Is There a Relation Between Mean Platelet Volume and Inflammation Markers Either in Patients with Type 2 Diabetes and Retinopathy or Neuropathy?

Retinopati veya Nöropatisi Olan Tip 2 Diyabetli Hastalarda Ortalama Trombosit Hacmi ve İnflamasyon Belirteçleri Arasında İlişki Var mıdır?

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ABSTRACT Objective: Patients with diabetes mellitus have an increased risk of developing complications such as retinopathy and neuropathy. Size of platelets and inflammation have been suggested to be involved in the pathogenesis of diabetic complications. The purpose of this study was to find out if there was a correlation of mean platelet volume with inflammatory markers in patients with diabetes and retinopathy or neuropathy. **Material and Methods:** The study has been carried out on 50 patients with type 2 diabetes without retinopathy or neuropathy, 52 with retinopathy, and 50 with neuropathy, and 50 healthy participants. After comparing all the parameters we seeked correlation of mean platelet volume with inflammation markers in all groups. **Results:** In diabetic group with retinopathy or neuropathy mean platelet volume levels were higher than patients with diabetes without those complications and the controls. We did not find any correlation between mean platelet volume and leucocyte count, sedimentation rate and high sensitivity C- reactive protein in all the groups. **Conclusion:** The mean platelet volume values of patients with diabetes were higher than individuals without diabetes, highest levels being in patients with diabetes with retinopathy and neuropathy. We do not think that there is a link between mean platelet volume and inflammation in patients with diabetes with or without retinopathy or neuropathy at least in our patients.

Key Words: Diabetes mellitus, type 2; diabetic retinopathy; diabetic neuropathies; blood platelets; inflammation

ÖZET Amaç: Diabetes mellituslu hastalar retinopati ve nöropati gibi komplikasyonları geliştirme riski altındadırlar. Trombosit boyutları ve inflamasyonun diyabetik komplikasyonların patogenezinde yer aldığı düşünülmektedir. Çalışmamızın amacı, retinopati veya nöropatisi olan diyabetli hastalarda ortalama trombosit volümü ile inflamatuar belirteçlerin arasında ilişki olup olmadığını saptamaktır. **Gereç ve Yöntemler:** Çalışmamız retinopati veya nöropatisi olmayan 50 tip 2 diyabetli hasta, 52 retinopati, 50 nöropatisi olan tip 2 diyabetli hasta ve 50 sağlıklı kişi ile gerçekleştirilmiştir. Tüm gruplarda bütün parametreler kıyaslandıktan sonra ortalama trombosit volümü ile inflamatuar belirteçlerin arasında korelasyon olup olmadığı araştırılmıştır. **Bulgular:** Retinopati veya nöropatisi olan diyabetli hasta gruplarında ortalama trombosit volümü, komplikasyonları olmayan diyabetikler ve kontrollerden daha yüksekti. Tüm gruplarda ortalama trombosit volümü ile lökosit sayımı, sedimantasyon ve yüksek sensitivite C- reaktif protein değerleri arasında korelasyon saptanmadı. **Sonuç:** Diyabetli hastalarda ortalama trombosit volümü non-diyabetiklerden yüksekti, en yüksek değerler retinopati ve nöropatisi olan diyabetli hastalarda idi. Retinopati ve nöropatisi olan ve olmayan diyabetli hastalarda ortalama trombosit volümü ve inflamasyon arasında bir bağlantı olmadığını düşünüyoruz; en azından bizim hastalarımızda.

Anahtar Kelimeler: Diabetes mellitus, tip 2; diyabetik retinopati; diyabetik nöropatiler; kan trombositleri; inflamasyon

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Postprandial hyperglycemia is one of the earliest and most important anomalies seen in type 2 diabetes mellitus (T2DM).[1] In recent studies correlation was found between postprandial hyperglycemia and diabetic complications either macro or microvascular possibly by inducing inflammation and endothelial dysfunction.[2,3] Inflammation with related cytokines, adhesion molecules and chemokins was also recognised to decrease beta cell secretion and increase insulin resistance.[4] Moreover inflammation and those relatives were also found guilty of the development and progression of diabetic complications.[5]

