Int J Clin Exp Med 2015;8(7):11420-11427
www.ijcem.com /ISSN:1940-5901/IJCEM0010341

Original Article

Association of hematological indicies with diabetes, impaired glucose regulation and microvascular complications of diabetes

Levent Demirtas[1], Husnu Degirmenci[2], Emin Murat Akbas[3], Adalet Ozcicek[1], Aysu Timuroglu[1], Ali Gurel[4], Fatih Ozcicek[1]

[1]Department of Internal Medicine, Mengücek Gazi Training and Research Hospital, School of Medicine, Erzincan University, Erzincan, Turkey; [2]Department of Cardiology, Mengücek Gazi Training and Research Hospital, School of Medicine, Erzincan University, Erzincan, Turkey; [3]Department of Endocrinology, Mengücek Gazi Training and Research Hospital, School of Medicine, Erzincan University, Erzincan, Turkey; [4]Department of Nephrology, Mengücek Gazi Training and Research Hospital, Erzincan, Turkey

Received May 18, 2015; Accepted July 10, 2015; Epub July 15, 2015; Published July 30, 2015

Abstract: In recent years, there has been renewed interest in hematological parameters as predictors of endothelial dysfunction and inflammation. The aim of our study is to evaluate the relationship between HbA1c and hematological indices, and to evaluate the relationship between these parameters and microvascular complications of diabetes. Three hundred and seven diabetic patients (124 male, 183 female; mean age 50.8±8.5), and 187 controls (76 male, 111 female; mean age 51.1±10.1) were included in the study. In the diabetic group, mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), white blood cell count (WBC), platelet count, platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) were significantly higher than the control group (P<0.05). Diabetic patients were divided into two group according to their HbA1c levels (Group 1; HbA1c <7 (n=82) and group 2; HbA1c ≥7 (n=225)). Mean platelet volume, PCT and PDW levels were significantly increased in group 2. Mean platelet volume was significantly increased in diabetic patients with retinopathy compared to those without retinopathy (P=0.006). The neutrophil to lymphocyte ratio and PLR levels were significantly higher in patients with nephropathy (P=0.004, P=0.004 respectively). There was statistically significant difference of lymphocyte count between patients with and without neuropathy. In correlation analysis, positive correlation between HbA1c and PCT (r_s=0.192, P<0.001), HbA1c and PDW (r_s=0.305, P<0.001), HbA1c and MPV (r_s=0.352, P<0.001) were determined. In binary logistic regression analysis; WBC, PDW and PLR levels were found to be independently associated with diagnosis of diabetes while WBC, MPV, PLR and NLR levels were found to be independently associated with impaired glucose regulation. This study demonstrates that altered hematological indices are closely associated with HbA1c levels in individuals with and without diabetes and some of these parameters are associated with diabetic microvascular complications. These associations may be explained by connection between these easy accessible and inexpensive hematological indices and inflammation, tendency to coagulation and thrombosis in patients with diabetes.

Keywords: Hematological parameters, diabetes mellitus, HbA1c, microvascular complications

Introduction

Diabetes is a disease of metabolism clinically expressed by chronic hyperglycemia and blood lipid and protein disorders that have been extensively reported as linked to several complications that cause morbidity and mortality. Diabetes and uncontrolled hyperglycemia are known to play a significant role in the development of cardiovascular disease (CVD) since Framingham study. [1, 2]. Additionally, besides the diabetes and classical risk factors, the presences of microvascular complications are also predictor of coronary heart events [3]. In addition to atheroma formation, the combination of hypercoagulability, impaired fibrinolysis and impaired vasodilation likely further increases the risk of vascular occlusion and cardiovascular events in diabetes [4].

