Mean Platelet Volume is Associated with Glycaemic Control and Retinopathy in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Objectives: *To investigate the relationship between mean platelet volume (MPV) and glycometabolic indices, to compare MPV according to HbA1c levels, and to analyse the difference in MPV between patients with and without microvascular complications.*

Methods: *This retrospective study was conducted on 60 Type 2 diabetic patients and 50 age- and sex-matched non-diabetic controls. We obtained demographic, clinical and laboratory data including MPV, platelet count, fasting and postprandial blood glucose (FBG and PBG), haemoglobin A1c (HbA1c), lipid profile, creatinine, systolic and diastolic blood pressure (BP) in patient and control groups, and diabetic microvascular complications including nephropathy, neuropathy, and retinopathy in the patient group. All analyses were performed using SPSS version 15.0 for Windows.*

Results: *Mean platelet volume in the diabetic group was higher than in the control group (*$p = 0.001$*). Mean platelet volume was positively correlated with FBG and HbA1c levels (*$p = 0.03$ *and* $p < 0.001$*, respectively). It was also negatively related to platelet count (*$p < 0.001$*). Mean platelet volume in patients with HbA1c > 7% was significantly higher than those with HbA1c ≤ 7% (*$p < 0.001$*). Mean platelet volume was significantly increased in patients with retinopathy compared to those without retinopathy (*$p = 0.04$*).*

Conclusion: *This study has shown that an increased MPV is closely associated with poor glycaemic control, which may be a risk factor for diabetic retinopathy. Nonetheless, further prospective studies are needed to assess the relationship between MPV, glycaemic indices and microvascular complications.*

Keywords: Diabetes mellitus, HbA1c, mean platelet volume, retinopathy

Volumen Medio de Plaquetas está Asociado con el Control Glucémico y la Retinopatía en Pacientes con Diabetes Mellitus Tipo 2

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RESUMEN

Objetivos: *Investigar la relación entre el volumen medio de plaquetas (MPV) y los índices glicometabólicos, comparar el MPV según los niveles de HbA1c, y analizar la diferencia de MPV entre los pacientes con y sin complicaciones microvasculares.*

Métodos: *Este estudio retrospectivo se realizó en 60 pacientes diabéticos tipo 2, y 50 controles no diabéticos pareados por sexo y edad. Obtuvimos datos demográficos, clínicos y de laboratorio – incluyendo MPV, conteo de plaquetas, glucosa en sangre en ayunas (FBG) y postprandial (PBG), hemoglobina A1c (HbA1c), perfil lipídico, creatinina, presión arterial (BP) sistólica y diastólica en los grupos de pacientes y de control, así como complicaciones microvasculares diabéticas, incluyendo nefropatía, neuropatía y retinopatía en el grupo de pacientes. Todos los análisis se realizaron utilizando el SPSS versión 15.0 para Windows.*

Resultados: *El volumen medio de plaquetas en el grupo diabético fue superior al del grupo control (*$p = 0{,}001$*). El volumen medio de plaquetas guardó una correlación positiva con el FBG y los niveles de*

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*HbA1c (*p = *0.03 y* p < *0.001, respectivamente). También se observó una correlación negativa con el conteo de plaquetas (*p < *0.001). El volumen medio de plaquetas en los pacientes con HbA1c > 7% fue significativamente mayor que en aquellos con HbA1c ≤ 7% (*p < *0.001). El volumen medio de plaquetas aumentó significativamente en los pacientes con retinopatía en comparación con aquellos sin retinopatía (*p = *0,04).*

Conclusión: *Este estudio mostró que el aumento de MPV está estrechamente relacionado con un control glicémico pobre, lo cual puede ser un factor de riesgo para la retinopatía diabética. Sin embargo, otros estudios prospectivos son necesarios para evaluar la relación entre MPV, los índices glicémicos, y las complicaciones microvasculares.*

Palabras claves: Diabetes mellitus, HbA1c, volumen medio de plaquetas, retinopatía

West Indian Med J 2013; 62 (6): 520

INTRODUCTION

Diabetes mellitus (DM) is a complex disease characterized by chronic hyperglycaemia, metabolic abnormalities and long term macro- and microvascular complications involving the blood vessels, eyes, kidneys and nerves. These complications are mainly due to hyperglycaemia and are responsible for the majority of morbidity and mortality associated with DM (1).

