Can Mean Platelet Volume Be a Surrogate Marker of Inflammation in Rheumatic Diseases?

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ABSTRACT

Background: *In humans, it has been suggested that low-level mean platelet volume (MPV) may be related to secondary thrombosis due to inflammation. For this reason, MPV can be used as a marker showing inflammation in the body.*

Objectives: *To evaluate the association of MPV with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Disease Activity Score-28 (DAS-28), and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in patients with rheumatic diseases.*

Methods: *The study consisted of 261 patients with rheumatoid arthritis (203 females, 77.8%; 58 males, 22.2%), 85 patients with ankylosing spondylitis (57 males, 67.1%; 28 females, 32.9%), 56 patients with familial Mediterranean fever (32 females, 57.1%; 24 males, 42.9%) and 194 patients (139 females, 71.6%; 55 males, 28.4%) with other rheumatic diseases (Behçet's disease, psoriatic arthritis, spondyloarthropathy, systemic lupus erythematosus, systemic sclerosis, or undifferentiated connective tissue disease).*

Results: *There was an inversely significant correlation between MPV and ESR and CRP in patients with rheumatoid arthritis ($r = -0.164$, $p = 0.008$). Mean platelet volume was negatively correlated with DAS-28-ESR/CRP ($r = -0.393$, $p < 0.001$) in rheumatoid arthritis. Mean platelet volume was inversely correlated with BASDAI ($r = -0.580$, $p < 0.001$) in ankylosing spondylitis. In the group with familial Mediterranean fever (especially M694V homozygous), there was a negative correlation between MPV and ESR and CRP ($p < 0.001$). Mean platelet volume and CRP were negatively correlated in psoriatic arthritis ($r = -0.599$, $p = 0.011$). Mean platelet volume and ESR were inversely related in patients with systemic lupus erythematosus ($r = -0.421$, $p = 0.045$). There was a negative correlation between MPV and ESR ($r = -0.219$, $p = 0.002$), and between MPV and CRP ($r = -0.208$, $p = 0.004$) in other rheumatic diseases.*

Conclusions: *The lower MPV level surrogates active and/or chronic inflammatory state in the body. Thus, MPV may be used as a negative acute-phase reactant in rheumatic diseases.*

Keywords: Inflammation, mean platelet volume, rheumatic diseases

¿Puede el Volumen Plaquetario Medio Ser un Indicador Sustituto de la Inflamación en las Enfermedades Reumáticas?

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RESUMEN

Antecedentes: *En los seres humanos, se ha sugerido que un bajo nivel del volumen plaquetario medio (VPM) puede estar relacionado con una trombosis secundaria debido a la inflamación. Por esta razón, el VPM puede utilizarse como un marcador que muestra inflamación en el cuerpo.*

Objetivos: *Evaluar la asociación del VPM con la velocidad de sedimentación globular (VSG), la proteína C reactiva (PCR), la puntuación de actividad de la enfermedad en 28 articulaciones (DAS-28), y el índice de actividad de la espondilitis anquilosante de Bath (BASDAI) en pacientes con enfermedades reumáticas.*

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Métodos: *El estudio consistió en 261 pacientes con artritis reumatoide (203 hembras, 77.8%; 58 varones, 22.2%), 85 pacientes con espondilitis anquilosante (57 varones, 67.1%; 28 hembras, 32.9%), 56 pacientes con fiebre mediterránea familiar (32 hembras, 57.1%; 24 varones, 42.9%) y 194 pacientes (139 hembras, 71.6%; 55 varones, 28.4%) con otras enfermedades reumáticas (enfermedad de Behçet, artritis psoriásica, espondiloartropatía, lupus eritematoso sistémico, esclerosis sistémica o enfermedad indiferenciada del tejido conjuntivo).*