In recent years, there has been renewed interest in hematological parameters such as white

Table 1. Demographical and laboratory specifications of diabetes and control group

Parameters	Diabetes Group (n=307)	Control Group (n=187)	*P* value
Age (year)*	52 (45-58)	52 (43-58)	>0.05
Gender (f/m)**	183/124	111/76	>0.05
BMI (kg/m²)*	30.8 (27.5-33.6)	30.7 (27.6-35.2)	>0.05
Waist circumference (cm)*	102 (97-109)	103 (96-110)	>0.05
SBP (mmHg)*	130 (120-140)	130 (115-135)	>0.05
DBP (mmHg)*	80 (70-80)	80 (70-80)	>0.05
TC (mg/dL)*	206 (174-233)	209 (177-239)	>0.05
HDL-C (mg/dL)*	45 (40-50)	47 (40-52)	>0.05
LDL-C (mg/dL)***	126.13±42.81	131.20±36.73	>0.05
TG (mg/dL)*	164 (118-225)	144 (110-208)	>0.05
Creatinine (mg/dL)*	0.71 (0.60-0.85)	0.71 (0.63-0.85)	>0.05
MPV (fL)*	9.2 (8.7-9.9)	8.8 (8.3-9.3)	<0.001
PCT (%)*	0.232 (0.195-0.269)	0.212 (0.186-0.238)	<0.001
PDW (fL)*	16.4 (15-17.8)	15.4 (14.2-16.5)	<0.001
Platelet count (x10³/uL)*	249 (214-297)	244 (209-275)	0.033
FPG (mg/dL)*	182 (125-243)	86 (80-92)	<0.001
HbA1c (%)*	8.6 (6.9-10.4)	5.3 (5.1-5.5)	<0.001
WBC (x10³/uL)*	7.4 (6.4-8.7)	6.8 (5.9-7.9)	<0.001
NLR*	1.75 (1.40-2.27)	1.58 (1.30-2.00)	0.001
PLR*	106.96 (84.96-135.00)	101.30 (80.70-119.70)	0.012

*Mann-Whitney U (Data are given as median (IQR)). **Chi-Square Test. ***T-Test (Data are given as mean ± SD). SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. TC: Total Cholesterol. HDL-C: High Density Lipoprotein Cholesterol. LDL-C: Low Density Lipoprotein Cholesterol. TG: Triglyceride. MPV: Mean Platelet Volume. FPG: Fasting Plasma Glucose. HbA1c: Glycosylated Hemoglobin.

blood count (WBC), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), platelet count, platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) and are designated as predictors of endothelial dysfunction and inflammation.

Elevated white blood cell count (WBC) is a classical inflammatory marker and is associated with several cardiovascular disease risk factors and diabetes [5-9]. The association of increased MPV, PDW, PCT and platelet count with diseases related to endothelial dysfunction and inflammation as metabolic syndrome, diabetes, coronary artery disease and malignancy have been shown [10-19]. In the last decades, PLR and NLR were introduced as potential markers to determine inflammation in cardiac and non-cardiac disorders [19-27].

In the light of mentioned studies, the aim of present study is to evaluate the relationship between HbA1c and hematological indices, and to evaluate the relationship between these parameters and microvascular complications of diabetes.

Material and methods

Patient population and study design

Three hundred and seven diabetic patients and a control group of 187 healthy people enrolled in this cross-sectional prospective study. Diabetic group was divided into two according to their HbA1c levels as group 1; HbA1c <7 (n=82) and group 2; HbA1c ≥7 (n=225). Patients with hematologic diseases, hepatic failure, renal failure, heart failure, acute illness, chronic diseases like chronic infections, alcohol abuse, that are on medication altering the platelet function, and atherosclerotic diseases except for arterial hypertension were not included in the study.

Evaluation of demographical and clinical specifications

Patients' blood pressure, height and weight measurements, age, gender, accompanying

Table 2. Demographic. clinical and laboratory features of the patients according to HbA1c groups

