# AİLEVİ AKDENİZ ATEŞLİ ÇOCUKLARDA ORTALAMA TROMBOSİT HACMİ ve TROMBOSİT DAĞILIM GENİŞLİĞİNİN DEĞERLENDİRİLMESİ

# Evaluation of the Mean Platelet Volume and Platelet Distribution width in Children with Familial Mediterranean Fever

**Fatma Duksal(0000-0001-6067-3424)[1], Ahmet Sami Güven(0000-0002-6085-1582)[1], Mesut Arslan(0000-0002-4450-6295)[1], Melih Timucin Dogan(0000-0003-3565-8606)[1], Utku Aygüneş(0000-0001-9903-2923)[2]**

*1 Sivas Cumhuriyet Üniversitesi Tıp Fakültesi, Çocuk SAğlığı ve Hastalıkları Anabilim Dalı, Sivas*

*2 SBÜ Konya Eğitim ve Araştırma Hastanesi, Çocuk Hematoloji-Onkoloji Kliniği, Konya*

***Sorumlu yazar yazışma adresi:***

*Fatma DUKSAL: Sivas Cumhuriyet Üniversitesi Tıp Fakültesi, Çocuk SAğlığı ve Hastalıkları Anabilim Dalı, Sivas Türkiye*

*E-mail: fatmaduksal@gmail.com*

*Geliş tarihi/Received: 26.03.2020*

*Kabul tarihi/Accepted: 18.05.2020*



*Güncel Pediatri 2020;18(2):208-219*

## ÖZ

**GİRİŞ ve AMAÇ:** Trombosit aktivasyonu ateroskleroz sürecinde anahtar rol oynamaktadır. Ateroskleroz riski ailevi Akdeniz ateşi (AAA) hastalığında artmıştır. Ortalama trombosit hacmi, trombosit dağılım genişliği ve trombosit sayısı, trombosit aktivasyonunda önemlidir. Çalışmanın amacı ortalama trombosit hacmi, trombosit dağılım genişliği ve trombosit sayılarıyla ataksız dönemdeki AAA'lı çocukların mutasyon tipinin arasındaki ilişkiyi incelemektir.

**YÖNTEM ve GEREÇLER:** Ortalama trombosit hacmi, trombosit dağılım genişliği ve trombosit sayıları, yaş, cinsiyet ve mutasyon tipleri, hastaların tıbbi kayıtları geriye dönük incelenerek kaydedilmiştir. Çalışmaya atak döneminde olmayan 368 AAA'lı çocuk hasta ve 379 sağlıklı çocuk dahil edilmiştir.

**BULGULAR:** Ortalama trombosit hacmi (MPV), hastalarda kontrol grubuna göre daha düşüktür ($p<0.001$). Fakat trombosit dağılım genişliği kontrol grubuna göre daha yüksektir ($p<0.001$). Trombosit sayıları açısından hasta ve kontrol grubu arasında fark bulunmamıştır ($p>0.05$). Homozigot, heterozigot, birleşik mutasyonlar 368 hastanın sırasıyla 51, 267 ve 51'inde saptanmıştır. OTH; homozigot mutasyonlu ($p=0.029$) ve heterozigot mutasyonlu hastalarda ($p=0.041$) birleşik mutasyonlu hastalardan daha yüksek bulunmuştur. Homozigot mutasyonlu hastalarla, heterozigot mutasyonlu hastalarda ortalama trombosit hacmi açısından fark bulunmamıştır ($p>0.05$). Ayrıca, trombosit dağılım genişliği ve trombosit sayılar açısından heterozigot, homozigot ve birleşik mutasyonlar arasında fark saptanmamıştır ($p>0.05$). En sık görülen mutasyonlar M694V (131), E148Q (82), M680I, (37), and V726A (32) olarak saptanmıştır. Bu mutasyonlar arasında MPV, trombosit dağılım genişliği ve trombosit sayıları açısından anlamlı fark saptanmamıştır ($p > 0.05$).