Platelets play an important role in homeostasis. Their size is thought to be a determinant of their function. Large platelets determined by mean platelet volume (MPV), react more actively and produce more thrombotic factors such as thromboxane A2 and β thromboglobulin.[6] In most of the studies about T2DM, MPV levels were found to be higher than the controls.[7-15] It was also proposed that MPV could play a role in diabetic nephropathy, diabetic retinopathy (DR), diabetic neuropathy (DN), and macrovascular diabetic complications.[16-31]

Studies emerging from the thought that MPV may be a useful indicator of systemic inflammation in acute and chronic inflammatory diseases, revealed conflicting results.[32-41] Moreover relation of MPV and inflammation markers was demonstrated in infectious and inflammatory diseases, cardiovascular disease and diabetes.[42-49]

Keeping in mind the close relations of MPV with diabetes and inflammation we planned 1) to compare MPV levels and inflammation markers of diabetic patients with and without retinopathy- neuropathy and compare those levels of normal subjects 2) to see if there is a correlation in MPV levels and inflammation markers, such as leucocyte count, sedimentation rate and high sensitivity C-reactive protein (hs-CRP) in diabetic and normal individuals.

MATERIAL AND METHODS

PATIENTS

A total of 152 type 2 diabetic patients [98 female (64.5%), 54 male (35.5%)], without neuropathy and retinopathy [31 female (62.0%), 19 male (38.0%)] and 50 with neuropathy [33 female (66.0%), 17 male (34.0%)] and 52 with retinopathy [34 female (65.4%), 18 male (34.6%)] aged from 22-90 years, were recruited from the Clinic of Ankara Training and Research Hospital from June 2009 to June 2012.[50] Patients were classified as having type 2 diabetes mellitus (T2DM) according to the WHO diagnostic criteria.[50] (The 1999 World Health Organization (WHO) criteria define diabetes as an fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L) or a two-hour post glucose challenge value ≥200 mg/dL (11.1 mmol/L). Our patients were receiving either insulin or oral hypoglycemic agents. Fifty aged matched normal people [36 female (72%), 14 male (28%)] examined in outpatient Clinic of Ankara Training and Research Hospital were chosen as the control group.

Our exclusion criteria were secondary or type 1 patients with diabetes, women having doubt of pregnancy, patients having glomerular filtration rate <60 mg/dl, having heart failure, functional thyroid disease (in history or nowadays), uncontrolled hypertension (HTA), active infection and anemia (females with Hb <11.5 g/dl, males with Hb <12.5 g/dl). Patients with known congenital or acquired platelet disease, hematologic disease, and acute stress, those receiving anti-coagulant and/or anti-aggregant treatments, which may potentially affect MPV were also excluded from the study. We also excluded the diabetic patients having both retinopathy and neuropathy.

After detailed physical examination, in all subjects body weight and height were measured. We calculated body mass index (BMI) as weight in kilograms divided by the square of height in meters (kg/m^2).

Systolic and diastolic blood pressure (SBP and DBP) were measured after a 5 minute rest in the semi-sitting position with a sphygmomanometer. Blood pressure was determined at least three times at the right upper arm, and the mean was used in the analysis. The patients who were taking antihypertensive drugs or patients whose determined mean blood pressure levels ≥140/90 mmHg were diagnosed as having HTA.[51] Our hypertensive pa-

tients were receiving either angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).

Blood was withdrawn after 12 hour of overnight fasting, at 08.30 a.m. for FPG, serum total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C), triglyceride (TG), and hemoglobin A1c (HbA1c), hs-CRP, creatinine levels, also for whole blood count, platelet counts, erythrocyte sedimentation rate (ESR) and MPV. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald Formula (LDL = Total cholesterol–(HDL-C+TG/5).

Hyperlipidemia (HL) was defined as having hypolipidemic treatment or presence of TC levels ≥200 mg/dl, and/or LDL-C levels ≥130 mg/dl, and/or TG levels ≥150 mg/dL and/or HDL-C levels ≤40 mg/dl for men and ≤50 mg/dl for women.[52] Our hyperlipidemic patients were having statins and/or fibrates.

