

Review

Mean Platelet Volume in Different Clinical Conditions with Special Reference to Diabetes and its Complications – A Short Review

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ABSTRACT

Platelets play a major role in integrity of normal haematopoiesis, and mean platelet volume (MPV) is an indicator for its function. The large platelets contain more dense granules are more potent than smaller platelets and hence more thrombogenic. Both the size and number of granules in platelets in circulation are under independent hormonal control and do not change during the life span of the platelet. Increase in MPV has been documented in patients with metabolic syndrome, stroke and diabetes mellitus (DM). Many studies have shown that increased MPV is one of the risk factors for myocardial infarction, cerebral ischemia and transient ischemic attacks. On the contrary, MPV is decreased in bone marrow failure. Both the situations are critical because high MPV can lead to blood clot formation and a low MPV may lead to bleeding or bruising. MPV, therefore, can be used as an important, effortless, simple and cost – effective tool for assessing functions of platelets and for predicting risk of cardiovascular diseases and the possibility of impending micro-vascular complications in diabetes mellitus.

KEYWORDS: Cardiovascular diseases, Mean platelet volume, Atherosclerosis, Diabetic complications, Metabolic syndrome

INTRODUCTION

Platelets play a major role in normal haematopoiesis, and mean platelet volume (MPV) is an indicator for its function¹. The large platelets contain more dense granules are more potent than smaller platelets and hence more thrombogenic¹. Both the size and number of granules in platelets in circulation are under independent hormonal control and do not change during the life span of the platelet^{2,3}. MPV is regarded as a marker for thrombosis,

atherosclerosis, and inflammation in various vascular diseases. Not only this, a recent study has focused that MPV level is independently associated with cerebral white matter hyper intensities in non-stroke individuals⁴.

Increase in MPV has been documented in patients with metabolic syndrome, stroke and diabetes mellitus (DM)⁵. Altered platelet morphology and function have been reported in patients with DM, and MPV was found to be significantly higher in diabetic patients^{6,7}. Many studies

have shown that increased MPV is one of the risk factors for myocardial infarction, cerebral ischemia and transient ischemic attacks⁸⁻¹².

Larger platelets are haemostatically more active and are a risk factor for developing coronary thrombosis, leading to myocardial infarction. Elevated MPV is associated with a worse outcome for acute ischemic cerebrovascular events independent of other clinical parameters¹³.

Mean platelet volume is a marker of platelet size which increases in type-2 diabetes mellitus. By altering the platelet morphology and its activity by increasing production of prothrombotic factors such as thromboxane A₂, which play an independent risk factor for atherothrombosis, MPV play a significant role in microvascular complications of diabetic patients⁵. It has also been observed that there is a strong association between a low vitamin D level and a high MPV¹⁴.

PLATELETS

Platelets are small nucleate cells that play a critical role in haemostasis and Thrombosis¹⁵. Platelets were described by Addison in 1841 as extremely minute granules in clotting blood. They were termed platelets by Bizzozero, who observed their adhesive qualities as increased stickiness when a vascular wall is damaged. Platelets play a major role in integrity of normal haematopoiesis, and mean platelet volume (MPV) is an indicator for its function. The large platelets contain more dense granules and are more potent than smaller platelets and hence more thrombogenic¹.

MEAN PLATELET VOLUME (MPV)

Measurement of peripheral blood platelet counts tells little about platelet related haemostatic function unless the platelet count is particularly low. However, most hematology analyzers measure another platelet parameter, the mean platelet volume which can give useful clinical and patho-physiological information about patients and vascular diseases. +MPV is a new and independent risk factor for atherothrombosis. Studies have shown that increased MPV is a risk factor for myocardial infarction, cerebral ischemia, and transient ischemic attacks events. Also recent studies have documented a significant increase in platelet-leukocyte aggregates in diabetics¹⁶.