Resultados: *Hubo una correlación inversamente significativa entre VPM y VSG y PCR en pacientes con artritis reumatoide (r = -0.164,* p = *0.008). El volumen plaquetario medio se correlacionó negativamente con DAS-28-VSG/PCR (r = -0.393,* p < *0.001) en la artritis reumatoide. El volumen plaquetario medio se correlacionó inversamente con el índice BASDAI (r = -0.580,* p < *0.001) en la espondilitis anquilosante. En el grupo con fiebre mediterránea familiar (sobre todo el M694V homocigótico), hubo una correlación negativa entre VPM y VSG y PCR (*p < *0.001). El volumen plaquetario medio y PCR se correlacionaron negativamente en la artritis psoriásica (r = -0.599,* p = *0.011). El volumen plaquetario medio y VSG se relacionaron inversamente en los pacientes con lupus eritematoso sistémico (r = -0.421,* p = *0.045). Se observó una correlación negativa entre VPM y VSG (r = -0.219,* p = *0.002) y entre VPM y PCR (r = -0.208,* p = *0.004) en otras enfermedades reumáticas.*

Conclusiones: *El nivel inferior de VPM reemplaza el estado inflamatorio activo y/o crónico en el cuerpo. De este modo, el VPM puede ser usado como un reactante de fase aguda negativo en las enfermedades reumáticas.*

Palabras claves: Inflamación, volumen plaquetario medio, enfermedades reumáticas

INTRODUCTION

It has been suggested that low-level mean platelet volume (MPV) in humans may be related to secondary thrombosis due to inflammation (1). As we know, several different pathways interact with each other so as to adapt or respond to inflammation. Signals to megakaryocytes located in the bone marrow can cause platelet overproduction. The higher inflammatory status triggers the lower diameter platelets. For this reason, MPV can be used as a marker showing inflammation in the body.

Several authors have studied MPV in some rheumatic diseases (2, 3). However, the data on this subject have still been controversial. Some authors claim that MPV does not reflect the inflammation, but others do. Herein, the authors of the current study wished to share the clinical observations in their rheumatology department, as well as to evaluate the association of MPV with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Disease Activity Score-28 (DAS-28), and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in patients with rheumatic diseases.

SUBJECTS AND METHODS

The study consisted of 261 patients with rheumatoid arthritis [RA] (203 females, 77.8%; 58 males, 22.2%), 85 patients with ankylosing spondylitis [AS] (57 males, 67.1%; 28 females, 32.9%), 56 patients with familial Mediterranean fever [FMF] (32 females, 57.1%; 24 males, 42.9%), and 194 patients (139 females, 71.6%; 55 males, 28.4%) with other rheumatic disease (Behçet's disease (17 females, 26 males), psoriatic arthritis [PSA] (30 females, 28 males), spondyloarthropathy [SpA] (9 males, 3 females), systemic lupus erythematosus [SLE] (20 females), systemic sclerosis (19 females, 4 males), or undifferentiated connective tissue disease (28 females, 15 males)). Data were retrospectively collected from patients' files.

Statistical analysis

For the registration and statistical analysis of the data, SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) 14.0 software package was used. Descriptive statistical data were presented as the mean ± standard deviation (median or minimum–maximum). The suitability of the data to a normal distribution was checked using the Kolmogorov-Smirnov and Shapiro-Wilk normality tests. Parametric tests were used for the evaluation of those data complying with a normal distribution, and non-parametric tests were used for the evaluation of those data not complying with a normal distribution. A comparison of continuous variables between the two groups was conducted using Student's *t*-test for parametric variables and the Mann-Whitney U test for non-normal variables. To evaluate the correlation between two continuous variables, the researchers used the Spearman's Rho correlation coefficient test for non-parametric variables. Values of $p < 0.05$ were considered statistically significant.

RESULTS

The mean age of the RA patients was 48.7 ± 13.9 (48, 18–83) years. The mean disease duration was 6.09 ± 7.7 (4, 1–39) years, and the mean MPV was 8.19 ± 1.7 (8.4, 4.6–12.1) in RA patients (Table). The mean ESR and CRP levels were 40.7 ± 25.9 mm/h and 1.9 ± 2.8 mg/dL in RA patients, respectively.

The mean DAS-28-CRP was 3.99 ± 1.12 in RA patients. Statistical analyses showed that there was an inverse statistically significant correlation between MPV and ESR and CRP in RA patients (r = -0.164, p = 0.008 and r = -0.082, p = 0.001). Mean platelet volume was negatively correlated with DAS-28-CRP (r = -0.393, $p < 0.001$) in RA. It was found that MPV levels were more significantly lower in seropositive (anti-cyclic citrullinated peptide [CCP] and rheumatoid factor [RF] positive) patients compared with seronegative patients ($p < 0.05$).