DN was diagnosed by neurologic examination by two experts. DN was defined in patients diagnosed earlier or if an abnormal neurologic examination that was consistent with the presence of peripheral sensorimotor neuropathy plus either abnormal nerve conduction in at least two peripheral nerves or equivocally abnormal autonomic nerve testing was present.[53]

DR was defined by ophtalmoscopic examination by two experts. Patients who had at least two microaneurysms and/or retinal hemorrhage, and/or other signs of retinal damage were accepted as having retinopathy.[54]

We formed 4 groups; Group I- Type 2 diabetic patients without retinopathy and neuropathy, Group II-Type 2 diabetic patients with retinopathy, Group III- Type 2 diabetic patients with neuropathy, Group IV: Control group. We compared all the parameters. Then we made correlation analysis of MPV with leucocyte count, ESR and hs-CRP in all groups.

This study was performed according to the Helsinki decleration 2008. The local ethics committee approved this study and all the subjects gave written informed consent.

LABORATORY METHODS

Plasma glucose, TC, TG and HDL-C concentrations were determined by enzymocalorimetric spectrophotometric method in a Roche/Hitachi molecular PP autoanalyser. HbA1c was examined by TOSOH HPLC, creatinine with Beckman Coulter AU2700, and blood count with LH-780 blood count device and MA with OLYMPUS AU400.

MPV's were analysed in 2 hours after they were withdrawn, using two different blood samples which were taken in test tubes with EDTA with automated whole blood counter. Blood Quality controls in our laboratory documented a good reproducibility of MPV measures, with intra-assay and inter-assay coefficients of variation ≤2.2% on commercial controls. Reference range of our MPV was 7.4-10.4 fL. Although Demirin et al. found that 95% of normal Turkish individuals had a MPV between 7.2 and 11.7 fL. we chose to stick to the values of our laboratory.[55]

STATISTICAL ANALYSIS

Calculations were performed using SPSS version 15,0. Data are presented as mean ± SD. When difference in groups was examined, Bonferroni corrected Kruskal Wallis H test was used. We also used Spearman Correlation for correlation analysis. A p value of <0.05 was considered as statistically significant.

RESULTS

A total 152 patients and 50 control subjects composed of 4 different groups were recruited to the study. The demographic and laboratory parameters of all the groups and their comparisons were shown in Table 1.

FBG, HbA1c, and MPV levels of Group IV were found to be significantly lower than Group I, II, III. As Groups I and II and also Groups I and III were compared, in Group II and III MPV values were higher, but in Group II and III MPV levels did not differ. None of the paremeters, including leucocyte count, ESR and hs-CRP were not statistically different in all groups.

TABLE 1: The biochemical and clinical characteristics of the groups.

	Group I DM (+) DR (-) DN (-) (n: 50)	Group II DM (+) DR (+) (n: 52)	Group III DM (+) DN (+) (n: 50)	Group IV Control (n: 50)
FBG (mg/dL)	165.3±74.1[a]	160.9±50.3[b]	175.5±53.8	92.5±12.2[c]
HbA1c (%)	9.9±2.4[a]	9.1±2.2[bb]	9.1±2.8	5.1±0.2[c]
Cr (mg/dL)	1.2 ±1.0	1.1±0.4	0.9±0.3	0.8±0.2
BMI (kg/m^2)	25.9±3.4	26.3±3.2	26.4±3.2	24.7±4.7
TC (mg/dL)	165.2±32.1	178.2±40.4	179.2±40.4	180.1±54.6
LDL-C (mg/dL)	98.1±23.1	104.2±25.1	104.6±25.1	101.1±50.3
HDL-C (mg/dL)	44.2±10.3	43.2 ±11.0	43.7±11.0	46.2±10.3
TG (mg/dL)	125.3±33.2	180.6±91.2	180.6±91.2	188.6±102.6
SBP (mm/Hg)	111.8±11.2	123.7±21.1	123.8±21.1	130.8±23.1
DBP (mm/Hg)	76.1±8.1	81.6±13.3	82.6±13.3	81.3±11.5
PC (x10^3/µL)	255.6±95.1	246.0±58.7	269.5±96.3	236.5±57.8
Leucocyte count (µL)	7444±1779	7798±1830	7431±1842	7701±1639
ESR (mm/h)	27.0±22.3	27.0±21.0	29.2±23.7	19.6±17.0
hs-CRP (mg/L)	1.7±1.1	2.1±1.4	1.4±1.3	1.9±1.7
MPV (fL)	8.8±1.1[a]	9.3±1.0 [bd]	9.3±1.6[e]	8.3±0.6[c]

Group I- Type 2 diabetic patients without retinopathy and neuropathy, Group II- Type 2 diabetic patients with retinopathy, Group III- Type 2 diabetic patients with neuropathy, Group IV: Control group.