Parameters	HbA1c <7 (n=82)	HbA1c ≥7 (n=225)	*P* value
Age (years)*	51.5 (45-57.3)	52 (45-58)	>0.05
Gender (f/m)**	45/37	138/87	>0.05
BMI (kg/m²)*	30.9 (28.4-33.7)	30.7 (27.2-33.6)	>0.05
Waist circumference (cm)*	103 (98-110)	102 (97-109)	>0.05
Disease duration (month)*	48 (24-72)	72 (36-132)	<0.001
SBP (mmHg)*	130 (114-140)	130 (120-140)	>0.05
DBP (mmHg)*	75 (65-81)	80 (70-80)	>0.05
TC (mg/dL)***	205.40±45.11	208.21±48.55	>0.05
HDL-C (mg/dL)*	45 (41-52)	45 (39-50)	>0.05
LDL-C (mg/dL)***	124.55±39.16	126.71±44.13	>0.05
TG (mg/dL)*	164 (131-198)	164 (112-233)	>0.05
Creatinine (mg/dL)*	0.72 (0.62-0.85)	0.70 (0.59-0.85)	>0.05
MPV (fL)***	8.9±0.8	9.4±0.9	<0.001
PCT (%)*	0.222 (0.195-0.258)	0.237 (0.195-0.280)	0.039
PDW (fL)*	16.0 (15.0-17.0)	16.6 (15.3-18.0)	0.002
Platelet Count (x10³/uL)*	251 (226-289)	248 (209-301)	>0.05
FPG (mg/dL)*	116 (110-121)	205 (172-255)	<0.001
HbA1c (%)*	6.5 (6.2-6.8)	9.5 (8.2-11.1)	<0.001
WBC (x10³/uL)*	7.3 (6.3-8.1)	7.5 (6.5-8.7)	>0.05
NLR*	1.92 (1.40-2.34)	1.71 (1.40-2.23)	>0.05
PLR*	107.61 (88.29-129.77)	106.81 (83.50-138.51)	>0.05
Albuminuria (mg/g Cr)*	8.83 (2.65-19.88)	18.43 (7.71-224.53)	<0.001

*Mann-Whitney U (Data are given as median (IQR)). **Chi-Square Test. ***T-Test (Data are given as mean ± SD) SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. TC: Total Cholesterol. HDL-C: High Density Lipoprotein Cholesterol. LDL-C: Low Density Lipoprotein Cholesterol. TG: Triglyceride. MPV: Mean Platelet Volume. FPG: Fasting Plasma Glucose. HbA1c: Glycosylated Hemoglobin.

disease history, smoking habits, medication history and medical history were recorded. Body mass index (BMI) was calculated by using Quetlet index with weigh/height² formula. In addition, patients with DM were evaluated regarding metabolic regulation, nephropathy, retinopathy and neuropathy. Retinopathy diagnosis was made based on the findings of at least two microaneurysms and/or retinal hemorrhage and/or retinal damage in the records [28]. The quantitative urine albumin/creatinine ratio in morning spot urine samples were used for standard albuminuria determination and diagnosis of nephropathy.

Diabetic neuropathy symptom score were queried to determine the presence of diabetic peripheral neuropathy in all diabetic patients [29].

Biochemical and hematologic evaluation

Serum glucose levels were calculated with glucose oxidase technique, creatinine levels with Jaffe method, total cholesterol (TC), and triglyceride (TG), High Density Lipoprotein Cholesterol (HDL-C) with enzymatic colorimetric method of HDL and low density Lipoprotein Cholesterol (LDL-C) with Friedewald formula. HbA1c was studied with HPLC method. NLR and PLR were calculated as the ratio of neutrophils to lymphocytes and platelets to lymphocytes respectively. Simultaneous complete blood count results were used to obtain data of WBC, MPV, PDW, PCT, neutrophil and lymphocyte counts. NLR and PLR were calculated as the ratio of neutrophils to lymphocytes and platelets to lymphocytes respectively.

Statistical analysis

Statistical analyses were carried out using the Statistical Package for Social Sciences, Windows version 20.0 (SPSS, Chicago, IL, USA). Descriptive statistics for each variable were determined. Normality of the data distribution was assessed with the Kolmogorov-Smirnov test. Results for continuous variables were

Table 3. Binary logistic regression of diagnosis of diabetes

Parameters	Odds Ratio	95% C.I.		*P* value
		Lower	Upper	
Age	0.997	0.975	1.021	>0.05
WC	1.013	0.988	1.040	>0.05
BMI	1.016	0.966	1.067	>0.05
Creatinine	0.905	0.260	3.147	>0.05
TC	0.994	0.984	1.005	>0.05
LDL-C	1.009	0.998	1.020	>0.05
HDL-C	1.002	0.975	1.029	>0.05
TG	1.000	0.996	1.003	>0.05
SBP	0.990	0.979	1.001	>0.05
WBC	0.708	0.576	0.870	0.001
PCT	23.253	0.000	1.025E+20	>0.05
PDW	0.810	0.710	0.925	0.002
MPV	0.472	0.160	1.392	>0.05
Platelet Count	0.993	0.955	1.033	>0.05
NLR	1.002	0.581	1.728	>0.05
PLR	0.981	0.969	0.994	0.003

