Relationship of Different Treatment Regimens in Used Type 2 Diabetes Mellitus Therapy with Mean Platelet Volume

Tip 2 Diabetes Mellitus Tedavisinde Kullanılan Farklı Tedavi Rejimlerinin Ortalama Trombosit Hacmi ile İlişkisi

Berçem AYÇİÇEK DOĞAN, MD,[a]
Hasan TUNCA, MD,[b]
Engin SENNAROĞLU, MD,[c]
Serhat IŞIK, MD,[a]
Ferit Kerim KÜÇÜKLER, MD,[a]
Ayşe ARDUÇ, MD,[a]
Dilek BERKER, MD,[a]
Serdar GÜLER, MD[a]

Clinics of
[a]Endocrinology and Metabolism,
[c]Internal Medicine,
Ankara Numune Research and Training Hospital, Ankara
[b]Clinic of Internal Medicine,
Mucur State Hospital, Kırşehir

Geliş Tarihi/*Received:* 04.01.2011
Kabul Tarihi/*Accepted:* 05.04.2011

Yazışma Adresi/*Correspondence:*
Berçem AYÇİÇEK DOĞAN, MD
Ankara Numune Research and Training Hospital,
Clinic of Endocrinology and Metabolism,
Ankara,
TÜRKİYE/TURKEY
bercemay@gmail.com

ABSTRACT Objective: Platelet activity and aggregation potential, which are essential components of thrombogenesis and atherosclerosis, can be conveniently estimated by measuring mean platelet volume (MPV). It has been shown that MPV levels were higher in type 2 Diabetes mellitus (T2DM) and this correlated with high HbA1c values; however, the effect of antidiabetic treatment on MPV levels which were independent from HbA1c has not been studied yet. The aim of this study was to investigate the relationship between MPV and different treatment regimens of T2DM. **Material and Methods:** 122 patients with T2 DM and 34 control subjects were enrolled to the study. Diabetic patients were separated according to their treatment regimens. Statistical analysis were performed with SPSS software, release 11.5. **Results:** In among groups of treatment regimen and control group was found statistically significant differences for MPV levels which correlated with HbA1c. Multiple linear regression analysis was used for investigating the statistical significance of relationship between parameters which were founded corelated with high MPV value and different treatment regimens of T2DM with MPV value. In these among, HbA1c levels were found to be most correlated with high MPV levels. **Conclusion:** Antidiabetic regimens can reduce the risk of thrombosis, this can be regardless of improving glycemic control, via affecting the value of MPV. Starting this idea, the first stage, the effects of antidiabetic treatment on MPV levels which were independent from HbA1c wereexamined in our cross-sectional study. In conclusion; while positive correlation between high MPV levels and high HbA1c values was seen, the relationship between MPV values and different antidiabetic regimens were not.

Key Words: Hemoglobin A1c protein, human; diabetes mellitus, type 2

ÖZET Amaç: Ateroskleroz ve tromboz gelişiminde trombosit aktivitesi ve agregasyonu önemli rol oynar ve bu tam kan sayımı parametresi olan ortalama trombosit hacmi (OTH)'nin ölçülmesi ile öngörülebilir. Tip 2 Diabetes mellitus (T2DM) hastalarının OTH düzeyleri ile HbA1c değerleri arasında pozitif korelasyon literatürde gösterilmiştir. Ancak antidiyabetik tedavilerin OTH üzerindeki- HbA1c'den bağımsız etkileri- henüz literatürde gösterilmemiştir. Bu çalışmada, T2DM tedavi rejimlerinin OTH ile ilişkisi incelendi. **Gereç ve Yöntemler:** Hastanemize başvuran 122 T2DM hastası ve 34 kontrol vakası çalışmaya alındı. Diyabetik hastalar aldıkları tedavi rejimlerine göre gruplara ayrıldı. İstatistiksel analiz için SPSS yazılım sürümü 11.5 kullanıldı. **Bulgular:** HbA1c ile korele seyreden OTH değerinin, tedavi grupları arasında ve kontrol grubu ile kıyaslanmasında farklılıklar izlendi. Bu farklılık istatistiksel olarak anlamlı idi. OTH ile korelasyonu saptanan parametreler ve farklı tedavi rejimlerinin OTH değeri ile ilişkisinin istatistiksel önemi çoklu lineer regresyon analizi ile değerlendirildi. İçlerinde OTH değerini en fazla etkileyen parametre HbA1c oldu. **Sonuç:** T 2DM hastalarında kullanılan antidiyabetik rejimler, glisemik kontrol sağlamalarının yanı sıra, OTH üzerindeki etkileri ile de tromboz riskini azaltabilirler. Bu fikirden hareketle, ilk aşamada yaptığımız kesitsel çalışmada antidiyabetik tedavi rejimlerinin -HbA1c'den bağımsız olarak- OTH değeri ile ilişkisi araştırıldı. Sonuç olarak, kötü glisemik kontrol ve OTH yüksekliği arasında, literatür ile uyumlu olarak pozitif korelasyon saptanırken, antidiyabetik tedavi rejimlerinin glisemik kontrolden bağımsız olarak OTH değeri ile ilişkisi gözlenmedi.