Fasting blood glucose (FBG), postprandial blood glucose (PBG) and haemoglobin A1c (HbA1c) are widely used to monitor glycometabolic control in patients with DM. Haemoglobin A1c is a more useful marker to determine mean blood glucose levels over a long time period (2, 3).

Diabetes mellitus is suggested as a prothrombotic state because platelet function and morphology are usually altered in these patients (4, 5). Mean platelet volume (MPV) is considered one of the important markers of platelet activation. It can be easily measured as part of whole blood count (6, 7). Whether MPV is related to glycometabolic markers such as FBG, PBG and HbA1c is unclear. There is a range of different data about this issue in the literature (8–13). Also, the relationship between MPV and diabetic microvascular complications remains to be clarified. Thus, the aim of this study was (i) to compare MPV between Type 2 diabetic patients and a non-diabetic control group, (ii) to analyse the correlations between MPV and FBG, PBG, HbA1c and other parameters in diabetic patients, (iii) to evaluate MPV according to HbA1c levels in the diabetic group, and (iv) to assess the difference in MPV between patients with and without microvascular complications.

SUBJECTS AND METHODS

Patients

This was a retrospective study conducted on 60 (40 female, 20 male) Type 2 diabetic patients and 50 age- and sex-matched non-diabetic controls. The patient and control groups were recruited from the outpatient clinic at the Department of Internal Medicine in Duzce University School of Medicine between August 2008 and November 2008. The control group was obtained from individuals without DM, as identified from their medical records. Patients were excluded if they had Type 1 or other types of DM, thrombotic or haematologic disorders, any medication affecting platelet function, serious cardiovascular, hepatic and renal disease, haemoglobin < 12.5 g/dL in men and < 11.5 g/dL in women, or a history of smoking and drinking. Controls were excluded if they had any types of DM and/or any exclusion criteria for the patient group. Type 2 DM was diagnosed according to the American Diabetes Association criteria (14).

Demographic and clinical characteristics of patients and controls were recorded from their medical records: age, gender, height, weight, systolic and diastolic blood pressure (BP), duration of disease and other medical history, medication, and laboratory data. The treatment of patients was as follows: 65% oral anti-diabetic drugs, 33% insulin, 28% angiotensin-converting enzyme inhibitor, 15% calcium channel blockers and 15% statin.

Laboratory

All biochemical, whole blood count and urine tests were performed at the Biochemistry Laboratory of Duzce University Medical Faculty. Blood samples were taken after an 8–12 hour period of fasting, in a sitting position. Samples for MPV and platelets collected using EDTA as anticoagulant were analysed on a Sysmex-xt-2000i auto-analyser. Biochemical tests were done following the manufacturer's recommendations on a Roche/Hitachi Diagnostic Systems cobas c 501. Glucose level was measured by the oxidase method (15). Haemoglobin A1c level was analysed by immunoturbidimetric inhibition method (16). Total cholesterol, triglyceride and high density lipoprotein (HDL) cholesterol were measured by commercial enzymatic methods (17–19). Low density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula (20).

Serum and urine creatinine levels were determined by the Jaffee method (21). Urinary albumin excretion was measured with the turbidimetric method (22). Urine albumin creatinine ratio (UACR) was calculated as mg/g in the morning first void urine.

Body mass index (BMI) was calculated as weight in kilogram by height in meters squared. Blood pressure was measured by a cuff-type sphygmomanometer device.

Korotkoff's first sound was recorded as systolic BP and Korotkoff's fifth sound was recorded as diastolic BP.

Diabetic retinopathy was diagnosed as follows: at least two microaneurysms and/or retinal haemorrhage, and findings of retinal damage (23). Diabetic nephropathy was defined as UACR between 30 and 300 mg/g in at least two of three analyses (24). Diabetic neuropathy was diagnosed according to the symptoms and physical examination of patients after excluding other reasons for neuropathy.