WC: Waist Circumference, BMI: Body Mass Index, TC: Total Cholesterol, HDL-C: High Density Lipoprotein Cholesterol, LDL-C: Low Density Lipoprotein Cholesterol, TG: Triglyceride, SBP: Systolic Blood Pressure, WBC: White Blood Cell Count, PCT: Plateletcrit, PDW: Platelet Distribution Width, MPV: Mean Platelet Volume, NLR: Neutrophil to Lymphocyte Ratio: PLR: Platelet to Lymphocyte Ratio.

demonstrated as mean ± standard deviation. Results for continuous variables without normal distribution were demonstrated as median [inter quartile range (IQR)]. Statistical significant differences between the groups were determined by chi-square test for categorical variables. For continuous variables, nonparametric statistics (Mann-Whitney U), and parametric statistics (t test) were all used, as appropriate. Associations between the variables were explored using the Spearman's rho (for data that was not normally distributed). Binary logistic regression analysis was also performed to define variables associated with diabetes in whole group and impaired glucose regulation in diabetic patients. A *P* value less than 0.05 was considered significant.

Results

A total of 307 patients (124 male, 183 female; mean age 50.8±8.5) and 187 controls (76 male, 111 female; mean age 51.1±10.1) were selected to the study. Comparison of the groups regarding demographical, clinical, biochemical and hematologic data are shown in **Table 1**. There were no statistically significant differences between the groups respecting the following variables; age, gender, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, TC, HDL-C, LDL-C, TG and creatinine levels whereas there were statistically significant difference between the groups respecting; MPV, PCT, PDW, WBC, platelet count, PLR, NLR, fasting plasma glucose and HbA1c ($P<0.05$).

As shown in **Table 2**, when patients separated in two groups according to HbA1c levels, there were no statistically significant differences between the groups respecting the following variables; age, gender, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, TC, HDL-C, LDL-C, TG, creatinine levels, WBC, platelet count, lymphocyte count, neutrophil count, NLR and PLR while there were statistically significant difference between the groups respecting; disease duration, MPV, PCT, PDW, fasting plasma glucose, HbA1c and albuminuria.

In the evaluation of association of retinopathy and hematological indices; there were statistically significant difference of MPV levels between patients with (n=67; MPV=9.54±0.88) and without (n=240; MPV=9.20±0.92) retinopathy ($P=0.006$) while other studied hematological indices were not differ statistically ($P>0.05$).

In the evaluation of association of nephropathy and hematological indices; there were statistically significant difference of NLR, PLR levels and absolute lymphocyte count between patients with [n=114; NLR=1.99 (1.50-2.62); PLR=116.43 (88.26-150.23); lymphocyte count=2.17 (1.80-2.75)] and without [n=193; NLR=1.68 (1.37-2.16); PLR=102.37 (83.98-127.77); lymphocyte count=2.46 (1.99-2.99)] nephropathy ($P=0.004$, $P=0.004$, $P=0007$ respectively) while other studied hematological indices were not differ statistically ($P>0.05$).

In the evaluation of association of neuropathy and hematological indices; there was statistically significant difference of lymphocyte count between patients with [n=104; 2.10 (1.81-2.78)] and without [n=203; 2.44 (1.98-2.93)] neuropathy ($P=0.046$) while other studied hematological indices were not differ statistically ($P>0.05$).

The correlation between HbA1c and hematological parameters were tested using bivariate correlation analysis. Positive correlation

Table 4. Binary logistic regression of impaired glucose regulation (HbA1c >7%)

Parameters	Odds Ratio	95% C.I.		*P* value
		Lower	Upper	
Age	1.012	0.978	1.046	>0.05
WC	0.987	0.951	1.025	>0.05
BMI	0.957	0.888	1.031	>0.05
Creatinine	0.495	0.092	2.656	>0.05
TC	0.997	0.983	1.012	>0.05
LDL-C	1.001	0.986	1.015	>0.05
HDL-C	0.977	0.942	1.013	>0.05
TG	1.002	0.997	1.006	>0.05
SBP	1.012	0.998	1.026	>0.05
WBC	1.637	1.165	2.300	0.004
PCT	0.000	0.000	2984029.470	>0.05
PDW	1.129	0.941	1.355	>0.05
MPV	7.047	1.397	35.551	0.018
Platelet Count	1.038	0.982	1.097	>0.05
NLR	0.321	0.143	0.720	0.006
PLR	1.028	1.007	1.049	0.008