FBG: Fasting blood glucose, HbA1c: Hemoglobin A1c, Cr: Creatinine, BMI: Body mass index, TC: Total cholesterol, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, TG: Triglyceride, SBP: Systolic blood pressure, PC: Platelet count; DBP: Diastolic blood pressure, ESR: Erytrocyte sedimentation rate, hs-CRP: high sensitive C-reactive protein, MPV: Mean platelet volume. Data are presented as mean ± SD.

a Difference between Group I and IV is statistically significant (p<0.05); b Difference between Group II and IV is statistically significant (p<0.05); c Difference between Group III and IV is statistically significant (p<0.05); d Difference between Group I and II is statistically significant (p<0.05); e Difference between Group I and III is statistically significant (p<0.05).

Later we made correlation analysis of MPV with leucocyte count, ESR and hs-CRP in all groups. There was no correlation with MPV and either parameters (Table 2).

DISCUSSION

It has been demonstrated that platelet volume is strongly correlated with the activity of platelets. Large platelets contain more granules, aggregate more easily and have higher capability of secretion and expression. Evidence has been accumulated that MPV may have a role in inflammation and infection. There are studies demonstrating the relationship between MPV and myocardial infarction, where inflammation is considered to have an important role.[43-47] A meta-analysis concluded that MPV was associated with restenosis after angioplasty and also mortality following myocardial infarction.[56] It was reported that following a myocardial infarction MPV was an independent risk factor for recurrent ischemia or death at 2 years of follow-up.[57] Pizzuli et al. demonstrated higher MPV in stable angina than controls, but the highest MPV in unstable angina.[28] MPV was also found to be associated with cerebrovascular and peripheral artery disease.[30,58,59]

Study results about infection and MPV were conflicting. Some authors demonstrated a negative correlation between MPV and inflammatory activity of the disease in pulmonary tuberculosis, acute appendicitis, acute pancreatitis and HIV infection, but some others have reported an association between MPV and the severity of infection like acute appendicitis, ascitic fluid infection, acute cellulitis, infective endocarditis, and sepsis.[33,34,36-40,60-63] Also in some of the infective diseases high MPV levels decreased after the treatment.[35,40]

In chronic inflammatory diseases, such as ulcerative colitis, Crohn's disease, cystic fibrosis, and Familial Mediterranean Fever a decrease in MPV levels was determined.[64-67] On the contrary, a sig-

TABLE 2: Correlation analysis of with leucocyte count, ESR and hs-CRP in all groups

	R	P
MPV- leucocyte count		
Group I	-0.044	NS
Group II	-0.061	NS
Group III	0.019	NS
Group IV	0.147	NS
MPV- ESR		
Group I	-0.032	NS
Group II	-0.062	NS
Group III	-0.085	NS
Group IV	0.052	NS
MPV-hs-CRP		
Group I	-0.036	NS
Group II	0.016	NS
Group III	0.174	NS
Group IV	0.045	NS

ESR: Erytrocyte sedimentation rate, hs-CRP: C-reactive protein, MPV: Mean platelet volume. Data are presented as mean ± SD. NS: Nonsignificant.

nificantly higher MPV was observed in the celiac disease and after introduction of a gluten-free diet, the MPV of the patients lessened.[68]

It is interesting that results of studies about MPV levels in various infective or inflammatory processes differ. We think that these different results may be explained by the acute or chronic state of the disease and also on which day the sample was taken. In our study MPV levels of our diabetic patients were higher than that of the control, like most of the studies with diabetes.[7-15] The patients with DR and DN had the highest MPV levels. This result was also in concordance with previous studies.[19-26] There was not any difference of MPV values in both of the complications of diabetes. This may support the idea that if the trigger of vascular pathology was pulled in diabetes, all the microvasculature would be affected.