PHYSIOLOGY OF PLATELET SIZE

MPV appears to be a marker, or even a determinant, of platelet function. Large platelets are more reactive than small platelets in vitro. They preferentially and more rapidly aggregate to platelet agonist including ADP, collagen and adrenaline produce more prothrombotic and vasoactive factors including arachidonic acid metabolites (e.g. Thromboxane A₂), serotonin, β -thromboglobulin and ATP, contains more dense granules, and have higher LDH activity¹⁶. MPV correlates with

platelet aggregation, whether measured in platelet rich plasma or whole blood, populations of subjects or in some disease states, e.g., Diabetes mellitus. Large platelets also express increased levels of adhesion molecules like P-selectin, GPIIb/IIIa, although the surface density of these glycoproteins is usually constant, independent of platelet volume¹⁶.

MEASUREMENT OF PLATELET VOLUME

The optimal method for measuring platelet volume utilises changes in either electrical impedance (as used in Coulter haematology analysers) or light diffraction (as used by Technicon) when a platelet passes through an arrow aperture. Alternative and less satisfactory methods include semi-quantitative measurement of diameter on platelet smears, or using flow cytometry¹⁶.

In the Coulter series, cell shield in fluid suspension are flown through a small aperture, thereby creating a change in voltage proportional to particle size. A raw histogram is generated, and a log-normal curve is fitted to the data. Platelet count is derived from this together with the MPV, which is calculated by numerical integration. Similarly, the Sysmex measures parameters with cells in fluid suspension, although in addition the cells are hydro-dynamically focused, ensuring that cells travel in a straight line through the aperture. This prevents cells flowing through attached of the aperture and causing spurious changes in the electrical field. It also differs from Coulter in that the upper and lower discriminators are both mobile¹².

In contrast, Technicon instruments uses laser-optic technology to measure the size and granularity of cells in suspension. A beam of light is passed through cells, and the amount of forward scatter is proportional to size of particles, whereas side scatter equates to density or granularity. A platelet histogram is derived from the data, and MPV is calculated as the mode. Differences of up to 40% have been found when Coulter and Technicon results have been compared¹².

Complete blood count specimens are usually ant coagulated in EDTA which causes platelet to swell in a time dependent manner. Most of the increase in MPV occurs during the first 1.5 hr but the process continues over the next 24 hrs. EDTA is thought to increase intracellular cyclic AMP and change plasma membrane permeability¹². This situation is further complicated since analysers utilising light diffraction measure particle size by assessing optical density. These analysers record decreasing MPV with times in platelet swelling results in a lower optical density. As a result, studies reporting raw MPV measurements made in EDTA are of questionable clinical or research value unless MPV is assessed data consistent time following phlebotomy, or once the swelling has ceased at 24 hrs. In contrast MPV measured in high concentration sodium citrate does not change with time and hence is considered as the gold standard¹⁶.

NORMAL VALUES FOR MPV¹⁶

The normal range for mean platelet volume has yet to be adequately determined, but studies show that MPV in normal subjects ranges from 7 – 11.7 fl. The day to day variation in MPV is small (CV=2.1%) compared with platelet count. (CV = 6.1%). Both the size and number of granules in platelets in circulation are under independent hormonal control and do not change during the life span of the platelets^{2,3}.

ALTERATIONS IN MPV¹⁷

High MPV may be due to cancer, cardiac disease etc. and low MPV may mean that the bone marrow is not functioning well and not producing enough new platelets; therefore, most of the platelets are old.

Causes of High MPV

- Cancer
- Massive hemorrhage
- Hyperthyroidism
- Diabetes
- Vitamin D deficiency
- Heart disease
- Hypertension

Causes of Low MPV

- Aplastic anemia
- Lupus
- Chemotherapy
- Hypothyroidism
- Iron deficiency anemia
- HIV/AIDS
- Autoimmune diseases
- Alcohol use disorders
- Genetic conditions

Cancer with high MPV – Gastric, Breast, Endometrium, Thyroid and Lung cancer.

Cancer with low MPV – Renal cell carcinoma, Gall bladder cancer.

Implication of altered MPV¹⁷

High MPV can lead to increased tendency of blood clotting. It is because of larger platelets which are more active. Increase in blood clotting poses a risk of stroke and deep vein thrombosis.

Low MPV, on the other hand, brings the situation of more bruising and/or bleeding. The reason behind the bruising is that older platelets, which are smaller, may not work properly.