WC: Waist Circumference; NLR: Neutrophil to Lymphocyte Ratio; PLR: Platelet to Lymphocyte Ratio; BMI: Body Mass Index; TC: Total Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; TG: Triglyceride; SBP: Systolic Blood Pressure; WBC: White Blood Cell Count; PCT: Plateletcrit; PDW: Platelet Distribution Width; MPV: Mean Platelet Volume; NLR: Neutrophil to Lymphocyte Ratio.

between serum HbA1c and WBC (r_s=0.145, *P*=0.001), HbA1c and PCT (r_s=0.192, *P*<0.001), HbA1c and PDW (r_s=0.305, *P*<0.001), HbA1c and MPV (r_s=0.352, *P*<0.001) were determined.

Binary logistic regression analysis was also performed to define the variables associated with diagnosis of diabetes in whole group (**Table 3**) and impaired glucose regulation (HbA1c ≥7%) in diabetic patients (**Table 4**). Age, waist circumference, BMI, creatinine, TC, LDL-C, HDL-C, TG, SBP, WBC, PCT, PDW, MPV, platelet count, NLR and PLR levels were included in this model. White blood cell count, PDW and PLR levels were found to be independently associated with diagnosis of diabetes while WBC, MPV, NLR and PLR levels were found to be independently associated with impaired glucose regulation.

Discussion

There are four main findings of the present study. First, several hematological parameters (MPV, PCT, PDW, WBC, platelet count, PLR and NLR) were significantly different between the normal and diabetic groups. Second, levels of MPV, PCT and PDW were significantly different between the regulated (HbA1c <7%) and unregulated (HbA1c ≥7%) diabetic patients and levels of these parameters were tend to increase in unregulated patients. Third, levels of MPV (in retinopathy), PLR (in nephropathy), NLR (in nephropathy) and lymphocyte counts (in nephropathy and neuropathy) were differ in patients with and without microvascular diabetic complications.

Finally, WBC, PDW and PLR levels were found to be independent predictor of diabetes while WBC, MPV, NLR and PLR levels were found to be independent predictor of impaired glucose regulation in diabetic patients.

Patients with type 2 diabetes mellitus (T2DM) have an increased risk of coagulation abnormalities and thromboembolic events. Platelets have a key role and increased adhesion, activation, and aggregation of platelets due to dysregulation of several signaling pathways and metabolic disturbances including insulin resistance, hyperglycemia, and dyslipidemia have been noted in diabetic patients [30, 31]. Systematic inflammation, oxidative stress, impaired calcium metabolism, decreased bioavailability of nitric oxide, increased phosphorylation and glycosylation of cellular proteins are responsible for increased platelet activation and increased release of prothrombotic and proinflammatory agents in diabetes [32]. Larger platelets which can be demonstrated by increased MPV are more active because of elevated prothrombic contents, such as thromboxane A2, thromboxane B2, platelet factor 4, serotonin, and platelet-derived growth factor [33].

Association of increased MPV with prediabetes, diabetes and vascular diabetic complications are stated in the literature [16, 34-39]. Moreover, association of MPV and impaired glucose regulation in diabetic patients also reported [12]. As with MPV, increased PDW is also reported to be associated with diabetes and vascular complications [16, 17, 38, 40-42]. Performed studies did not report a relation

between increased PCT, diabetes and related complications [16, 42, 43]. Conflicting results have been reported for the relation of platelet count and diabetes. Several studies reported no relation [12, 16, 17, 42] while some reported positive association [39, 44] between diabetes and platelet count.

Inflammation is closely associated with both secretory function of beta cell and insulin resistance [45-47]. Circulating inflammatory molecules can decrease beta cell functions directly by secretory dysfunction or uncontrolled apoptosis [45, 46]. As a result glucotoxicity and lipotoxicity occurs and causes enhanced inflammatory process and a vicious cycle [46]. Elevated WBC is a classical inflammatory marker and reveals association of inflammation with impaired glucose metabolism, insulin resistance and DM [5-7]. In recent years PLR and NLR were introduced as novel inflammatory markers in cardiac and non-cardiac disorders [19-27]. Additionally, elevated levels of PLR and NLR were stated in diabetes and diabetic nephropathy [25, 26]. Beside the thromboembolic disorders, associations of platelet indices with inflammation, disease activity of inflammatory disorders and response to anti inflammatory therapies have been also shown [33].

