 (22,7) | 4 (8,5) | 10 (23,8) | 13 (43,3) | [d]0,002 | [e]1>2>3 |

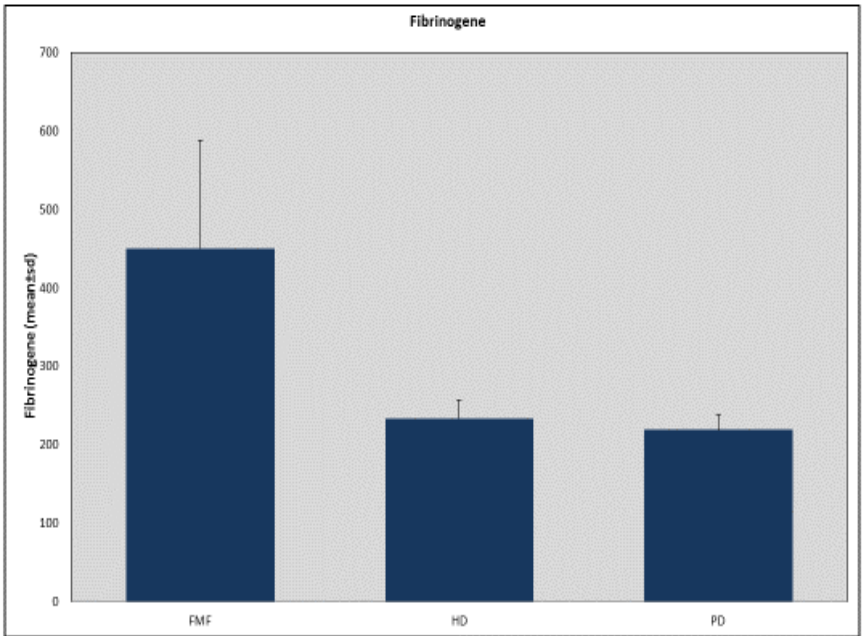
FMF: Familial Mediterrian Fever, HD:Hemodialysis, PD: Peritoneal Dialysis.
[a]One-way analysis of variance [b]Tukey HSD test [c]Pearson's Chi-Square test
[d]Kruskal-Wallis test [e]Mann Whitney U test * p<0,05 **p<0,01

**Figure 1**. Comparison of CRP levels in thegroup of FMF withhemodialysisandperitonealdialysisgroups.




CRP: C- reactive proteine, FMF: FamilialMediterrian Fever, HD: Hemodialysis, PD: PeritonealDialysis.

**Figure 2.** Comparison of fibrinogenelevels in thegroup of FMF withhemodialysisandperitonealdialysisgroups.




A statistically significant differences were found to be between groups, regarding homocysteine values of the patients (p: 0,001; p<0,01). It was determined that the mean homocysteine values of FMF group patients were statistically significantly less than the mean homocysteine values of HD and PD group patients (p: 0,001; p:0,001; p<0,01; respectively). It was determined to that the mean homocysteine values of HD group patients were statistically significantly less than the mean homocysteine values of PD group patients (p: 0,031; p<0,05) (Table 2). When the mean serum homocysteine values of all dialysis patients were compared with themean

**Table 3.** Relationship of microalbuminuria and proteinuria with other parameters in the patients with FMF.

| | Microalbuminüria | | Proteinüria | |
|---|---|---|---|---|
| | **r** | ***p*** | **R** | ***p*** |
| Age | 0,088 | 0,557 | -0,017 | 0,910 |
| Body massindex | 0,196 | 0,193 | 0,144 | 0,341 |
| C- reactive proteine | 0,234 | 0,114 | 0,130 | 0,384 |
| Homocysteine | -0,161 | 0,280 | -0,146 | 0,326 |
| Fibrinogene | 0,002 | 0,992 | 0,063 | 0,673 |
| LDL- cholesterole | -0,088 | 0,557 | -0,028 | 0,850 |
| HDL- cholesterole | -0,279 | 0,057 | -0,153 | 0,305 |
| Triglyseride | 0,094 | 0,535 | 0,092 | 0,543 |

r:Spearman korelasyon katsayısı *p<0,05

serum homocysteine values of FMF patients, odds ratio for homocysteine was found to be 30,22 (95% CI: 10,98-83,17) in dialysis patient groups and increasing of this ratio that it was found to be related to dialysis treatments and comparison of FMF group patients with the dialysis patients.