MPV AND AGE

It used to be thought that the platelet size decreased with age, but more recent evidence suggests that MPV and other platelet parameters and therefore platelet protein content and reactivity, are determined primarily at or before thrombopoiesis by the platelet precursor cell, the MK³⁰. Khalid et al.³¹ concluded that Increased MPV was found in a significant number of patients and was more in the males and patients with age greater than 50 years¹⁸.

MPV AND GENDER

Gender dependent differences in platelet count have been demonstrated in few studies. Butkiewicz et al.³² conducted a study on healthy blood donors divided into groups: 60 women and 65 men. No statistically significant differences were found in the mean platelet volume, though there was a slight increase in females¹⁹.

MPV AND HYPERTENSION

Coban et al. selected 36 essential hypertensive patients, 36 white coat hypertensive subjects and 36 normotensive control subjects matched for age, gender, and body mass index. MPV was very significantly higher in essential hypertensives and white coat hypertensives than in normotensives ($P < 0.00$); it was also higher in essential hypertensives than in white coat hypertensives ($P < 0.05$). MPV was positively correlated with ambulatory diastolic blood pressure in essential hypertension and white coat hypertension groups ($P < 0.05$)²⁰.

MPV AND METABOLIC SYNDROME

Giuseppe Lippi et al. performed a retrospective analysis. Cumulative results for MPV, FPG, HDL and triglycerides were retrieved for 3337 outpatients & gt; 35 years of age over the 2 year period. The mean MPV of subjects with all biochemical markers suggestive of the metabolic syndrome was slightly higher but not significantly different from that of control subjects, i.e., 8.7 fL (95% CI 7.7, 9.6) versus 8.6 fL (95% CI 7.5, 9.6), respectively ($p = 0.119$)²¹.

MPV AND SMOKING

Butkiewicz et al. designed a study to assess platelet parameters in smoking healthy subjects with reference to sex. In the group of women, 27% were smokers, in the group of men 49%. Irrespective of gender the smoking did not have any effect on

the following parameters: mean platelet volume, percentage of large platelets, concentration of thrombopoietin, absolute count of reticulated platelet and concentration of thromboglobulin.

Slavka et al.³⁵, in their study concluded that increased MPV may carry increased risk of mortality due to ischemic heart disease which was as much as that due to smoking or obesity²².

MPV AND ISCHEMIC HEART DISEASE

Khandekar et al.²³ studied a total of 210 cases, 94 patients had unstable angina (UA) or acute myocardial infarction (AMI), 70 patients had stable coronary artery disease (stable CAD) or were admitted for a coronary angiography or coronary artery bypass graft procedure and 30 age and sex matched healthy controls with no history of heart disease and a normal electrocardiogram. Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), and Platelet Large Cell Ratio (P-LCR)—were significantly raised in patients with AMI and UA (mean MPV, 10.43 (SD, 1.03) fL; mean PDW, 13.19 (SD, 2.34) fL; mean P-LCR, 29.4% (SD, 7.38%) compared with those with stable CAD (mean MPV, 9.37 (SD, 0.99) fL; mean PDW, 11.35 (SD, 1.95) fL; mean P-LCR, 22.55% (SD, 6.65%) and the control group (mean MPV, 9.2 (SD, 0.91) fL; mean PDW, 10.75 (SD, 1.42) fL; mean P-LCR, 20.65% (SD, 6.14%).

Agrawal et al.²⁴ concluded that MPV was significantly higher in patients with AMI in comparison to the control subjects. However, there was no significant difference in MPV values of patients with ST elevation and non ST elevation MI. When atherosclerotic plaque ruptures or erodes; platelets are recruited to the exposed sub endothelial region and partially occluded vessel becomes completely occluded with the newly formed thrombus. Larger platelets have greater prothrombotic potential and are biologically more potent. Increased platelet volume has been shown to be more reactive with greater production of thromboxane A₂, and serotonin. These are mechanisms by which platelets contribute to development of myocardial infarction via platelet mediated vasoconstriction and inflammation.

In fact Huczek et al.²⁵ observed that abciximab (GPIIb/IIIa antagonist) reduced mortality significantly only in patients of myocardial infarction who had high MPV.