DISCUSSION

Rheumatoid arthritis and other inflammatory diseases have various effects on haematopoiesis. Anaemia and thrombocytosis are the most commonly observed findings in some rheumatic diseases (4, 5). Cytokines such as interleukin (IL)-1, IL-3, IL-4, IL-6, IL-11, tumour necrosis factor (TNF), and growth factors mediate thrombocytosis. In addition, recent studies have emphasized the importance of thrombocyte-related alterations in various chronic diseases. Studies have demonstrated that MPV, like thrombocyte count, could also serve as a marker for certain diseases. The evidence from these studies indicates that MPV levels can be used to assay the activity of inflammatory diseases, and to predict the efficacy of anti-inflammatory treatment (3).

Table: Characteristic features and MPV levels of the RA, AS and FMF patients

	RA	AS	FMF
Gender (F/M) (%)	203 (77.8%)/58 (22.2%)	28 (32.9%)/57 (67.1%)	32 (57.1%)/24 (42.9%)
Age (years)			
Mean ± SD	48.7 ± 13.9	34.5 ± 10.1	32.2 ± 13
(median, min–max)	(48, 18–83)	(33, 19–64)	(27, 17–81)
Disease duration (years)			
Mean ± SD	6.09 ± 7.7	8.8 ± 5.2	8.0 ± 6.2
(median, min–max)	(4, 1–39)	(10, 1–20)	(6, 2–21)
MPV			
Mean ± SD	8.19 ± 1.7	8.6 ± 1.7	8.07 ± 1.77
(median, min–max)	(8.4, 4.6–12.1)	(8.6, 4.6–13)	(7.9, 4.6–12.3)

MPV: mean platelet volume; RA: rheumatoid arthritis; AS: ankylosing spondylitis; FMF: familial Mediterranean fever; SD: standard deviation; min: minimum; max: maximum

In the AS group, the mean age was 34.5 ± 10.1 (33, 19–64) years, mean disease duration was 8.8 ± 5.2 years, and mean MPV was 8.6 ± 1.7 (8.6, 4.6–13) [Table]. The mean ESR and CRP were 26.5 ± 21.9 mm/h and 1.5 ± 2.4 mg/dL in AS patients, respectively. The mean BASDAI was 4.11 ± 1.37. In addition, MPV was correlated with BASDAI inversely (r = -0.580, $p < 0.001$) in AS. We could not determine the relationship between HLA-B27 and MPV due to insufficient data.

The mean age of the FMF group was 32.2 ± 13 (27, 17–81) years (Table). The mean disease duration was 8.0 ± 6.2 (6, 2–21) years. Of the patients, 22 had E148Q (10 homozygous, 12 heterozygous), 24 had M694V (10 homozygous, 14 heterozygous), 4 had V726A (1 homozygous, 3 heterozygous), 4 had R202Q (1 homozygous, 3 heterozygous), 1 had R761H (heterozygous) and 1 had M680I (homozygous). Mean platelet volume levels of all patients with attack-free period were investigated. In the FMF group (especially M694V homozygous), there was negative correlation between MPV and ESR, CRP [r = -0.206, $p < 0.001$, and r = -0.216, $p < 0.001$].

Mean platelet volume and CRP were negatively correlated in PSA (r = -0.599, p = 0.011). Mean platelet volume and ESR were inversely related in SLE patients (r = -0.421, p = 0.045). In addition, we could not compare C3, C4, anti-ds DNA levels and MPV in SLE patients due to insufficient data. There was a negative correlation between MPV and ESR (r = -0.219, p = 0.002), and MPV and CRP (r = -0.208, p = 0.004) in other rheumatic diseases.