Statistical analysis

All analyses were performed using Statistical Package for Social Sciences (SPSS) version 15.0 for Windows. Data are expressed as mean ± standard deviation. One-sample Kolmogorov-Smirnov test was performed to prove the data distributions. Numerical variables were compared by the *t*-test or Mann-Whitney U test. Bivariate correlation analyses were made using the Pearson correlation test. Categorical variables were analysed by Chi-square test. Probability values were two-tailed, and a *p*-value of less than 0.05 was considered significant.

RESULTS

Clinical and demographic characteristics were similar in the patient and control groups except for MPV (Table 1). Mean platelet volume level was found to positively correlate with FBG and HbA1c levels. Mean platelet volume level was negatively related to platelet count. There was no significant correlation between MPV and PBG, duration of DM, lipid profile, creatinine, systolic and diastolic BP (Table 2).

When the patient group was divided into two groups according to their HbA1c levels (group 1: HbA1c ≤ 7 and group 2: HbA1c > 7), MPV levels in group 2 were higher than in group 1 ($p < 0.001$). However, platelet count was lower in group 2 than group 1 (Table 3). The ratio of diabetic microvascular complications including nephropathy, neuropathy and retinopathy was higher in group 2 than in group 1 (60% *vs* 23%; 50% *vs* 23%; 57% *vs* 23%; $p < 0.001$, $p = 0.03$ and $p = 0.01$, respectively).

Table 1: Demographic and clinical characteristics of the patient and control groups, presented as mean ± SD

Parameters	Patient group (n = 60)	Control group (n = 50)	*p*
Age (years)	53.67 ± 7.21	51.28 ± 8.86	0.12
Body mass index (kg/m^2)	30.62 ± 5.95	29.50 ± 4.34	0.28
MPV (fl)	10.91 ± 1.11	10.23 ± 1.02	0.001
Platelet (×10^3/μ)	247.85 ± 62.69	254.02 ± 60.57	0.60
Triglycerides (mmol/L)	2.15 ± 1.13	1.79 ± 0.81	0.06
Total cholesterol (mmol/L)	4.82 ± 0.87	4.99 ± 1.02	0.36
HDL-cholesterol (mmol/L)	1.17 ± 0.28	1.24 ± 0.26	0.15
LDL-cholesterol (mmol/L)	2.73 ± 0.93	2.90 ± 0.86	0.31
Creatinine (μmol/L)	58.72 ± 42.70	61.00 ± 14.48	0.30
Systolic blood pressure (mmHg)	128.67 ± 22.60	131.78 ± 16.40	0.41
Diastolic blood pressure (mmHg)	81.67 ± 8.31	80.90 ± 11.18	0.68

MPV: mean platelet volume, HDL: high-density lipoprotein, LDL: low-density lipoprotein

Table 2: The association between mean platelet volume and other parameters

Parameters	r	*p*
Age (years)	0.009	0.94
Body mass index (kg/m^2)	-0.115	0.38
Duration of DM (years)	0.137	0.29
Fasting glucose (mmol/L)	0.277	0.03
Postprandial glucose (mmol/L)	0.172	0.19
HbA1c (%)	0.486	< 0.001
Platelet (×10^3/μ)	-0.347	< 0.001
Triglycerides (mmol/L)	0.064	0.62
Total cholesterol (mmol/L)	0.209	0.10
HDL-cholesterol (mmol/L)	0.136	0.30
LDL-cholesterol (mmol/L)	0.186	0.15
Creatinine (μmol/L)	-0.211	0.10
Systolic blood pressure (mmHg)	-0.005	0.97
Diastolic blood pressure (mmHg)	-0.053	0.68

DM: diabetes mellitus, HbA1c: haemoglobin A1c, HDL: high-density lipoprotein, LDL: low-density lipoprotein

Table 3: Characteristics of the patients according to HbA1c levels, presented as mean ± SD