Martin et al. also found that greater MPV correlated with subsequent mortality and nonfatal myocardial reinfarction²⁶.

Pereg et al. revealed that thrombolytic failure rate in STEMI was significantly higher in patients with high MPV²⁷.

MPV AND STROKE

Bath et al. in a sub-study of The Perindopril Protection against Recurrent Stroke Study (PROGRESS) trial followed 3134 individuals for an average of 3.9 years and assessed the

association of MPV with the risk of stroke. MPV was positively associated with the risk of stroke, with an 11% increased relative risk (95% CI, 3% to 19%) of stroke per femtoliter greater MPV. There was no clear association of MPV with the risk of major coronary events (9% decreased relative risk; 95% CI, 23% to 7%). Perindopril did not alter MPV. This study concluded that MPV is an independent predictor of the risk of stroke among individuals with a history of stroke or transient ischemic attack²⁸.

Shahab et al. concluded that Increased MPV has been observed as independent of other established determinants and have seen the association of ischemic stroke with increased MPV in diabetic patients. However, this doesn't apply to haemorrhagic strokes or strokes of unknown etiology¹⁸.

MPV IN TYPE 2 DIABETES MELLITUS

Kodiatte et al. studied 166 male diabetics and 89 female diabetics in the study (255 in total). There were 145 non-diabetic males and 106 non-diabetic females in the study (251 in total). MPV was higher in diabetics compared to the non-diabetic subjects [8.29 ± 0.74 fl versus 7.47 ± 0.73 fl (P= 0.001), respectively. MPV showed a strong positive correlation with FBS, PPBS and HbA1C levels (P=0.001). No statistical correlation was seen between MPV and the duration of DM, BMI and the vascular complications in the diabetic group. In the diabetic group, the mean MPV in subjects with complications (8.35 ± 0.73 fl) were higher than that of subjects without complications (8.2 ± 0.74 fl) but independent student t-test did not show any statistical significance²⁹.

Hekimsoy et al. studied MPV in diabetics. MPV was measured in 145 consecutive Type 2 diabetic patients and 100 non-diabetic control subjects. MPV was significantly higher in diabetics compared to non-diabetic healthy controls [10.62 ± 1.71 fl vs. 9.15 ± 0.86 fl (P=.00)], respectively⁷.

Yenigün et al.³⁰ evaluated MPV in patients with type II diabetes mellitus (DM) and its association with diabetic microvascular and macrovascular complications. A total of 48 patients with type II DM and 30 age and gender matched healthy subjects constituted the study population. 12 of the diabetics (25 %) had macrovascular complications, 26 patients (54.2 %) had HT, 15 patients (31.3 %) had retinopathy, 16 patients (33.3 %) had nephropathy and 39 patients (81.2 %) had neuropathy. Mean HbA1c was 8.73 ± 2. MPV was significantly higher in patients with type II DM than the healthy controls (9.25 ± 1.49 and 8.47 ± 0.49, respectively) (p < 0.01). The diabetic patients were divided into subgroups depending on the presence of microvascular complications. Patients with at least one of the microvascular complications had slightly higher MPV compared to the ones without any of the complications (9.38 ± 1.47 fl and 7.85 ± 0.88 fl, respectively) (p= 0.048). In type II diabetic patients there was no association between MPV and age, duration of diabetes, lipid profile, HbA1C, and FBS^{30,31}.

MECHANISM

Platelets from patients with diabetes express more surface P-selectin and glycoprotein (GP) IIb/IIIa receptors leading to the initial step in platelet aggregation, that is adhesion of platelets or platelet shape change. This platelet shape change is reflected in change of mean platelet volume and are more sensitive to agonist stimulation than platelets from patients without diabetes³². Platelets in DM have dysregulated signaling pathways that lead to an increased activation and aggregation in response to a given stimulus (platelet hyper-reactivity)^{33,34}. DM has been considered as a “prothrombotic state” with increased platelet reactivity³⁵. Platelet hyperactivity has been reported in diabetics and animals, both in vivo and in vitro^{36,37}.