The present study reports a negative correlation between the parameters indicating disease activity and MPV in RA patients, *ie* reactive thrombocytosis-dependent MPV values were lower in case of active disease. Similarly, there was a negative correlation between BASDAI and MPV in AS patients. According to the literature, Kisacik *et al* conducted a study and compared 32 active RA patients with 26 osteoarthritis patients, and 30 active AS patients with 29 healthy controls with a similar age (3). In this retrospective study, the authors found that MPV levels were significantly lower in both RA and AS patients compared to the control group. In addition, the authors also observed a significant increase in MPV values in both RA and AS patients after two months of treatment. While the authors did not find a correlation between BASDAI and MPV levels at the baseline, they found a significantly negative correlation between BASDAI and MPV after two months of treatment, which is consistent with the findings of the present study. However, the authors found no significant correlation between DAS-28 and MPV, which is not contradictory to the findings of the present study. We believe that the underlying reason for the different results is the lack of pre-treatment and post-treatment discrimination.

In a similar study that investigated the effect of treatment on MPV levels, Gasparyan *et al* found that MPV levels were elevated in RA patients in the third month of TNF treatment compared to the baseline levels (6). In another study by Milovanovic *et al*, the authors argued that MPV would reflect the disease activity in RA patients (7). Unlike these studies, Yazici *et al* have shown an increase of MPV values in RA patients; furthermore, conventional treatment or with TNF blockers decreased MPV levels (2). In addition, the authors found a positive correlation between MPV and DAS-28 index. In another study by Yazici *et al*, the authors demonstrated that MPV values increase in active AS, and found a positive correlation between MPV and BASDAI (8). Moreover, similar to their study on RA patients, the authors observed a decrease in MPV levels as a response to the anti-inflammatory treatment. According to a study on 400 RA patients, MPV levels were significantly higher in RA patients compared to the control group, and the authors emphasized the correlation between these higher levels with hypertension (9). Seropositivity in RA patients has long been recognized as an indicator of poor prognosis, and extra-articular findings are more frequent in these patients. In the present study, the researchers found that MPV levels were lower in RA patients who were RF- and/or anti-CCP-positive. This finding might suggest that inflammation could be more severe in seropositive patients, and correspondingly, with lower MPV levels. At the same time, this finding also supports that MPV could represent a negative acute-phase reactant.

Psoriatic arthritis is a chronic inflammatory disease of the axial skeleton and peripheral joints, which is seen in 7–34% of psoriasis patients. Unlike the other inflammatory rheumatologic diseases, MPV levels in PSA have been evaluated in only few studies. Canpolat *et al* carried out this study on 48 psoriasis patients with PSA (Group 1), 58 psoriasis patients without PSA (Group 2), and 95 healthy controls [Group 3] (10). The authors found that MPV levels were higher in both Groups 1 and 2, compared to the control group. In addition, the authors found a significantly positive correlation between PASI score and MPV, and between disease duration and MPV in psoriasis patients. However, the correlation between PSA activity and MPV was not evaluated in this study. In this aspect, the present study is one of the pioneering studies to evaluate the correlation between disease activity and MPV in PSA patients. Studies investigating the correlation between PSA and MPV are present in the literature (11). In the present study, the researchers found a negative correlation between CRP and MPV in PSA.