Parameters	HbA1c ≤ 7 (n = 30)	HbA1c > 7 (n = 30)	*p*
Age (years)	54.07 ± 7.44	53.27 ± 7.08	0.67
Body mass index (kg/m^2)	32.03 ± 6.33	29.20 ± 5.27	0.65
Duration of DM (years)	6.23 ± 4.51	9.03 ± 5.41	0.03
Fasting glucose (mmol/L)	8.58 ± 2.90	13.28 ± 4.22	< 0.001
Postprandial glucose (mmol/L)	12.14 ± 3.78	17.44 ± 4.74	< 0.001
MPV (fl)	10.29 ± 0.87	11.53 ± 0.96	< 0.001
Platelet (×10^3/μ)	268.43 ± 63.86	227.27 ± 55.16	0.01
Triglycerides (mmol/L)	2.04 ± 0.94	2.26 ± 1.29	0.44
Total cholesterol (mmol/L)	4.63 ± 0.83	5.02 ± 0.88	0.08
HDL-cholesterol (mmol/L)	1.12 ± 0.30	1.22 ± 0.24	0.16
LDL-cholesterol (mmol/L)	2.51 ± 0.92	2.95 ± 0.90	0.06
Systolic blood pressure (mmHg)	130.50 ± 16.20	126.83 ± 27.74	0.53
Diastolic blood pressure (mmHg)	82.00 ± 7.38	81.33 ± 9.27	0.75

HbA1c: haemoglobin A1c, DM: diabetes mellitus, MPV: mean platelet volume, HDL: high-density lipoprotein, LDL: low-density lipoprotein

Diabetic microvascular complications were present as follows: nephropathy in 25 patients (42%), neuropathy in 22 patients (37%) and retinopathy in 24 patients (40%). Mean platelet volume level was significantly increased in patients with diabetic retinopathy compared to those without retinopathy ($p = 0.04$). Mean platelet volume was higher in patients with nephropathy and neuropathy, but not statistically significant ($p = 0.34$ and $p = 0.09$, respectively) [Table 4].

Table 4: Mean platelet volume and diabetic microvascular complications

Parameters	Patients with microvascular complications	Patients without microvascular complications	*p*
Neuropathy	11.23 ± 0.95	10.73 ± 1.16	0.09
Nephropathy	11.07 ± 1.13	10.80 ± 1.09	0.34
Retinopathy	11.26 ± 1.08	10.68 ± 1.68	0.04

DISCUSSION

This study suggests that MPV is increased and associated with poor glycometabolic control and it may be related to retinopathy in Type 2 diabetic patients.

Platelet hyper-reactivity is known as a contributing factor to the prothrombotic condition in diabetic patients, along with increased coagulation, impaired fibrinolysis and endothelial dysfunction. Hyperglycaemia and insulin deficiency and resistance are suggested as important factors increasing platelet reactivity in these patients (25).

Mean platelet volume is a parameter to assess platelet size, and is a potential marker of platelet reactivity. It has been shown that larger platelets are more active than smaller platelets (26). Osmotic swelling owing to increased blood glucose and some glucose metabolites are suggested as possible mechanisms for an increased MPV in diabetic patients (27).

There are several studies indicating the positive relationship between MPV and glycaemic indices, especially FBG and HbA1c (11, 12, 28). On the other hand, some studies have shown that MPV is not related to FBG and HbA1c (8–10, 13). Mean platelet volume is found to correlate with duration of diabetes in one study (9), but not in another (13). Therefore, it has been proposed that the increase in MPV is due to diabetic status alone (10).

In our study, MPV in diabetic patients was higher than in the non-diabetic control group as usually noted in the literature. Moreover, there was a positive correlation between MPV and FBG and HbA1c, but not between MPV and duration of DM and PBG. We found that MPV was significantly higher in patients with HbA1c > 7% compared to those with HbA1c ≤ 7%, which may indicate the importance of glycaemic control in platelet reactivity. Demirtunc *et al* reported that MPV significantly decreased after improved glycaemic control (12). This is a very important result because (i) it suggests that the increase in MPV may be associated with osmotic swelling of platelets and not diabetic status alone, and (ii) the potential role of platelets in the development of diabetic vascular complications may be attenuated by a decrease in MPV.