**TARTIŞMA ve SONUÇ:** Ateroskleroz riski yüksek MPV değerlerinde artmış olsa da, şimdiki çalışmada bu ilişkiyi bulamadık. Bu, belki de tüm hastaların kolşisin tedavisi altında olduğundan kaynaklanmış olabilir. Diğer yandan PDW değerleri kontrol grubuna göre daha yüksek saptanmıştır. PDW ve MPV arasındaki ilişkiyi açıklığa kavuşturmak için daha fazla çalışmaya ihtiyaç vardır.

**Anahtar Kelimeler:** çocuk, ailevi Akdeniz ateşi, ortalama trombosit hacmi, mutasyon, trombosit dağılım genişliği

## *ABSTRACT*

**INTRODUCTION**: Platelet activation plays a key part in the process of atherosclerosis. The risk of atherosclerosis increased in familial Mediterranean fever (FMF). Mean platelet volume (MPV), platelet distribution width (PDW) and platelet counts are important in platelet activation. The aim of present study was to evaluate the relationship between the MPV, PDW, PLT counts and mutation types of FMF in children in attack free period.

**MATERIALS and METHODS**: PLT counts, MPV, PDW, age, sex and mutation types of patients were recorded retrospectively from medical records of patients. Three hundred sixty-eight children with FMF in attack-free period and 379 healthy children were included in the study.

**RESULTS**: MPV of the patients were lower than those of control ($p<0.001$). However PDW counts of the patients were higher than those of control groups ($p<0.001$). The PLT counts were not different between patients and control subjects ($p>0.05$). Of 368 patients; homozygous, heterozygous, and compound mutations were seen, respectively, in 51, 267, and 51 patients. The MPV of patients with homozygous ($p=0.029$) and heterozygous($p=0.041$) mutations were found higher than that of patients with compound mutations. There was no difference between heterozygous and homozygous mutation in terms of MPV ($p>0.05$). In addition, there was no difference between heterozygous, homozygous and compound mutations in terms of PDW and PLT counts ($p>0.05$). The most common mutations were M694V (n=131), E148Q (n=82), M680I, (n=37), and V726A (n=32). There wasn't seen significant difference among these mutations in terms of MPV, PDW and PLT counts ($p > 0.05$).

**CONCLUSIONS:** Although, atherosclerosis risk is increased in high MPV levels, we couldn't find this relationship in current study. It may be due to all the patients were under colchicine treatment. On the other hand PDW levels were found higher in patients than control group. To verify this relationship between PDW and MPV values, further investigations are needed.

**Key words:** children, familial Mediterranean fever, mean platelet volume, mutation, platelet distribution width

## *INTRODUCTION*

Familial Mediterranean Fever (FMF) is an autosomal recessive and autoinflammatory disease, characterized by recurrent fever and serositis (e.g., abdominal, articular and pleural attacks) symptoms [1]. FMF results from point mutations in the Mediterranean Fever (MEFV) gene which is located on the short arm of chromosome 16. This gene encodes pyrin/marenostrin [2] that plays an important role in the regulation of apoptosis, inflammation and cytokines [3]. FMF is observed especially in the Mediterranean region and surrounding regions and it is seen mostly in Turkish, Armenian, Jewish and Arabic communities [3, 4]. The most commonly seen mutations in the Middle Eastern region are E148Q, M680I, M694V, M694I and V726A mutations [5].

Platelets are considered to be essential in proinflammatory environments, including atherosclerosis. Platelet activation plays a key part in the process of atherosclerosis. To begin with, high MPV associates with low-grade inflammatory conditions and cardiovascular/cerebrovascular disorders. High MPV value is a reliable indicator of increased platelet activity and an indicator of possibility of atherosclerosis [6].

On the other hand low levels of MPV, associates with high-grade inflammatory diseases, such as attacks of familial Mediterranean fever and active rheumatoid arthritis [7]. In addition, it was reported that large platelets were used during inflammation, and surviving smaller platelets lead to reduction in MPV [8]. And inflammation in FMF leads to endothelial dysfunction increasing the risk of systemic complications including atherothrombosis and amyloid deposition in organs [6, 9].