Another chronic inflammatory disease is FMF, which is of autosomal recessive inheritance. Recurrent self-limiting attacks, abdominal, chest and joint pain, as well as fever are observed in FMF, and dysregulation of immune inflammatory mechanisms is the major reason for disease pathogenesis. Under normal conditions, pyrin protein functions to regulate inflammation. The inflammatory response, which is normally kept under control in the presence of wild-type pyrin, can get out of control in the presence of mutant pyrin, as in the case of FMF (12). Therefore, MPV values could be affected in FMF. The number of studies in the literature on the FMF-MPV correlation is considerably huge. While some studies report that MPV levels decrease in FMF patients, others report that MPV levels are elevated in the disease conditions. Moreover, some studies also report that MPV levels do not differ between patients and controls. Coban and Adanir compared 35 FMF patients with 35 healthy controls, and found that MPV levels were significantly higher in the FMF group (13). In addition, the authors found a negative correlation between MPV levels and the duration of colchicine treatment and a positive correlation between MPV levels and the delay in diagnosis. In another study, Makay *et al* found that MPV levels were lower in FMF patients having attacks compared to healthy controls and FMF patients who were not having attacks (14). In this study, the authors did not find a significant difference in MPV levels between FMF patients who did not have attacks and healthy controls. Similar to the present study, the authors determined a negative correlation between disease severity score and MPV in FMF patients who did not have attacks. In another study, Ozkayar *et al* compared 74 FMF patients without amyloidosis and 29 FMF patients with amyloidosis with 180 healthy controls (15). The authors found significantly higher MPV levels in FMF patients without amyloidosis compared to the controls, but lower MPV levels in FMF patients with amyloidosis compared to FMF patients without amyloidosis and controls. In another study, Sakalli and Kal found that MPV values were higher in paediatric and adult FMF patients compared to healthy controls (16). The authors found that MPV levels were lower in paediatric FMF patients compared to adult FMF patients. Unlike the results of the study by Ozkayar *et al,* Sakalli and Kal found that MPV levels were higher in patients with proteinuria in all age groups (both paediatric and adult patients). Sahin *et al* also compared FMF patients who had attacks and FMF patients who did not have attacks with a control group, and found lower MPV values in the patients (17). The authors argued that secondary thrombocytosis was responsible for this outcome. However, contrary to the study by Sahin *et al*, Arica *et al* found that MPV levels were higher in FMF patients with/without attacks compared to the control group (18). Again, in the same study, the authors determined a positive correlation between the disease severity and MPV values. Contrary to all of these studies, Abanonu *et al* did not find a difference in MPV levels between FMF patients and the control groups (19). In the present study, the researchers found that MPV levels were lower in FMF patients, even in the attack-free period; the researchers believe that this observation could be especially related to subclinical inflammation. This correlation was more prominent in the M694V homozygous group. To date, there is no study investigating the effect of MEFV mutation of MPV in the literature.

Systemic lupus erythematosus is a chronic, multisystem, autoimmune disease with varying clinical and laboratory findings, and the disease aetiology is unclear. In the present study,

the researchers found a correlation between ESR, which can be elevated in SLE patients in the case of both active disease and infection, and MPV. Elevated ESR levels in SLE might be correlated with infection and/or to a lesser degree with disease activity. According to the literature, Yavuz and Ece found higher MPV values in SLE patients compared to the control group (20). In addition, the authors found a negative correlation between MPV and serum complement and albumin levels, and a positive correlation between MPV and SLEDAI and ESR.

Behçet's disease is a widespread vasculitis, which progresses with recurrent oral and genital ulcers, eye findings, as well as muscoskeletal, neurological and gastrointestinal involvement. The underlying pathology is the inflammatory response including the arteries and veins. Acikgoz *et al* found that MPV levels were higher in patients with Behcet's disease compared to the control group (21). In addition, the authors found higher MPV levels in patients with venous thrombosis compared to patients who did not have this condition. However, unlike the present study, the authors did not determine a correlation between MPV and Behcet's disease activity. In the present study, in addition to Behcet's disease, the researchers also found an inverse relation between MPV-ESR, and MPV-CRP in systemic sclerosis, SpA, and undifferentiated connective tissue disease.

Kapsoritakis *et al* demonstrated that MPV decreased significantly in active inflammatory bowel disease (22). However, the definitive clinical benefit and validity of MPV to evaluate disease activity have not been proven yet; some authors argue its use to follow up inflammatory diseases (22). The correlation between various thrombocyte markers, including MPV, and thrombosis and inflammation has been investigated in different studies. Evidence, especially from prospective studies and meta-analyses, indicates a correlation between increased MPV and thrombosis risk.

In daily practice, haemogram is requested in each control visit for the follow up of rheumatologic diseases. Therefore, the evaluation of MPV does not bring any additional cost to the patient. The lower MPV level can surrogate active and/or chronic inflammatory state in autoimmune-autoinflammatory diseases. Thus, MPV may be used as a negative acute-phase reactant in rheumatic diseases. Disregarding patients' treatment regimes and the lack of a control group can be considered as the limitations of the present study. Comprehensive studies are required to achieve conclusive results.

AUTHORS' NOTE

The authors declare that they have no conflicts of interest.

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