An inverse relationship is described between MPV and platelet count, reflecting the tendency to keep haemostasis by preserving a constant platelet mass (29). We found that MPV was inversely related to platelet count. Moreover, platelet count in patients with HbA1c > 7% was significantly lower than those with HbA1c ≤ 7%. This result supports the opinion that an enhanced destruction and osmotic swelling of platelets may affect this relationship (30).

Hypertension is known as one of the diseases enhancing platelet activity. Mean platelet volume is usually increased in patients with elevated systolic BP and target organ damage (31). Mean platelet volume is not associated with systolic and diastolic BP in the present study. It has been reported that BP control is related to decreasing MPV (30). Renin-angiotensin system blockade with medication and a well-controlled BP in our patients may be a reason for this result.

Micro- and macrovascular complications are often seen in DM and represent the main causes of morbidity and mortality, which are closely associated with glycaemic control (32). Mean platelet volume is usually established to associate with macrovascular complications such as myocardial infarction and restenosis after percutaneous coronary intervention (26).

There are different results about the relationship between MPV and diabetic microvascular complications in the literature. Mean platelet volume was not found to be different between patients with and without microvascular complications (12, 13). However, it was shown that MPV is significantly related to diabetic nephropathy in other studies (8, 9). Furthermore, MPV was determined to be associated with retinal neovascularization of diabetic retinopathy (33).

We found that MPV in patients with diabetic retinopathy was significantly higher compared to those without diabetic retinopathy. Moreover, MPV is higher in patients with nephropathy and neuropathy than those without nephropathy and neuropathy, but not statistically significant. This result has shown that MPV may be a target to prevent diabetic retinopathy.

Despite several important findings in the present study, it has some limitations including its relatively small sample size and retrospective design. The difference in MPV between patients with and without neuropathy was close to the significance level. This difference might be found statistically significant in a larger sample size. Furthermore, more useful information about the relationship between MPV and diabetic microvascular complications would have been provided if the study had been designed prospectively.

In conclusion, this study has shown that (i) MPV is increased in diabetic patients, (ii) it is associated with the degree of glycaemic control and (iii) MPV is increased in patients with diabetic retinopathy. However, further prospec-

tive studies with larger samples are needed, especially to investigate the relationship between MPV and diabetic microvascular complications and their progression.