Platelet distribution width (PDW) represents the variation in platelet size. For the second indicator of platelet activity, PDW [10], it can be said that an increase in platelet activity is usually considered as a vascular risk factor which is important in the pathophysiology of thrombosis and atherosclerosis. The degree of platelet activation has been demonstrated to be correlated with platelet distribution width. Large PDW can be an indicator of prothrombotic status. In addition, platelets also induce inflammation [11].

Recently it has been shown that the risk of atherosclerosis increased in patients with FMF [11-13]. Platelet (PLT) number, MPV and PDW measurements can be easily obtained from routine complete blood count (CBC). The relations between these parameters and the various diseases were shown in many studies [14-21]. There are a few studies investigating the relationship between these parameters and patients with FMF [2,11,22-26]. However, these

studies have reported conflicting results. To clarify this issue, there is a need of studies with a large group of patients. In addition, we did not find any study that examined these parameters according to mutation types in children with FMF.

In the current study, it was aimed to investigate the interrelationship between PLT number, MPV and PDW in a large group of children with FMF. In addition, the comparison between these parameters and mutation types were also studied.

## *MATERIALS and METHODS*

Medical records of 368 children with FMF who were followed up by our pediatric immunology and allergy department were evaluated retrospectively. In addition, 379 healthy controls participated to the study. Diagnosis of FMF was made according to Tel Hashomer criteria [27]. Patients were taken into the study during attack free period. According to the study; it was observed that patients were in attack free period if physical examination and levels of acute phase reactants were normal for at least 2 weeks from the end of an FMF attack period [28]. All patients were under colchicine treatment. Information of patients for current study was obtained retrospectively from their medical records. PLT counts, MPV and PDW values, age, sex and mutation types of patients were recorded. PLT counts, MPV and PDW values are easily obtained from routine CBC test. Patients with additional systemic diseases were excluded from the study. This study was conducted at the Cumhuriyet School of Medicine, Cumhuriyet University in between 2010-2013.

FMF patients and control groups were compared between each other in terms of PLT counts, MPV and PDW values. In addition, FMF patients were divided into 3 subgroups according to the type of mutation; homozygous, heterozygous and compound mutations. And these mutations were also compared between each other in terms of PLT counts, MPV and PDW values.

*Statistical Analysis:* The statistical evaluation was conducted by using the SPSS software version 15.0 (SPSS Inc. Chicago, IL, USA). Categorical data were presented as numbers and percentages and continuous data were expressed as means± standard deviation. Student T test was used to compare FMF patients and control groups. ANOVA test was used to compare the means of more than two samples and Tukey HSD test was used for post-hoc analysis. A $p < 0.05$ was considered to be statistically significant.

*Ethical disclosures:* The current study was approved by the ethics committee of the Cumhuriyet School of Medicine, Cumhuriyet University.

## *RESULTS*

Patient and control subjects did not have a significant age difference (12.61± 2.3 and 12.75 ± 2.41 years; p=0.734). As expected, IDA patients had lower Hb (mean 10.61±0.99 g/dl), hematocrit (mean 34.24±3.97), MCV (mean 71.13±7.58) and serum iron levels (mean 32.05±13.49) (p=0.000, for each). TIBC was elevated in the patient group (297.89±60.82) (p=0.000) (Table 1). According to these results, MPV of the patients (8.50±1.26 fl) were lower than those of control (9.04±1.02 fl) (p<0.001). However, PDW counts of the patients (23.99±15.01%) were higher than those of control (16.13±4.095%) (p<0.001). The PLT counts were not different between patients and control subjects (p>0.05).

**Table 1:** Demographic characteristics, MPV, PDW and PLT counts of patients and control groups

| Parameters | Patients with FMF (n=368) | Control (n=379) | *p* |
|---|---|---|---|
| Age (year) | 10.97±3.46 | 10.65±3.35 | >0.05 |
| Female (n%) | 192 (52) | 186(48) | >0.05 |
| MPV (fl) | 8.50±1.26 | 9.04±1.02 | **<0.001** |
| PLT ($\times 10^3/mm^3$) | 308.52±83.30 | 310.72±79.55 | >0.05 |
| PDW (%) | 23.99±15.01 | 16.13±4.095 | **<0.001** |

*FMF: familial Mediterranean fever; MPV: mean platelet volume; PDW: platelet distribution width, PLT: Platelet*

Patients were divided into 3 subgroups according to mutation types; homozygous mutations (n=51), heterozygous mutations (n=267), and compound mutations (n=51). The MPV of patients with homozygous (p=0.029) and heterozygous (p=0.041) mutations were found higher than that of patients with compound mutations. There was no difference between heterozygous and homozygous mutation in terms of MPV (p>0.05). In addition, there was no difference between heterozygous, homozygous and compound mutations in terms of PDW and PLT counts (p>0.05) (Table 2).