Consistent with the literature, our results reveals that inflammation, tendency to coagulation and thrombosis can be detected with these easy accessible and inexpensive hematological indices. Moreover some of these parameters may help to aware clinicians about impaired glucose regulation and vascular diabetic complications. According to our extensive literature, there has been no study researching association of these parameters together with diabetes and diabetic complications.

Our study has some limitations. First, since it involves one single institution, it may not represent the general population. Second, we cannot determine a cause and effect relationship due to the cross-sectional nature of our study. Despite the limitations, the strength of our study is relatively the large cohort of individuals.

Results of the present study reveal that inflammation and tendency to coagulation and thrombosis can be detected with easy accessible and inexpensive hematological indices. However, large scaled studies need to be conducted in order to evaluate its usability and efficiency.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Levent Demirtas, Department of Internal Medicine, Mengücek Gazi Training and Research Hospital, Erzincan University, Erzincan, Turkey. Tel: + 90 5057172130; Fax: + 90 4462122211; E-mail: drleventdemirtas@hotmail.com

References

[1] Kannel WB and McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA 1979; 241: 2035-2038.

[2] Laakso M. Hyperglycemia and cardiovascular disease in type 2 diabetes. Diabetes 1999; 48: 937-942.

[3] Avogaro A, Giorda C, Maggini M, Mannucci E, Raschetti R, Lombardo F, Spila-Alegiani S, Turco S, Velussi M, Ferrannini E; Diabetes and Informatics Study Group, Association of Clinical Diabetologists, Istituto Superiore di Sanità. Incidence of coronary heart disease in type 2 diabetic men and women: impact of microvascular complications, treatment, and geographic location. Diabetes Care 2007; 30: 1241-1247.

[4] Beckman JA, Creager MA and Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology and management. JAMA 2002; 287: 2570-2581.

[5] Twig G, Afek A, Shamiss A, Derazne E, Tzur D, Gordon B and Tirosh A. White blood cells count and incidence of type 2 diabetes in young men. Diabetes Care 2013; 36: 276-282.

[6] Jiang H, Yan WH, Li CJ, Wang AP, Dou JT and Mu YM. Elevated white blood cell count is associated with higher risk of glucose metabolism disorders in middle-aged and elderly Chinese people. Int J Environ Res Public Health 2014; 11: 5497-5509.

[7] Vozarova B, Weyer C, Lindsay RS, Pratley RE, Bogardus C and Tataranni PA. High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. Diabetes 2002; 51: 455-461.

[8] Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR, Renlund DG, Muhlestein JB and Intermountain Heart Collaborative Study G. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol 2005; 45: 1638-1643.

[9] Lee CD, Folsom AR, Nieto FJ, Chambless LE, Shahar E and Wolfe DA. White blood cell count and incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in African-American and White men and women: atherosclerosis risk in communities study. Am J Epidemiol 2001; 154: 758-764.

[10] Abali G, Akpinar O and Soylemez N. Correlation of the coronary severity scores and mean platelet volume in diabetes mellitus. Adv Ther 2014; 31: 140-148.

[11] Aypak C, Turedi O, Bircan MA and Yuce A. Could mean platelet volume among complete blood count parameters be a surrogate marker of metabolic syndrome in pre-pubertal children? Platelets 2014; 25: 393-398.

[12] Ozder A and Eker HH. Investigation of mean platelet volume in patients with type 2 diabetes mellitus and in subjects with impaired fasting glucose: a cost-effective tool in primary health care? Int J Clin Exp Med 2014; 7: 2292-2297.

[13] Li JY, Li Y, Jiang Z, Wang RT and Wang XS. Elevated Mean Platelet Volume is Associated with Presence of Colon Cancer. Asian Pac J Cancer Prev 2014; 15: 10501-10504.

[14] Ozyurtlu F, Yavuz V, Cetin N, Acet H, Ayhan E and Isik T. The association between coronary slow flow and platelet distribution width among patients with stable angina pectoris. Postepy Kardiol Interwencyjnej 2014; 10: 161-165.

