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Clinical Evaluation of the Mean Platelet Volume in Patients Diagnosed with Type 2 Diabetes Mellitus and Correlation with the Condition

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Abstract
Mean Platelet Volume (MPV) is an indicator of the average size and activity of platelets. Larger platelets contain more dense granules and hence are more potent and thrombogenic. This suggests a relationship between the platelet function especially MPV and diabetic vascular complications thus indicating changes in MPV reflect the state of thrombogenesis. The data of MPV value in diabetics and their association with vascular complications are scarse in India. Hence based on above findings the present study was planned for clinical evaluation of the mean platelet volume in patients diagnosed with type 2 diabetes mellitus and correlation with the condition.
The present study was planned in Anugrah Narayan Magadh Medical College, Gaya, Bihar From Jan 2017 to july 2017. Total 100 cases of diabetes and 50 cases of the normal patients were enrolled in the present study. In the 100 diabetes patients were divided as per the with complication and without complications. MPV and platelet counts were measured in the above subjects using an automated blood counter. The blood glucose (fasting, post-prandial) levels and HbA1c levels were also measured along with urine for microalbuminuria.
The data generated from the present study concludes that MPV is increased in Diabetes mellitus (DM) and that platelets become more reactive and agreeable. The increased platelet size may be a risk factor for atherosclerosis associated with DM and its vascular complications. Hence, MPV would be a useful prognostic marker of cardio-vascular complications in Diabetes mellitus (DM).

Keywords: Mean Platelet Volume (MPV), Diabetes mellitus, Type II, etc

Introduction
Type 2 diabetes (T2D), formerly known as adult-onset diabetes, is a form of diabetes that is characterized by high blood sugar, insulin resistance, and relative lack of insulin [6]. Common symptoms include increased thirst, frequent urination, and unexplained weight loss [3]. Symptoms may also include increased hunger, feeling tired, and sores that do not heal [3]. Often symptoms come on slowly. Long-term complications from high blood sugar include heart disease, strokes, diabetic retinopathy which can result in blindness, kidney failure, and poor blood flow in the limbs which may lead to amputations. The sudden onset of hyperosmolar hyperglycemic state may occur; however, ketoacidosis is uncommon [1].
Type 2 diabetes primarily occurs as a result of obesity and lack of exercise. Some people are more genetically at risk than others. Type 2 diabetes makes up about 90% of cases of diabetes, with the other 10% due primarily to type 1 diabetes and gestational diabetes. In type 1 diabetes there is a lower total level of insulin to control blood glucose, due to an autoimmune induced loss of insulin-producing beta cells in the pancreas. Diagnosis of diabetes is by blood tests such as fasting plasma glucose, oral glucose tolerance test, or glycated hemoglobin (HbA1C) [2].
Type 2 diabetes is largely preventable by staying a normal weight, exercising regularly, and eating properly [1]. Treatment involves exercise and dietary changes. If blood sugar levels are not adequately lowered, the medication metformin is typically recommended. Many people may eventually also require insulin injections. In those on insulin, routinely checking blood sugar levels is advised; however, this may not be needed in those taking pills. Bariatric surgery often improves diabetes in those who are obese [3].
Rates of type 2 diabetes have increased markedly since 1960 in parallel with obesity. As of 2015 there were approximately 392 million people diagnosed with the disease compared to around 30 million in 1985. Typically it begins in middle or older age, although rates of type 2 diabetes are increasing in young people. Type 2 diabetes is associated with a ten-year-shorter life expectancy. Diabetes was one of the first diseases described. The importance of insulin in the disease was determined in the 1920s [4].
The classic symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss. Other symptoms that are commonly present at diagnosis include a history of blurred vision, itchiness, peripheral neuropathy, recurrent vaginal infections, and fatigue. Many people, however, have no symptoms during the first few years and are diagnosed on routine testing. A small number of people with type 2 diabetes can develop a hyperosmolar hyperglycemic state (a condition of very high blood sugar associated with a decreased level of consciousness and low blood pressure) [5].
Type 2 diabetes is typically a chronic disease associated with a ten-year-shorter life expectancy. This is partly due to

a number of complications with which it is associated, including: two to four times the risk of cardiovascular disease, including ischemic heart disease and stroke; a 20-fold increase in lower limb amputations, and increased rates of hospitalizations. In the developed world, and increasingly elsewhere, type 2 diabetes is the largest cause of nontraumatic blindness and kidney failure. It has also been associated with an increased risk of cognitive dysfunction and dementia through disease processes such as Alzheimer's disease and vascular dementia. Other complications include acanthosis nigricans, sexual dysfunction, and frequent infections. There is also an association between type 2 diabetes and mild hearing loss [6].