Platelet hyper-reactivity and increased baseline activation in patients with diabetes is Multifactorial^{38,39}. It is associated with biochemical factors such as hyperglycemia and hyperlipidaemia, insulin resistance, an inflammatory and oxidant state and also with increased expression of glycoprotein receptors and growth factors. Hyperglycemia can increase platelet reactivity by inducing non enzymatic glycation of proteins on the surface of the platelet, by the osmotic effect of glucose and activation of protein kinase C. Such glycation decreases membrane fluidity and increases the propensity of platelets to activate platelet function which is directly regulated by insulin via a functional insulin receptor (IR) found on human platelets^{33,34,39}.

In vivo experiments have confirmed that insulin inhibits platelet interaction with collagen and attenuates the platelet aggregation effect of agonists in healthy non-obese individuals.

In inflammation, superoxide increases intraplatelet release of calcium after their activation and thus enhancing platelet reactivity. Superoxide limits the biologic activity of nitric oxide (NO) because the oxidative stress impairs endothelial function that reduces production of NO and prostacyclin. Decreasing the effect of NO brings about increased platelet reactivity^{33,34,39}.

Platelet activation contributes to the pathology by triggering thrombus formation and causing microcapillary embolization with the release of constrictive, oxidative, and mitogenic substances such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) that accelerate progression of local vascular lesions like the neovascularization of lens in diabetic retinopathies³².

Larger platelets are younger, more reactive and aggregable. Hence, they contain denser granules, secrete more serotonin and β -thromboglobulin, and produce more thromboxane A₂ than smaller platelets^{39,40,41}. All these can produce a pro-coagulant effect and cause thrombotic vascular complications. There might be small bleeds due to the rupture of atherothrombotic plaques leading to increased platelet recruitment, hyper reactivity, and bone marrow stimulation. Hyperglycemia leads to a compatible osmolyte hypothesis in which there is injurious shift of the intracellular electrolytes and water into the platelets due to accumulation of sorbitol,

myoinositol and taurine. This shift may increase the volume of the platelets. High MPV is emerging as a new risk factor for the vascular complications of DM of which atherothrombosis plays a major role¹³.

MPV AND DIABETIC RETINOPATHY

Diabetic retinopathy (DR) is the most common and specific microangiopathy of diabetes mellitus (DM)⁴². There are clearly defined risk factors for DR, such as hyperglycemia, hypertension, dyslipidaemia, and diabetes duration⁴³. It has also shown that functional and structural changes in retinal arterioles are also a risk factor for DR⁴⁴.

Mardiya Sari et al. found that PDR group had the highest MPV value compared than NPDR and normal fundoscopy group and also explained in diabetics sustained hyperglycemia leads to a series of interrelated alterations that can cause endothelial dysfunction and vascular lesion in diabetic complications. Formation of advanced glycation end products, activation of protein kinase C and disturbance in polyol pathways are mechanisms by which increased glucose induces vascular abnormalities⁴⁵.

It can be explained because DM is a prothrombotic that chronically activate platelets, activate the coagulation system and decrease the ability of fibrinolysis. These phenomena, together with impaired prostanoid metabolism, phosphoinositide turn over and enhanced calcium mobilization contribute to enhanced risk of small vessel occlusions⁴⁵.

MPV value above the upper limit normal suggests that platelets in the circulation were younger, bigger and more reactive to aggregate because it will secrete more serotonin, α -thromboglobulin and produce more thromboxane A₂ than normal platelets. This will produce a procoagulant effect and lead to vascular complications⁴⁵.

Orhan et al. concluded that Occlusions and micro aneurysms result in hypoxia in diabetic retinopathy which is a strong stimulus for new vessel formation. Vascular endothelial growth factor, which is released in response to hypoxia, strongly induces neovascularization. Platelet-derived growth factor, transforming growth factor-beta, epidermal growth factor, insulin like growth factor-1, growth hormone and basic fibroblast growth factor induce collagen synthesis and cause proliferative retinopathy via neovascularization. However, significantly increased levels of MPV in proliferative retinopathy suggest that growth factors released from activated platelets indirectly contribute to the disease progression⁴⁰.