[15] Li S, Zhu CG, Guo YL, Xu RX, Zhang Y, Sun J and Li JJ. The relationship between the plasma PCSK9 levels and platelet indices in patients with stable coronary artery disease. J Atheroscler Thromb 2015; 22: 76-84.

[16] Jabeen F, Fawwad A, Rizvi HA and Alvi F. Role of platelet indices, glycemic control and hs-CRP in pathogenesis of vascular complications in type-2 diabetic patients. Pak J Med Sci 2013; 29: 152-156.

[17] Zaccardi F, Rocca B, Pitocco D, Tanese L, Rizzi A and Ghirlanda G. Platelet mean volume, distribution width, and count in type 2 diabetes, impaired fasting glucose, and metabolic syndrome: a meta-analysis. Diabetes Metab Res Rev 2015; 31: 402-10.

[18] Ergelen M and Uyarel H. Plateletcrit: a novel prognostic marker for acute coronary syndrome. Int J Cardiol 2014; 177: 161.

[19] Mete Ural U, Sehitoglu I, Bayoglu Tekin Y and Kir Sahin F. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in patients with endometrial hyperplasia and endometrial cancer. J Obstet Gynaecol Res 2015; 41: 445-8.

[20] Turkmen K, Erdur FM, Ozcicek F, Ozcicek A, Akbas EM, Ozbicer A, Demirtas L, Turk S and Tonbul HZ. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. Hemodial Int 2013; 17: 391-396.

[21] Raungkaewmanee S, Tangjitgamol S, Manusirivithaya S, Srijaipracharoen S and Thavaramara T. Platelet to lymphocyte ratio as a prognostic factor for epithelial ovarian cancer. J Gynecol Oncol 2012; 23: 265-273.

[22] Noh H, Eomm M and Han A. Usefulness of pretreatment neutrophil to lymphocyte ratio in predicting disease-specific survival in breast cancer patients. J Breast Cancer 2013; 16: 55-59.

[23] Kaya A, Kurt M, Tanboga IH, Isik T, Gunaydin ZY, Kaya Y, Topcu S and Sevimli S. Relation of neutrophil to lymphocyte ratio with the presence and severity of stable coronary artery disease. Clin Appl Thromb Hemost 2014; 20: 473-7.

[24] Ergelen M, Uyarel H, Altay S, Kul S, Ayhan E, Isik T, Kemaloglu T, Gul M, Sonmez O, Erdogan E and Turfan M. Predictive value of elevated neutrophil to lymphocyte ratio in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction. Clin Appl Thromb Hemost 2014; 20: 427-32.

[25] Akbas EM, Demirtas L, Ozcicek A, Timuroglu A, Bakirci EM, Hamur H, Ozcicek F and Turkmen K. Association of epicardial adipose tissue, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with diabetic nephropathy. Int J Clin Exp Med 2014; 7: 1794-801.

[26] Akbas EM, Hamur H, Demirtas L, Bakirci EM, Ozcicek A, Ozcicek F, Kuyrukluyildiz U and Turkmen K. Predictors of epicardial adipose tissue in patients with type 2 diabetes mellitus. Diabetol Metab Syndr 2014; 6: 55.

[27] Bakirci EM, Demirtas L, Degirmenci H, Topcu S, Demirelli S, Hamur H, Buyuklu M, Akbas EM, Ozcicek A, Ozcicek F, Ceyhun G and Topal E. Relationship of the total atrial conduction time to subclinical atherosclerosis, inflammation and echocardiographic parameters in patients with type 2 diabetes mellitus. Clinics (Sao Paulo) 2015; 70: 73-80.

[28] Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, Ferris FL 3rd, Klein R and American Diabetes A. Diabetic retinopathy. Diabetes Care 2003; 26: 226-229.

[29] Meijer JW, Smit AJ, Sonderen EV, Groothoff JW, Eisma WH and Links TP. Symptom scoring systems to diagnose distal polyneuropathy in diabetes: the Diabetic Neuropathy Symptom score. Diabet Med 2002; 19: 962-965.

[30] Kim JH, Bae HY and Kim SY. Response: clinical marker of platelet hyperreactivity in diabetes mellitus (diabetes metab j 2013;37:423-8). Diabetes Metab J 2014; 38: 160-161.