Anahtar Kelimeler: Hemoglobin A1c proteini, insan; diabetes mellitus, tip 2

Turkiye Klinikleri J Cardiovasc Sci 2011;23(2):109-14

Altered platelet morphology and function have been reported in patients with diabetes by Mazzanfi et al in 1977. One study was showed that level of beta-thromboglobulin which is granule of platelet and the mean platelet volume (MPV) was significantly important higher in the diabetic group than in the control subjects.[1] MPV increase might contribute to the diabetes-associated vascular damage, especially considering that, in this disease, platelets are not only larger, but also circulate in an activated state, as demonstrated by the presence of markers of platelet activation, by higher plasma and urinary concentrations of thromboxane A2 which is granule of platelet and by an increased spontaneous platelet aggregation.[2]

This is in agreement with other studies that have also reported the increase in MPV in diabetic patients in comparison with healthy controls.[3] It has also been shown that among diabetic patients, those with retinopathy and other complications have higher MPV values than those who do not have this complication.[4]

Besides of type 2 Diabetes mellitus (T2DM) disease, different diseases related to MPV were showed in the literature; A study showed that MPV was increased in the presence of the metabolic syndrome and, more precisely, that MPV values were independently associated with the number of components of the syndrome, being especially correlated with waist circumference, body mass index (BMI), fasting blood glucose and blood pressure.[5] A relationship between blood pressure and MPV was also reported by other studies, Coban and Afacan reported higher MPV values in patients with hypercholesterolaemia than that in healthy controls.[6,7]

According to Coban et al there is a positive correlation between BMI and MPV.[8]

Importantly, in patients with previous cerebrovascular diseases, the PROGRESS study showed that MPV could predict the risk of a second stroke up to 4 years before the acute event.[9]

Fourteen of the 16 studies demonstrated that patients with AMI had higher MPVs than those without AMI.[10] Similarly, altered platelet morphology and function have been reported in patients acute coronary syndrome.[11]

Basic and clinical evidences suggest that antidiabetic treatment such as gliclazide and metformin (MET) work as an antioxidative drug, independently from its ability to reduce hyperglycemia, such as could improve the imbalance between free radical-induced increased lipid peroxidation and decreased plasma and cellular antioxidant defense.[12,13] Because of these evidences, we aimed to investigate whether relationship with MPV and different regimens of T2DM was existence regardless of glycaemic control. If this relationship would been showed, it may be added to the literature another data about effects of different regimens of T2DM on thrombosis which is regardless of glycemic control in T2DM patients.

MATERIAL AND METHODS

The study group included 122 consecutive patients with T2DM (56 females and 66 males), of age was 32-74 years. The mean duration of diabetes was 10.2 ± 2.4 years. Diabetic patients were evaluated for glycaemic status. Diabetic patients were divided into the four groups according to their treatment of T2DM: Group 1 consisted of 32 conventional insulin treatment patients, Group 2 consisted of 29 MET-treated patients, Group 3 consisted of 31 MET and insulin-treatment patients and Group 4 consisted of 30 gliclazide and MET-treated patients. These patients have been taken these treatments at least 3 months.