hs-CRP is a protein of an acute phase, which is secreted by liver, and by many other tissues in response to an inflammation state. It is lately considered to be a marker of pro-inflammatory activity as well as inflammation and a marker of atherosclerosis.[69] Leucocyte count, being a marker of inflammation was found to be correlated with worsening of insulin sensitivity, diabetes and also coronary heart disease.[70,71] ESR and hs-CRP was also found to be significantly correlated with insulin resistance.[72,73] Moreover it was demonstrated that anti-inflammatory treatment improved beta cell function in T2DM.[74,75] Keeping in mind the relation of inflammatory markers such as sedimentation rate, leucocyte count and hs-CRP, and also MPV we wanted to find out if there is a relation with MPV and these inflammatory markers in our groups. Although MPV levels were different in our diabetic and control groups, we could not obtain any difference in leucocyte count, ESR and hs-CRP in all groups. Moreover in correlation analysis we did not find any positive or negative correlation in diabetic and control individuals. In the literature relation of MPV and inflammation markers were demonstrated in infectious and inflammatory diseases, cardiovascular disease and diabetes.[42-49] In most of these studies inflammatory markers especially hs-CRP levels were higher than our results, but on the contrary in all our groups leucocyte count, ESR and hs-CRP values were near normal levels and they did not differ among groups. We may explain why we were not able to find a correlation between MPV levels and inflammatory markers. Perhaps in our patients inflammation was not so serious to take an important part in the pathogenesis of the diabetic complications.

It was demonstrated that in inflammation and insulin resistance adipocytes were primarily involved. These cells affect insulin secretion and insulin resistance by adipocytokines, such as leptin, adiponectin, omentin, resistin and visfatin.[76] Adipose tissue also secretes dipeptidyl-4 peptidase which degrades glucagon like peptide -1.[77] Moreover cytokines in the circulation such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1) and interferon gamma (IFN-γ) affect insulin release. TNF- α also by increasing the expression of islet amyloid polypeptide augments beta cell inflammation.[78] IL-1, IL-6 and TNF-α were shown to stimulate cell adhesion molecules and profibrotic growth factors. In our study we did not investigate the levels of cytokines. If we had had the chance of examining the relation of MPV levels with those cytokines and vascular cell adhesion molecule-1, and intracellular adhesion molecule-1 our study

might be more satisfying. We are planning a new study keeping in mind these thoughts.

It was shown that metformin treatment significantly decreased MPV values in diabetic patients, unrelated to HbA1c levels.[79] It was also demonstrated that values of MPV were significantly higher in patients on oral hypoglycemic therapy than patients on insulin treatment.[80] Although insulin treatment was shown to decrease the activation and expression of cytokines, in a study neither insulin nor metformin was shown to reduce inflammatory marker levels such as hs-CRP and IL-6.[81,82] Gliclazide and peroxiome proliferator activated receptor-γ (PPAR-γ) agonists were shown to lessen inflammatory cytokines and also to prevent degenerative changes in diabetic nerves.[83] In our study we did not discriminate the treatment modalities of our diabetic patients. It would be interesting if we seeked correlation of MPV's of our patients with inflammatory markers after grouping the patients with diabetes according to their therapeutic modalities.

It was found that statins significantly decreased MPV levels and various ACEIs and ARBs had different effects on MPV levels.[84,85] Effects of statins and ACEIs on inflammation in diabetic complications were also controversial.[86] As in this study either of these drugs were used, our results may likely have been weakened.

Major strength of our study is its newness. As far as we searched the literature we could not find another study seeking correlation of MPV levels with inflammation markers in diabetic complications and comparing the results in patients either having neuropathy and retinopathy. One of our limitations is the sample size of the study, which is relatively small. Second limitation is that our patients were not classified according to their medications such oral antiplateles with diabetes and insulin and also antihypertensives and antilipemics. Third limitation is the MPV value, which is evaluated only once in time. Another limitation is about smoking which has not been mentioned in our groups. It was demonstrated that smoking had effects on MPV levels. The last limitation is that our findings are limited to our groups, which included only adults from our district, so our results may not be easily applicable to all our country or other nationalities.

In conclusion, our results suggest that MPV levels of our diabetic patients with diabetic complications are not related to inflamation markers where inflammation was not so serious. We hope that in the future prospective, multicentric studies with larger size may enlighten the pathophysiology of diabetic complications and new therapy modalities interfering major pathological pathways having role on the diabetic complications may be discovered.

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