[31] Suslova TE, Sitozhevskii AV, Ogurkova ON, Kravchenko ES, Kologrivova IV, Anfinogenova Y

and Karpov RS. Platelet hemostasis in patients with metabolic syndrome and type 2 diabetes mellitus: cGMP-and No-dependent mechanisms in the insulin-mediated platelet aggregation. Front Physiol 2014; 5: 501.

[32] El Haouari M and Rosado JA. Platelet signalling abnormalities in patients with type 2 diabetes mellitus: a review. Blood Cells Mol Dis 2008; 41: 119-123.

[33] Gasparyan AY, Ayvazyan L, Mikhailidis DP and Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des 2011; 17: 47-58.

[34] Zuberi BF, Akhtar N and Afsar S. Comparison of mean platelet volume in patients with diabetes mellitus, impaired fasting glucose and non-diabetic subjects. Singapore Med J 2008; 49: 114-116.

[35] Hekimsoy Z, Payzin B, Ornek T and Kandogan G. Mean platelet volume in Type 2 diabetic patients. J Diabetes Complications 2004; 18: 173-176.

[36] Bavbek N, Kargili A, Kaftan O, Karakurt F, Kosar A and Akcay A. Elevated concentrations of soluble adhesion molecules and large platelets in diabetic patients: are they markers of vascular disease and diabetic nephropathy? Clin Appl Thromb Hemost 2007; 13: 391-397.

[37] Tavil Y, Sen N, Yazici H, Turfan M, Hizal F, Cengel A and Abaci A. Coronary heart disease is associated with mean platelet volume in type 2 diabetic patients. Platelets 2010; 21: 368-372.

[38] Xiao W, Huang Y, Dong J, Zhang X and Hu J. Relationship between platelet volume indices with macrovascular and peripheral neuropathy complications in type 2 diabetic patients. J Diabetes 2014; 6: 298-303.

[39] Lippi G, Salvagno GL, Nouvenne A, Meschi T, Borghi L and Targher G. The mean platelet volume is significantly associated with higher glycated hemoglobin in a large population of unselected outpatients. Prim Care Diabetes 2015; 9: 226-30.

[40] Bekler A, Ozkan MT, Tenekecioglu E, Gazi E, Yener AU, Temiz A, Altun B, Barutcu A, Erbag G and Binnetoglu E. Increased Platelet Distribution Width Is Associated With Severity of Coronary Artery Disease in Patients With Acute Coronary Syndrome. Angiology 2014; 66: 638-43.

[41] Jindal S, Gupta S, Gupta R, Kakkar A, Singh HV, Gupta K and Singh S. Platelet indices in diabetes mellitus: indicators of diabetic microvascular complications. Hematology 2011; 16: 86-89.

[42] Erdogan S, Ozdemir O, Dogan HO, Sezer S, Atalay CR, Meric F, Yilmaz FM and Koca Y. Liver enzymes, mean platelet volume, and red cell distribution width in gestational diabetes. Turk J Med Sci 2014; 44: 121-125.

[43] Citirik M, Beyazyildiz E, Simsek M, Beyazyildiz O and Haznedaroglu IC. MPV may reflect subcinical platelet activation in diabetic patients with and without diabetic retinopathy. Eye (Lond) 2014; 29: 376-9.

[44] Akinsegun A, Akinola Olusola D, Sarah JO, Olajumoke O, Adewumi A, Majeed O, Anthonia O, Ebele U, Olaitan O, Olanrewaju A and Kingsley A. Mean platelet volume and platelet counts in type 2 diabetes: mellitus on treatment and non-diabetic mellitus controls in Lagos, Nigeria. Pan Afr Med J 2014; 18: 42.

[45] Das A and Mukhopadhyay S. The evil axis of obesity, inflammation and type-2 diabetes. Endocr Metab Immune Disord Drug Targets 2011; 11: 23-31.

[46] Agrawal NK and Kant S. Targeting inflammation in diabetes: Newer therapeutic options. World J Diabetes 2014; 5: 697-710.

[47] Akbas EM, Demirtas L, Guclu A, Erdur FM, Ozcicek F and Turkmen K. The Emerging Role of Sirtuin 1, -3 and -4 in Glucose and Lipid Metabolism and in Diabetes Mellitus. J Mol Gene Med 2014; S1: 018.