Whereas it was reported in the literature that MPV was affected by hypertension (HT), we had to include this disease in our study, because of as we know that HT is high prevelance in patients with T2DM. Because of showing many diseases and drugs affect MPV levels in the literature all patients and subjects of control group compared in terms of age, gender, BMI, HT, lipid profiles. The age, body mass index, and sex-matched control group consisted of healthy nondiabetic subjects (18 females, 16 males; age 43.3 ± 10.2 years). None of the diabetic patients and controls had any thrombotic and hematological diseases and nonobese (BMI <30 kg/m^2). None of them had received anti-

coagulant, antilipemic, steroid and propranolol medications. Male patients with hemoglobin below 12.5 g and female patients below 12 g were excluded from the study. Other exclude criteria of our study that have had chronic obstructive lung disease, malignancy, thyroid diseases, cerebrovasculer diseases, cardiac insufficiency, renal insufficiency and hyperlipidemia (Triglyceride<150 mg/dL, total cholesterole <200 mg/dL).

Blood samples for total blood count with MPV, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), HbA1c, and fasting glucose measurements were obtained 8:00 a.m. after overnight fasting.

Blood samples were obtained from the antecubital vein in an upright position. Venous blood (1.8 mL) was taken and mixed with 0.2 mL of 3.8% sodium citrate solution (9:1) in order to perform a total blood count and MPV measurement. Measurements were completed within 1 hour using Coulter Beckman LH 750 equipment. HbA1c, glucose, and lipid profile measurements and albumin levels in 24 h urine specimen were conducted using the Roche-Hitachi PP Modular analyzer. The blood glucose level was determined by glucose oxidase method and HbA1c was determined by Turbidimetric Inhibition Immunoassay (TINA).

All statistical analysis were done with statistical programme of SPSS for Windows 11.5 software. Descriptive statistics for continuous measurement variables as mean ± standard deviation of the nominal variables and the number of cases (%) as shown. Continuous measurement variables between the groups in terms of whether there is a statistically significant difference were examined by one-way analysis of variance or Kruskal-Wallis test. The effects of gender, hypertension on MPV investigated by Mann Whitney U test. Nominal variables were evaluated with Pearson's chi-square test. The size of the linear relationship of between continuous variables were assessed by Spearman's "rho" coefficient. If both of as a result of the univariate statistical assessments of the factors that have statistically significant and the clinical significance of risk factor's effects on MPV values were $p< 0.25$, it was investigated as a candidate variable by Multiple Linear Regression analysis. Regression coefficient of each risk factor, 95% confidence interval and significance levels were calculated. $p< 0.05$ was considered statistically significant for the results.

RESULTS

The mean demographic and metabolic characteristics of all groups were given in Table 1. There was no significant difference between the patient groups and controls with regard to age, sex, BMI, HT, serum creatinine, creatinine clearance, platelet count, and platelet mass.

When examinated distribution of lipid profiles between the groups, HDL-cholesterol was statistically significant elevated in the control group ($p= 0.015$) (Table 2). Examined in terms of HbA1c, statistically significant difference were found between with Groups 1 and 3, all groups than control group ($p= 0.000$). HbA1c values were high found in Group 1 and Group 3 compared with group 4 which was positive correlates with MPV levels ($p=$

TABLE 1: Demographic data.

Variables	Control (n= 34)	Group 1 (n= 32)	Group 2 (n= 29)	Group 3 (n= 31)	Group 4 (n= 30)	p
Age, (years)	43.3 ± 10.2	56.9 ± 11.6[c]	51.2 ± 10.1[d]	51.7 ± 11.6[d]	57.8 ± 11.8[c]	<0.001[a]
Gender (M/F)	16/18	16/16	17/12	16/15	15/15	0.923[b]
BMI, (kg/m^2)	24.9 ± 2.8	25.4 ± 3.0	25.8 ± 2.4	26.4 ± 2.4	26.1 ± 2.7	0.162[a]
HT, (%)	%17.6	%34.4	%31.0	%32.3	%30.0	0.589[b]

M: Male, F: Female, BMI: Boddy-mass index, HT: Hypertension

[a] One-way analysis of variance.

[b] Pearson Chi-Square test.

[c] The difference between the control group with statistically significant ($p< 0.001$).

[d] The difference between the control group with statistically significant ($p< 0.05$)

TABLE 2: Distribution of laboratory measurements in groups.