Several studies have demonstrated that, platelets accumulate in retinal vasculature and induce the release of local growth factors by causing inflammation. In another study, an increased level of platelet derived growth factor in vitreous fluid of patients with proliferative DRP has been shown⁴⁶.

MPV AND DIABETIC NEPHROPATHY

Microalbuminuria is one of the earliest markers of diabetic nephropathy. Microalbuminuria (MA), a reversible phase of diabetic nephropathy, is also a disease risk, independent of risk factors both traditional (e.g., hypertension) and non-traditional (e.g., C-reactive protein).

Bayram et al. found that MPV levels were significantly higher in patients with T2DM having microalbuminuria than in the controls⁴⁷.

Zdrojewski et al., demonstrated non-diabetic patients with glomerular disease, spontaneous thrombocyte aggregation and MPV values were found to be increased⁴⁸.

Yarlioglu et al. demonstrated with primary hypertensives, urine albumin/creatinine ratio was found to be correlated with MPV⁴⁹.

Turgutalp et al. demonstrated positive correlation with serum creatinine and negative correlation with glomerular filtration rate with MPV in their diabetic nephropathic patients⁵⁰.

In Bavbek et al. study with type 2 diabetics, Creatinine Clearance in patients with high MPV values was lower than in patients with normal and low MPV values, and there was no difference between patients with normal and low MPV values⁵¹.

MPV AND DIABETIC NEUROPATHY

Papans et al., concluded that mean platelet volume was significantly ($p=0.03$) higher in patients of group A (cases) (15.2 ± 1.6 fl) than in those of group B (control) (11.3 ± 1.1 fl) and no association was observed in neuropathic patients between MPV and severity of neuropathy. Indeed, diabetes mellitus is thought to cause major disruption of severe metabolic and vascular mechanisms which contribute to development of neuropathy. For this reason despite some evidence of small role for platelet activation in pathophysiology of neuropathy there is much more to be determined⁵².

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REFERENCES

- Shetty A, Vijaya C, Jayalakshmi VJ, Lekha MB. Comparison of Mean Platelet Volume, Platelet Count, Total Leucocyte and Neutrophil Co in Normoglycemics, Impaired Fasting Glucose and Diabetics. *Int J Sci St* 2014; 2(2):24-27.
- Mangalesh S., Dudani S., Malik A. Platelet indices and their kinetics predict mortality inpatients of sepsis. *Indian J. Hematol. Blood Trans.* 2021; 37 (4): 600-608.
- Gao Y., Li Y., Yu X., Guo S., et al. The impact of various platelet indices as prognostic markers of septic shock. *PLOS ONE*. 2014; 9(8):e103761.
- Choi, J W, Lee K O, Jang Y J, Kim H K et al. High mean platelet volume is associated with cerebral white matter hyperintensities in non-stroke individuals. *Yonsei Med J*. 2023; 64(1): 35-41.
- Tavil Y, Sen N. Yarici HU, Hiral F. Abaci A, Cengel A. Mean platelet volume in patients with metabolic syndrome and its relationship with coronary artery disease. *Thromb Res* 2007; 120-245-50.
- Papanas N. Symeonidis G. Maheros E, Mavridis G., Karavageli E, Vonakidis T. Lakasas G. Mean platelet volume in patients with type 2 diabetes mellitus *Platelets* 2004; 15:475-8.
- Hekimsay Z. Payzin B. Ormek T. Kandoğan G. Mean platelet volume in Type 2 diabetic patients. *J Diabetes Complications* 2004; 18:173-6.
- Khandekar MM. Khurana AS. Deshmukh SD, Kakrani AL., Katdare AD Inamdar AK. Platelet volume indices in patients with coronary artery disease and acute myocardial infarction: an Indian scenario. *J Clin Pathol* 2006c 59:146-9.
- Kiliçli-Camur N. Demirtung R. Konuralp C. Eskiser A, Başaran Y. Could mean platelet volume be a predictive marker for acute myocardial infarction, *Med Sci Monit* 2005, 11:CR387-92.
- Nadar SK, Lip GY. Blann AD. Platelet morphology, soluble P selectin and platelet P-selectin in acute ischaemic stroke. The West Birmingham Stroke Project. *Thromb Haemost* 2004; 92:1342-8.
- McCabe DJ, Harrison P. Sidhu PS, Brown MM, Machin SJ. Circulating reticulated platelets in the early and late phases after ischaemic stroke and transient ischaemic attack. *Br J Haematol* 2004; 126:861-9.
- O'Malley T, Langhorne P, Elton RA, Stewart C. Platelet size in stroke patients. *Stroke* 1995; 26:995-9.
- 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): 114-116.
- Cure MC, Cur E, Yuce S, Yazici T et al. Mean platelet volume and vitamin D level. *Ann Lab Med*. 2014; 34: 98-103.
- Boulton AJM, Gries FA, Jervell JA. Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. *Diabet Med* 1998; 15:508-514.