**Table 2:** MPV, PDW, PLT counts of patients with FMF according to mutation types

| Parameters | Homozygous (n=51) | Heterozygous (n=267) | Compound (n=51) | p | p for homozygous and heterozygous | p for homozygous and compound | p for heterozygous and compound |
|---|---|---|---|---|---|---|---|
| **MPV(fl)** | 8.71±1.35 | 8.54±1.23 | 8.08±1.24 | **0.023*** | >0.05 | **0,029*** | **0,041*** |
| **PDW (%)** | 20.83±12.22 | 24.24±15.35 | 25.82±15.56 | >0.05 | >0.05 | >0.05 | >0.05 |
| **PLT($\times 10^3/mm^3$)** | 307.39±73.92 | 25.82±15.56 | 311.72±80.28 | >0.05 | >0.05 | >0.05 | >0.05 |

*FMF: familial Mediterranean fever; MPV: mean platelet volume; PDW: platelet distribution width, PLT: Platelet*

In the current study, the most common mutations (M694V, n=131; E148Q, n=82; M680I, n=37; and V726A, n=32) were also compared among each other in terms of MPV, PDW and PLT counts. According to these results, there was no significant difference between these mutations (p> 0.05).

## *DISCUSSION*

In the current study, it was revealed that MPV levels were lower while PDW levels were higher in FMF patients in attack free period as compared to controls one. Mean platelet volume has been investigated recently in studies as an indicator of thrombosis and atherosclerosis [10]. MPV is associated with platelet function and activity [10, 29]. The risk of atherosclerosis increases with larger platelets [24]. Similar to MPV, PDW is also a marker for showing platelet activation [10]. Together, they can give an idea for the development of atherosclerosis [13]. Increased and decreased MPV levels have been reported in various inflammatory diseases [30]. For example, an increase in MPV was observed in metabolic syndrome, myocardial infarction, atrial fibrillation, acute ischemic stroke, Alzheimer's disease, diabetes mellitus, pulmonary tuberculosis, congestive heart failure and hydatid cyst disease [14-21]. But, a reduction in MPV was observed in inflammatory bowel disease, rheumatic arthritis, ankylosing spondylitis, acute pancreatitis and appendicitis [31-34].

Bakan et al [35] investigated MPV values and their association with proteinuria in patients with amyloidosis and amyloidosis secondary to FMF. They found negative correlation between MPV and thrombocyte count in all groups, In another study, MPV levels were found

significantly high during acute attack when compared with the control group. However, they showed no statistically significant difference between acute attack and attack-free period [36]. It is known that megakaryocyte and platelet number was regulated by IL-1, IL-6, trombopoetin and cytokines during inflammatory process [8, 37-39]. These cytokines may be even elevated during the subclinical inflammation at the attack-free periods in FMF patients, resulting in increased MPV and increased risk of atherosclerosis [6]. Subclinical inflammation may also induce development and progression of atherosclerosis [36].

In the current study, MPV level was found decreased in FMF patients as compared to the control group. FMF is an inflammatory disease and inflammation can affect MPV level [1, 30]. It is not clear why the MPV values decreased during inflammation. It was reported that large platelets were used during inflammation, and surviving smaller platelets lead to reduction in MPV [8].

Subclinical inflammation can be seen in FMF even in attack free remission period [40-42]. And inflammation in FMF leads to endothelial dysfunction increasing the risk of systemic complications including atherothrombosis and amyloid deposition in organs [6, 8]. Therefore, it seems important to represent subclinical inflammation in FMF patients [36].