Variables	Control (n= 34)	Group 1 (n= 32)	Group 2 (n= 29)	Group 3 (n= 31)	Group 4 (n= 30)	p
HDL, mg/dL	48.8 ± 11.2	42.8 ± 12.8[c]	40.6 ± 8.9[c]	42.4 ± 15.4[c]	40.7 ± 9.2[c]	0.015[a]
LDL, mg/dL	113.5 ± 23.8	109.0 ± 30.2	112.0 ± 29.0	106.3 ± 7.8	108.9 ± 20.3	0.835[b]
TG, mg/dL	120.6 ± 46.8	110.7 ± 42.2	119.0 ± 50.0	130.7 ± 51.9	118.1 ± 46.0	0.711[a]
TC, mg/dL	186.6 ± 29.3	172.4 ± 37.2	176.8 ± 34.5	177.4 ± 5.0	175.9 ± 28.5	0.495[b]
HbA1c,%	5.4 ± 0.8	9.1 ± 2.5d,[e]	8.3 ± 2.7[d]	9.8 ± 2.1d,[e]	7.9 ± 1.6[d]	<0.001[a]
MPV,fl	8.2 ± 0.8	8.7 ± 1.1f,[g]	8.5 ± 1.5	8.7 ± 0.9f,[g]	8.1 ± 1.0	0.013[a]
FG, mg/dL	85.2 ± 9.1	190.0 ± 79.2[d]	170.2 ± 73.0[d]	203.9 ± 75.7[d]	164.3 ± 74.1[d,h]	<0.001[a]
PPG, mg/dL	104.6 ± 21.4	252.5 ± 76.1[d]	225.2 ± 100.8[d,h]	267.6 ± 76.6[d]	220.2 ± 76.9[d,h]	<0.001[a]

HDL: High density lipoprotein, LDL: Low density lipoprotein, TC: Total cholesterol, MPV: Mean Platelet volume, FG: Fasting glucose, PPG: Postprandial glucose.
[a]Kruskal-Wallis test.
[b] One-way analysis of variance.
[c] The difference between the control group with statistically significant (p< 0.01).
[d] The difference between the control group with statistically significant (p< 0.001).
[e] The difference between of Group 3 was statistically significant (p< 0.01).
[f] The difference between of Group 4 was statistically significant (p< 0.01).
[g] The difference between the control group with statistically significant (p< 0.05).
[h] The difference between of Group 3 was statistically significant (p< 0.05).

0.013). Similarly, it was found that MPV values were statistically significant different in groups of diabetic patient compared with control group (Figure 1). When examinated fasting glucose (FG) (between with all groups, it was statistically significant different found that amog group 3 and group 4 and all groups compared with control subjects (p< 0.001). Examined the distribution of postprandial glucose (PPG) there were found statistically significant difference in between of group 2, group 3 compared with group 4 (p< 0.001) (Table 2).

The variables that may affect MPV value are age, BMI, lipid panel, HbA1c, fasting glucose, postprandial glucose were analyzed and was found to be statistically significant correlation between with MPV and HbA1c, fasting glucose, postprandial glucose (p< 0.001) (Table 3).

When examinated MPV relation with distribution of gender, HT in between of all groups, it was not found significant different (p= 0.667, p= 0.183, p= 0.279).

As a result of the univariate analysis; HbA1c, FG, PPG which were significant related to MPV (p values < 0.25) and may be thought related to MPV such as HDL-C, TC, HT were analyzed with multiple linear regression. In these among, HbA1c levels were found to be most related to MPV levels (Figure 1). Regression coefficient of each risk factor, 95% confidence interval and significance levels were shown in Table 4.

Among the groups of treatment regimen, Group 4 (gliclazide/MET group) seemed to be increased MPV levels comparing with control group. Both the HT prevalence and increased TC levels, and the boundary p-value (0.046) in Group 4 suggested that,

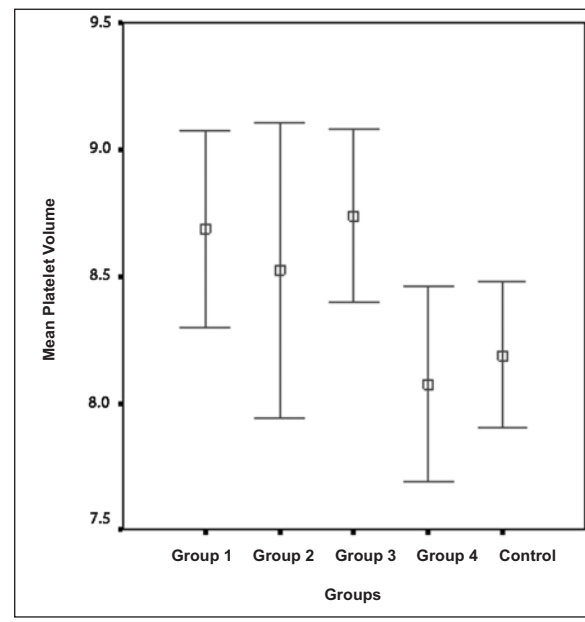

FIGURE 1: Distribution levels of MPV values in between groups.