When each of the three group of patients were compared regarding the LDL-cholesterole values that it was determined to be between groups statistically significant difference (p: 0,011; p<0,05). It was found that the LDL-cholesterole values of HD group patients were statistically significantly less than the LDL-cholesterole values of PD group patients (p: 0,010; p<0,05). No statistically significant difference was determined to between FMF group patients and HD and PD group patients, regarding the values of LDL-cholesterole (p>0,05) (Table 2).

It was determined that there was a statistically significant difference between groups, regarding the values of serum HDL-cholesterole of the patients (p: 0,045; p<0,05). While it was determined that the values of serum HDL-cholesterole in the patients of FMF group were statistically significantly higher than the values of serum HDL-cholesterole in the patients of HD group (p: 0,035; p<0,05). No statistically significant difference was determined between PD group patients with FMF and HD group patients, regarding the values of serum HDL-cholesterole (p>0,05) (Table 2).

No statistically significant difference was determined between each of the three groups, regarding the levels of serum triglyceride (p>0,05) (Table 2).

When the rates of presence of atherosclerotic plaque in the carotid intima artery were compared to the dialysis treatment groups with FMF disease group, it was found that there was a statistically significant difference between the groups (p: 0,002; p<0,01). It was determined that the rates of presence of atherosclerotic plaque in the FMF group patients were statistically significantly less than the rates of HD and PD group patients (p:0,048; 0,001; p<0,05; respectively). No statistically significant difference was found between HD and PD group patients, regarding the rates of presence of atherosclerotic plaque (p>0,05) (Table 2). When the presence of atherosclerotic plaque in all of dialysis patients were compared with the presence of atherosclerotic plaque in FMF patients, we determinaed that the odds ratio for the presence of carotid intima plaque had been 5,046- fold higher in the all dialysis patients (95% CI: 1,62-15,75) (Table 2) .

When were evaluated the mean correlation of proteinuria and micro albuminuria values and demographic characteristics, acute phase reactants, ınflammatory and biochemical parameters, it was found to have affect on each other in the patients of FMF group, no statistically significant correlation was determined (p>0,05) (Table 3).

## DISCUSSION

FMF disease principally affects Mediterrian populations, it is a hereditary auto-ınflammatory disorder commonly encountered in various geographical regions and races in the world (Yamazaki K et al., 2009). It was reported that cardiovascular diseases was seen more commonly in FMF patients compared to general population and the reason for this was atherosclerosis (Basar N, et al., 2014).

While the most serious complication of FMF is amyloidosis development, it is difficult to predetermine the patient group which will develop amyloidosis and the other complications of the disease. The presence of genetic mutations is shown as the most important reason for this condition and the studies on this subject are continuing. It is known, that MEFV gene is responsible for the disease. However, it has been shown in the studies that more than 80 disease-associated mutations have been identified in MEFV gene and each mutational change in the alleles of MEFV gene can affect the clinical manifestation of the disease and there can begenetic mutations related to the races (Caglayan AO, et al., 2010; Booty MG, et al., 2009).

Today, the development of complications despite early diagnosis and lifelong colchicum treatment can be tried to explain genetic mutations, disequilibrium of antioxidant/oxidant system other than positive family history and presence of inflammation continuing even in the periods when the disease is stabile.

Cardiovascular diseases are the most important cause of morbidity and mortality in the dialysis patients. As a consequence, the studies was able to demonstrate that chronic ınflammation was the most important factor in the development of cardiovascular disease in each period of the chronic renal disease. Also in FMF patients, it was supported with the studies that risk of cardiovascular disease increased compared to the general population (Basar N, etall, 2014). In our study, we also aimed to show the importance of ınflammation when receiving regular treatment in FMF patients by comparing the dialysis patients who could be considered to be the most risky in the development of cardiovascular disease.

Inflammation is a major factor in the development of atherosclerosis. Although; CRP is the ınflammatory marker, which can contribution to the development of atherosclerosis, actually it is considered to be an acute phase protein (Ferri Cet al., 2007). While it has been shown in the studies that serum CRP levels have been an important phase in the predetermination of the cardiovascular disease, CRP is the most common aspect that is evaluated together with many factors like age, gender, dyslipidemia, treatments administered (use of statin and aspirin etc.) and primary disease might be meaningful (Corrado E, Novo S, 2007).