16. Bath PMW, Butterworth RJ. Platelet size: measurement, physiology and vascular disease. *Blood* 1996;7:157-61.
17. Briggs C, Bain B J. Mean platelet volume in Dacie and Lewis Practical Hematology. 12th Ed. 2017.
18. Shahab K. Mehr MT. Marwat MA. Amanullah. Quantification of mean platelet volume in diabetic patients presenting with cerebrovascular diseases. *J Postgrad Med Inst* 2016; 30(3): 268-71.
19. Butkiewicz AM, Kemona H. Dymicka-Piekarska V. Matowicka-Karna J. Radziwon P and Lipska A. Platelet count, mean platelet volume and thrombocytopoietic indices in healthy women and men. *Thrombosis Research* 2006; 118(2):199-204.
20. Coban E, Yazicioglu G, Berkant AA, Akcıt F. The Mean Platelet Volume in patients with essential and white coat hypertension. *Platelets* 2005, 16(7):435-4.
21. Lippi G. Salvagno GL. Targher G and Guidi GC. Relationship between Mean Platelet Volume and Biochemical Components of metabolic syndrome. *Clin Drug Invest* 2007;27(10): 731-732.
22. Slavka, G., Perkmann, T., Haslacher, II., Greisenegger, S., Marsik, C., Wagner O. F. and Endler, G. (2011). Mean platelet volume may represent a predictive parameter for overall vascular mortality and ischemic heart disease *Arterioscler Thromb Vasc Biol*, 31, 1215-8.
23. Khandekar MM, Khurana AS, Deshmukh S D, Kakrani AL, Katdare AD. Inamdar AK. Platelet volume indices in patients with coronary artery disease and acute myocardial infarction: an Indian scenario. *J Clin Pathol* 2006; 59: 146-149.
24. Agrawal, BK., Manchanda, B., Garg, A., Mittal, A., Mahajan, NC. and Agrawal, U. Mean platelet volume in acute myocardial infarction: a case- controlled study *Journal of Cardiovascular Research*, 2015;1:4.
25. Huczek, Z, Kochman, J., Filipiak, K. J., Horszczaruk, G. J., Grabowski, M. Piatkowski, R., Wilczynska, J., Zielinski, A., Meier, B. and Opolski, G. Mean platelet volume on admission predicts impaired reperfusion and long- term mortality in acute myocardial infarction treated with primary percutaneous coronary intervention. *J Am Coll Cardiol* 2005; 46,284-90.
26. Martin, J., Bath, PMW. and Borr, ML. Increased platelet size following myocardial infarction is associated with subsequent death and non-fatal reinfarction. *Lancet*. 1991;1-409-1411.
27. Pereg, D., Berlin, T. and Mosseri, M. Mean platelet volume on admission correlates with impaired response to thrombolysis in patients with ST- elevation myocardial infarction: *Platelets* 2010;117-21.
28. Bath P, Algert C. Chapman N. Neal B. Association of mean platelet volume with risk of stroke among 3134 individuals with history of cerebrovascular diseases. *Stroke* 2004; 35: 622-626.
29. Kodiatte T A, Manikyam Y K, Rao S B, et al. Mean Platelet Volume in Type 2 Diabetes Mellitus. *J Lab Physicians* 2012 Jan-Jun: 4(1):5.9.
30. Yenigün E C, Okyay G U, Pirpir A, et al. Increased mean platelet volume in type 2 diabetes mellitus *Dicle Medical Journal* 2014; 41(1):17-22.
31. Sharpe P C, Trinick T. Mean platelet volume in diabetes mellitus. *The Quarterly journal of medicine* 11/1993; 86(11):739-42.
32. Yngen M. Norhammar A. Hjemdahl P. Wallén NH. Effects of improved metabolic control on platelet reactivity in patients with type 2 diabetes mellitus following coronary angioplasty. *Diab Vase Dis Res* 2006-312-6.
33. Schneider DJ. Factors contributing to increased platelet reactivity in people with diabetes. *Diabetes Care* 2009, 32:525-7.
34. Kakouros N. Rade JJ. Kourliouros A, Resar JR. Platelet function in patients with diabetes mellitus, from a theoretical to a practical perspective *Int Endocrinol*. 2011.
35. Jindal S, Gupta S, Gupta R. Kakkar A, Singh HV, Gupta K, et al. Platelet indices in diabetes mellitus: indicators of diabetic microvascular complications. *Hematology* 2011;16:86-9.
36. Bern MM. Platelet functions in diabetes mellitus. *Diabetes* 1978;27:542-50.
37. Bae SH, Lee J, Roh KH. Kim J. Platelet activation in patients with diabetic retinopathy. *Korean J Ophthalmol* 2003, 17:140-4.
38. Colwell JA, Nesto RW. The platelet in diabetes-focus on prevention of ischemic events. *Diabetes Care* 2003;26:2181-8.
39. Vinik AI, Erbas T, Park TS, Nolan R, Pittenger GI. Platelet dysfunction in type 2 diabetes. *Diabetes Care* 2001; 24:1476-85.
40. Orhan A, İlhami K, Habip B, Mustata K, et al. Association of Mean Platelet Volume with the Degree of Retinopathy in Patients with Diabetes Mellitus *European Journal of General Medicine* 2009, 6(2):99-102.
41. Chang HA. Hwang HS. Park HK. Chun MY. Sung JY. The Role of Mean Platelet Volume as a Predicting Factor of Asymptomatic Coronary Artery Disease. *Korean J Fam Med*. 2010.31.600-6.
42. Mohamed Q. Gillies MC, Wong TY. Management of diabetic retinopathy, a systematic review *JAMA* 2007, 298.902-916.