TABLE 3: The correlation coefficients and Significance Levels of between MPV with age, BMI, serum lipid levels, HbA1c, FG and PPG.

Variables	rho	p
Age	0.039	0.625
BMI	-0.052	0.519
HDL	0.098	0.226
LDL	0.079	0.328
TG	-0.016	0.840
TC	0.134	0.096
HbA1c	0.367	<0.001
FG	0.323	<0.001
PPG	0.311	<0.001

BMI:Boddy-mass-index, HDL:High density lipoprotein, LDL:Low density lipoprotein, TC: Total cholesterol, MPV: Mean Platelet volume, FG: Fasting glucose, PPG: Postprandial glucose. TG: triglyceride

TABLE 4: According to Multiple Linear Regression Analysis, together effects of risk factors which migt thougt to be effect on MPV.

Independent variables	Regression coefficient (B)	P	95% confidence interval (B)	
			Lower limit	Upper limit
Insulin	0.0263	0.485	-0.0480	0.1006
MET	0.0337	0.353	-0.0378	0.1051
Insulin+MET	0.0342	0.387	-0.0437	0.1122
Gliclazide+MET	0.0713	0.046	0.0014	0.1411
HT	-0.0089	0.681	-0.0514	0.0337
HDL	0.0008	0.402	-0.0011	0.0026
TC	0.0003	0.370	-0.0004	0.0010
HbA1c	0.0164	0.011	0.0039	0.0289
FG	0.0002	0.222	-0.0001	0.0006
PPG	0.00004	0.812	-0.0003	0.0004
Invariable Terms	1.5773	<0.001	1.0876	2.0670

MET:Metformin, HT: Hypertension, HDL:High density lipoprotein, LDL:Low density lipoprotein, TC: Total cholesterol, FG: Fasting glucose, PPG: Postprandial glucose.

MPV increase could be an incidental finding in gliclazide/metformin treated patients.

DISCUSSION

Patients with T2DM have an increased risk of cardiovascular disease (CVD) when compared with individuals without diabetes. Conventional risk factors such as dyslipidaemia, smoking and/or hypertension do not fully explain the extent of cardiovascular mortality in patients with diabetes. Mechanisms related to inflammation as well as endothelial function have been implicated in the pathophysiological process leading from the formation of atherosclerotic plaques to clinical events of thrombosis in patients with diabetes.[14]

Patients with diabetes have increased platelet activation compared to nondiabetic subjects. Platelet hyperactivity is accompanied by an increased synthesis of thromboxane and/or a decreased prostacycline production. As part of complete blood count is MPV is a marker of platelet function and activation.[15]

A relationship between blood pressure and MPV was also reported by other studies, but sometimes this relationship, as well as our study was not confirmed.[6,16]

Although Coban and Afacan reported higher MPV values in patients with hypercholesterolaemia than that in healthy controls, aforesaid study and others were unable to find any relationship with MPV, similarly this relationship could not been confirming by regression analysis in our study too.[5,7,8]

Importantly, in accordance with the literature we founded a significant correlation between MPV and HbA1c in patients with T2DM in our study too.[3,4] Although as it is known that improvements in glycemic control are associated with thrombogenicity reduction in patients with poorly controlled T2DM, one study showed that increased

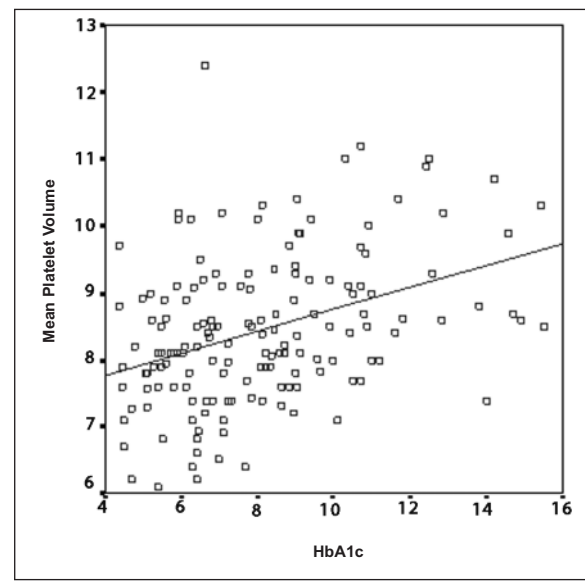

FIGURE 2: Scatter grafic between MPV and HbA1c.