Arıca et al [23] studied the MPV and platelet values in children with FMF patients during attack (n=53) and during attack-free periods (n=64). They found that the MPV values in the FMF both in attack and attack free period were higher than those in healthy children. They suggested that MPV value may be used as an early indicator of atherosclerosis in children with FMF. However, in another study, although MPV was found lower in FMF patients during attack period (n=48) than attack free period time, it was found similar in attack free patients (n=63) and healthy controls [24]. Cetin et al [40] studied the relationship between MPV and FMF in 89 adult patients and they reported that low level of MPV was associated with subclinical inflammation in FMF patients during attack free period. Similar to previous studies, in the current study also it was found that MPV levels of FMF patients in attack free period were lower than that of control participants while PDW levels of FMF were higher than that of controls. There was no significant difference between the control and the patient in terms of PLT count. In addition, MPV level in heterozygous and homozygous mutations was higher than that of compound mutations. But no difference was found between the most common mutations in terms of MPV level.

Ozkayar et al [10] reported that MPV level was significantly higher in FMF patients than in healthy control. But it was lower in FMF patients with secondary amyloidosis than in the

FMF and healthy control groups [10]. In the study of Uluca et al [13], MPV and PDW values were studied in FMF patients in attack and attack free period and in healthy control group. They found no significant difference between groups. In another study, MPV was found higher in FMF patients in the attack-free group than the control group [26]. In the current study, all patients were in attack free period, and MPV levels of patients were found lower than that of the control. Patients with FMF were under colchicine treatment. Perhaps, different results in different studies may be due to this situation.

Platelet distribution width level was also studied in FMF patients. And in one study, PDW level in FMF was found similar to PDW level in the control group [13]. In the current study, although MPV levels were lower in FMF patients than that of control, PDW level was also found higher in FMF patients than that of control and PLT levels were similar between two groups. In addition, similar to previous studies [10, 13]. PLT levels was not found different between patients and the control. So, we suggest that MPV and PDW levels were inversely affected due to inflammation in FMF.

In the current study, when the patients were divided into 3 subgroups according to the type of mutation, it was seen that MPV levels of compound mutations were lower than that of heterozygous and homozygous mutations. But it was similar between heterozygous and homozygous mutations. In addition PDW and PLT counts were similar in 3 subgroups.

In the current study, it was also aimed to compare the most common mutations (M694V, E148Q, M680I, V726A) in terms of MPV, PDW and PLT levels and there was no difference between these mutations in terms of these levels.

The risk of atherosclerosis increased in FMF as well as in other inflammatory disorders [23,24, 43]. MPV is an indicator of platelet function and is considered to have a bridge function between inflammation and thrombosis [44]. The importance of MPV in the atherosclerosis has been emphasized in several diseases and in FMF with conflicting results [2, 10, 21-25, 45-47]. In order to prevent these contradictory results, a large amount of patients was taken to the current study. In the current study, it was tried to investigate the relationship between FMF and atherosclerosis by looking MPV, PDW and PLT levels of all patients. Although, atherosclerosis risk is increased in high MPV levels, we couldn't find this relationship in current study. It may be due to all the patients were under colchicine treatment. This current study suggests that altough MPV is an early atherosclerosis marker, it is not elevated in pediatric FMF patients on colchicine treatment.

Our results showed that PDW levels were higher in patients than control group. To verify this relationship between PDW and MPV values, further investigations are needed.

*Conclusions:* The current study was carried out with a large group of children with FMF in attack free period. Therefore, we think that results of this study will contribute positively to the literature. A decrease in MPV and an increase in PDW were observed in patients but this study did not reveal a difference between patients and control in terms of PLT number. In conclusion, FMF is an autoinflammatory disease and all FMF patients should be closely monitored in terms of atherosclerosis.

*Limitation of study:* Patients with FMF were under colchicine treatment. Perhaps different results in different studies may be due to this situation. In a further study, newly diagnosed patients with FMF and patients under colchicine treatment can be compared in terms of MPV, PDW and PLT for the risk of atherosclerosis for more meaningful results.

***Conflict of Interest:*** No potential conflict of interest was reported by the authors.

***Funding:*** No funding was received.

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