43. Cheung N, Mitchell A, Wong TY. Diabetic retinopathy. *Lancet* 2019, 376 124-136.
44. Curtis TM, Gardiner TA, Stitt AW. Microvascular lesions of diabetic retinopathy: clues towards understanding pathogenesis. *je* 2009, 23: 1496- 1508.
45. Sari M, Lindarto D, and Gator D. Mean platelet volume increases in proliferative retinopathy among diabetes mellitus subjects. *Uniy Med* 2014;33:43-8.
46. Citirik M et al. MPV may reflect subclinical platelet activation in diabetic patients with and without diabetic retinopathy. *JAMA* 2001, 111.
47. Bayram S M,et al. The relationship of mean platelet volume with microalbuminuria in type 2 diabetic patients. *Turk Med Sci.* (2016) 46:251- 258.
48. Zdrojewski Z, Lizakowski S, Raszeja-Specht A, Skibowska A, Rutkowski B Influence of spontaneous thrombocyte aggregation on progression of glomerular disease. *Nephron* 2002, 92: 36-42.
49. Yarlioglues M, Kaya MG, Ardic I, Dogdu O. et al. Relationship between mean platelet volume levels and subclinical target organ damage in newly diagnosed hypertensive patients. *Blood Pres* 2011;20: 92-97.
50. Turgutalp K, O'zhan O, Akbay E, Tombak A. et al. Mean platelet volume and related factors in patients at different stages of diabetic nephropathy: a preliminary study. *Appl .Thromb. Hemost.* 2014; 20: 190-195.
51. Bavbek N, Kargılı 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: 391-397.
52. Papanas N, Mavridis G, Karavageli E, Symeonidis G, Maltezos E. Peripheral neuropathy is associated with increased mean platelet volume in type 2 diabetic patients. *Platelets*, 2005 Dec: 16(8):498-9.