activation of platelets in patients with T2DM had not been depend on glycaemic control.[1,4]

Reducing vascular complication of DM is antioxidative mechanism which were showed in the literature related to metformin and gliclazide. Antidiabetic regimens can reduce the risk of thrombosis, this can be regardless of improving glycaemic control, via affecting the value of MPV. Starting this idea, the first stage, the relationship with antidiabetic treatment and MPV levels which is independent from HbA1c was examined in our cross-sectional study. But, we did not observed any relationship with different antidiabetic treatment regimens and MPV value which is independent from HbA1c. Only, we found a significant correlation between baseline MPV and baseline HbA1c in patients with T 2 DM as well as the another studies in the literature (Figure 2).

In conclusion; even though our study not prospective design, it can be said that improving glycaemic control is valuable rather than kinds of treatments of T2DM on vascular thrombosis. For confirming this data, will need to prospective and randomise study.

REFERENCES

1. Wojszel J, Czyzewska J, Dymicka-Piekarska V, Matowicka-Karna J, Jakubowska I, Kemona H. [Platelets activation in depending on glycaemic control in diabetes type 2]. Pol Merkur Lekarski 2008;25(148):335-9.
2. Vizioli L, Muscari S, Muscari A. The relationship of mean platelet volume with the risk and prognosis of cardiovascular diseases. Int J Clin Pract 2009;63(10):1509-15.
3. Hekimsoy Z, Payzin B, Ornek T, Kandoğan G. Mean platelet volume in Type 2 diabetic patients. J Diabetes Complications 2004;18 (3): 173-6.
4. Zuberi BF, Akhtar N, Afsar S. Comparison of mean platelet volume in patients with diabetes mellitus, impaired fasting glucose and non-diabetic subjects. Singapore Med J 2008;49(2): 114-6.
5. Tavil Y, Sen N, Yazici HU, Hizal F, Abaci A, Cengel A. Mean platelet volume in patients with metabolic syndrome and its relationship with coronary artery disease. Thromb Res 2007;120(2):245-50.
6. Coban E, Yazicioglu G, Berkant Avci A, Akcit F. The mean platelet volume in patients with essential and white coat hypertension. Platelets 2005;16(7):435-8.
7. Coban E, Afacan B. The effect of rosuvastatin treatment on the mean platelet volume in patients with uncontrolled primary dyslipidemia with hypolipidemic diet treatment. Platelets 2008;19(2):111-4.
8. Coban E, Ozdogan M, Yazicioglu G, Akcit F. The mean platelet volume in patients with obesity. Int J Clin Pract 2005;59(8):981-2.
9. Bath P, Algert C, Chapman N, Neal B; PROGRESS Collaborative Group. Association of mean platelet volume with risk of stroke among 3134 individuals with history of cerebrovascular disease. Stroke 2004;35(3):622-6.
10. Chu SG, Becker RC, Berger PB, Bhatt DL, Eikelboom JW, Konkle B, et al. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. J Thromb Haemost 2010;8(1):148-56.
11. Yeşilbursa D, Yuvanç U, Akın S, Odabaşı A, Cordan J. [Changes in platelet size and count in acute coronary syndromes and stable angina]. Turkiye Klinikleri J Cardiol 2003; 16(2):93-6.
12. Tessier D, Maheux P, Khalil A, Fülöp T. Effects of gliclazide versus metformin on the clinical profile and lipid peroxidation markers in type 2 diabetes. Metabolism 1999;48(7):897-903.
13. Cosić V, Antić S, Pesić M, Jovanović O, Kundalić S, Djordjević VB. Monotherapy with metformin: does it improve hypoxia in type 2 diabetic patients? Clin Chem Lab Med 2001;39(9):818-21.
14. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 2005;112(20): 3066-72.
15. Demirtunc R, Duman D, Basar M, Bilgi M, Teomete M, Garip T. The relationship between glycemic control and platelet activity in type 2 diabetes mellitus. J Diabetes Complications 2009;23(2):89-94.
16. Martin JF, Bath PM, Burr ML. Influence of platelet size on outcome after myocardial infarction. Lancet 1991;338(8780):1409-11.