In our study, we determined that serum CRP and leucocyte levels were higher in FMF group patients compared to hemodialysis and peritoneal dialysis group patients. When we compared each of these three group of patients, we determined that FMF group patients were at low-risk for atherosclerotic risk factors such as similar serum LDL-cholesterole levels with dialysis groups and higher HDL-cholesterole levels compared to dialysis groups, the presence of stage 1-3 chronic kidney disease and younger mean age of patient group. Despite the determination of higher serum CRP values in FMF group patients that this condition can be caused an acute phase response and the subclinical ınflammation. Additionally, if it is also taken into consideration that end-stage renal disease patients (stage 5 chronic renal disease) are at high-risk for development of atherosclerosis, determination of lower serum CRP values in dialysis group patients and higher serum CRP values in FMF group patients by us may support the thought of serum CRP values might be increased as an acute phase response.

In our study, we found serum fibrinogene levels to be higher in FMF group patients compared to dialysis group patients. Fibrinogene has a role in development of many physiological and pathophysiological processes apart from being an acute phase protein. With understanding of molecular mechanism of fibrinogene, the effect of widespread polymorphism of fibrinogene gene on acquired and hereditary diseases has been tried to be explained.In fact, it has been shown that some mutations in fibrinogene gene were more common in different ethnic groups and they had correlations with some diseases (atherothrombotic diseases, cardiovascular diseases etc.)(Ou NJ , Tang MZ, 2014).

It is known that the risk of atherosclerosis increases and cardiovascular diseases can be seen more frequently in FMF group patients compared to the normal population.In our study, determination of higher levels of fibrinogene, which are acute phase response and ınflammation marker, in FMF group patients compared to the dialysis group patients by us may show that the clinical presentations of presence of continuous ınflammation in FMF disease are significant. Hovewer; FMF disease that it can be correlation the between gene mutations causing FMF disease and fibrinogene gene mutations and additionally these fibrinogene gene mutations can be caused to the cardiovascular diseases which may be development during the clinical course of disease.

İt is known; increasing of serum homocysteine levels lead to the endothelial dysfunction and increasing of the oxidative stress which can be caused to the development of atherosclerosis. Correlation of between higher serum homocysteine levels and development of vascular diseases were supported by many studies (Pushpakumar SB, et al., 2014). It has been shown in the studies that increasing of carotid intima media thickness and presence of atherosclerotic plaque can be marker demonstrated to existence of widespread atherosclerosis. İt is suggested; in healthy population who is a correlation between increase of carotid intima media thickness and presence of atherosclerotic plaque with higher serum homocysteine levels (Jung JM, et al., 2013; Shakeri A, et all, 2011).

In our study, we also demonstrated to the FMF patients whose serum homocysteine levels were higher and presence of atherosclerotic plaque decreased in carotid intima, comparison with the dialysis patients . We determinated; no differences were between both dialysis groups regarding the levels of serum homocysteine and presence of the atherosclerotic plaque. This condition may be explained tothe higher risk of atherosclerosis in dialysis patients. İt was suggested to that application of appropriate renal replacement therapies in appropriate patients have not been superiority of types of dialysis, development of the morbidity and mortality in long term (Suzuki K et al., 2012).

We determinaed that there was no correlation between the presence of proteinuria and microalbuminuria and ınflammation parameters in FMF group patients. It is known that microalbuminuria levels >300 mg/dL in 24-hour urines can lead to increase of the risk of cardiovascular diseases that this condition can be more important other than the contribution of reduction of creatinine clearance and increase of progression of the chronic renal disease (Agrawal V et al., 2009).

Presence of proteinuria and microalbuminuria are among important complications of FMF disease and it is association with clinical features and gene mutations

The disease. No presence of correlation the between proteinuria and microalbuminuria and inflammatory parameters were determinated to the patients with FMF group that this condition can be explained to the group with FMF disease can be low-risk for complications of renal involvement, in our the study. Absence of positive family history of amyloidosis and not determination of proteinuria in nephroticrange can be supported to the our study results.

The levels of serum leukocyte, CRP and fibrinogene were higher determinated to the group of FMF, there can be predictor of continuous ınflammation in the course of disease and would be development of complication risks. However, due to characteristics of patient group and absence of correlation between ınflammation and proteinuria, microalbuminuria, it can be considered that progression of renal involvement may be slower.

We believe, in FMF disease will be continuous of subclinical ınflammation and its severity will be contributed to development of the important complications.

## CONCLUSION

We thought, that correlation of between distinct pathophysiological effects of acute phase proteins and ınflammation can be important to development of complications of FMF disease. Determination of MEFV gene mutations and investigation of correlation of MEFV gene mutations and fibrinogene gene polymorphism can cause to prior estimating, will be development of complications such as anemia, splenomegaly, atherothrombotic disease etc. This condition can cause of using early treatment therefore severity of the complications and frequency of the complications can be prevented to the disease.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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