REFERENCES

1. Powers AC. Diabetes mellitus. In: Kasper DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. New York: McGraw Hill; 2012: 2968−3003.
2. Marshall SM, Barth JH. Standardization of HbA1c measurements: a consensus statement. Diabet Med 2000; **17:** 5−6.
3. McCane DR, Hanson RL, Charles MA, Jacobsson LTH, Pettitt DDJ, Bennett PH et al. Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. BMJ 1994; **308:** 1323−8.
4. Papanas N, Symeonidis G, Maltezos E, Mavridis G, Karavageli E, Vosnakidis T et al. Mean platelet volume in patients with type 2 diabetes mellitus. Platelets 2004; **15:** 475−8.
5. Bath PM, Missouris CG, Buckenham T, MacGregor GA. Increased platelet volume and platelet mass in patients with atherosclerotic renal artery stenosis. Clin Sci 1994; **87:** 253−7.
6. Bath PM, Butterworth RJ. Platelet size: measurement, physiology and vascular disease. Blood Coagul Fibrinolysis 1996; **7:** 157−61.
7. Thompson CB, Jakubowski JA. Platelet size as a determinant of platelet function. J Lab Clin Med 1983; **101:** 205−13.
8. Ünübol M, Ayhan M, Güney E. The relationship between mean platelet volume with microalbuminuria and glycemic control in patients with type II diabetes mellitus. Platelets 2012; **23:** 475–80. doi: 10.3109/09537104.2011.634934. Epub 2011 Nov 29.
9. Bavbek N, Kargili A, Kaftan O, Karakurt F, Kosar A, 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:** 391−7.
10. Sharpe PC, Trinick T. Mean platelet volume in diabetes mellitus. Q J Med 1993; **86:** 739−42.
11. Dalamaga M, Karmaniolas K, Lekka A, Antonakos G, Thrasyvoulides A, Papadavid E et al. Platelet markers correlate with glycemic indices in diabetic, but not diabetic-myelodysplastic patients with normal platelet count. Dis Markers 2010; **29:** 55−61.
12. 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:** 89−94.
13. Hekimsoy Z, Payzin B, Ornek T, Kandoğan G. Mean platelet volume in Type 2 diabetic patients. J Diabetes Complications 2004; **18:** 173−6.
14. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004; **27:** S5−S10.
15. Kunst A, Draeger B, Ziegenhorn J. Monosaccharides and derivatives. In: Bergmeyer HU, ed. Methods of enzymatic analysis. 3rd ed. Volume VI. Metabolites 1: Carbohydrates. Weinheim, Germany: Verlag Chemie; 1984: 163−72.
16. Zander R, Lang W, Wolf HU. Alkaline haematin D-575, a new tool for the determination of haemoglobin as an alternative to the cyanhaemiglobin method. I. Description of the method. Clin Chim Acta 1984; **136:** 83−93.
17. Greiling H, Gressner AM, eds. Lehrbuch der Klinischen Chemie und Pathobiochemie, 3rd ed. Stuttgart/New York: Schattauer; 1995.
18. Sugiuchi H, Uji Y, Okabe H, Irie T, Uekama K, Kayahara N et al. Direct measurement of high-density lipoprotein cholesterol in serum with polyethylene glycol-modified enzymes and sulfated α-cyclodextrin. Clin Chem 1995; **41:** 717−23.
19. Wahlefeld AW, Bergmeyer HU, eds. Methods of Enzymatic Analysis. 2nd English ed. New York, NY: Academic Press Inc; 1974: 1831.
20. Friedewald WF, Levy RI, Frederickson DS. Estimation of LDL-cholesterol concentration without use of the preparative ultracentrifuge. Clin Chem 1972; **18:** 499−502.
21. Fabiny DL, Ertinghausen G. Automated reaction-rate method for determination of serum creatinine with the CentrifiChem. Clin Chem 1971; **17:** 696−700.
22. Multicenter study of Tina-quant albumin in urine and β-N-acetyl-glucosaminidase (β-NAG) in urine. Workshop Munich, November 29–30, 1990. Wien klin Wschr 1991; **103 (Suppl 189):** 1−64.
23. Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD et al. Diabetic retinopathy. Diabetes Care 2003; **26 (Suppl 1):** s99−s102.
24. Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH et al; American Diabetes Association. Nephropathy in diabetes. Diabetes Care 2004; **27 (Suppl 1):** S79−S83.
25. Ferreiro JL, Gómez-Hospital JA, Angiolillo DJ. Platelet abnormalities in diabetes mellitus. Diab Vasc Dis Res 2010; **7:** 251−9.
26. 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:** 148−56.
27. Martyn CN, Matthews DM, Popp-Snijders C, Tucker J, Ewing DJ, Clarke BF. Effects of sorbinil treatment on erythrocytes and platelets of persons with diabetes. Diabetes Care 1986; **9:** 36−9.
28. Shah B, Sha D, Xie D, Mohler ER 3rd, Berger JS. The relationship between diabetes, metabolic syndrome, and platelet activity as measured by mean platelet volume: The National Health and Nutrition Examination Survey, 1999–2004. Diabetes Care 2012; **35:** 1074−8.
29. Thompson CB, Jakubowski JA. The pathophysiology and clinical relevance of platelet heterogeneity. Blood 1988; **72:** 1−8.
30. Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des 2011; **17:** 47−58.
31. Boos CJ, Beevers GD, Lip GY. Assessment of platelet activation indices using the ADVIATM 120 amongst 'high-risk' patients with hypertension. Ann Med 2007; **39:** 72−8.
32. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; **321:** 405−12.
33. Zhong ZL, Han M, Chen S. Risk factors associated with retinal neovascularization of diabetic retinopathy in type 2 diabetes mellitus. Int J Ophthalmol 2011; **4:** 182−5.