The development of type 2 diabetes is caused by a combination of lifestyle and genetic factors. While some of these factors are under personal control, such as diet and obesity, other factors are not, such as increasing age, female gender, and genetics. Obesity is more common in women than men in many parts of Africa. A lack of sleep has been linked to type 2 diabetes. This is believed to act through its effect on metabolism. The nutritional status of a mother during fetal development may also play a role, with one proposed mechanism being that of DNA methylation. The intestinal bacteria Prevotella copri and Bacteroides vulgatus have been connected with type 2 diabetes [7].

Type 2 diabetes is due to insufficient insulin production from beta cells in the setting of insulin resistance. Insulin resistance, which is the inability of cells to respond adequately to normal levels of insulin, occurs primarily within the muscles, liver, and fat tissue. In the liver, insulin normally suppresses glucose release. However, in the setting of insulin resistance, the liver inappropriately releases glucose into the blood. The proportion of insulin resistance versus beta cell dysfunction differs among individuals, with some having primarily insulin resistance and only a minor defect in insulin secretion and others with slight insulin resistance and primarily a lack of insulin secretion [8].

Other potentially important mechanisms associated with type 2 diabetes and insulin resistance include: increased breakdown of lipids within fat cells, resistance to and lack of incretin, high glucagon levels in the blood, increased retention of salt and water by the kidneys, and inappropriate regulation of metabolism by the central nervous system. However, not all people with insulin resistance develop diabetes, since an impairment of insulin secretion by pancreatic beta cells is also required [8].

The World Health Organization definition of diabetes (both type 1 and type 2) is for a single raised glucose reading with symptoms, otherwise raised values on two occasions, of either:[49] fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) or with a glucose tolerance test, two hours after the oral dose a plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

A random blood sugar of greater than 11.1 mmol/l (200 mg/dl) in association with typical symptoms [23] or a glycated hemoglobin (HbA1c) of ≥ 48 mmol/mol (≥ 6.5 DCCT %) is another method of diagnosing diabetes. In 2009 an International Expert Committee that included representatives of the American Diabetes Association (ADA), the International Diabetes Federation (IDF), and the European Association for the Study of Diabetes (EASD) recommended that a threshold of ≥ 48 mmol/mol (≥ 6.5 DCCT %) should be used to diagnose diabetes. This recommendation was adopted by the American Diabetes Association in 2010. Positive tests should be repeated unless the person presents with typical symptoms and blood sugars >11.1 mmol/l (>200 mg/dl) [9].

Threshold for diagnosis of diabetes is based on the relationship between results of glucose tolerance tests, fasting glucose or HbA1c and complications such as retinal problems. A fasting or random blood sugar is preferred over the glucose tolerance test, as they are more convenient for people. HbA1c has the advantages that fasting is not required and results are more stable but has the disadvantage that the test is more costly than measurement of blood glucose. It is estimated that 20% of people with diabetes in the United States do not realize that they have the disease [10].

Type 2 diabetes is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. This is in contrast to type 1 diabetes in which there is an absolute insulin deficiency due to destruction of islet cells in the pancreas and gestational diabetes that is a new onset of high blood sugars associated with pregnancy. Type 1 and type 2 diabetes can typically be distinguished based on the presenting circumstances. If the diagnosis is in doubt antibody testing may be useful to confirm type 1 diabetes and C-peptide levels may be useful to confirm type 2 diabetes, with C-peptide levels normal or high in type 2 diabetes, but low in type 1 diabetes [11].

Mean platelet volume (MPV) is a machine-calculated measurement of the average size of platelets found in blood and is typically included in blood tests as part of the CBC. Since the average platelet size is larger when the body is producing increased numbers of platelets, the MPV test results can be used to make inferences about platelet production in bone marrow or platelet destruction problems. MPV is higher when there is destruction of platelets. This may be seen in inflammatory bowel disease, immune thrombocytopenic purpura (ITP), myeloproliferative diseases and Bernard-Soulier syndrome. It may also be related to pre-eclampsia and recovery from transient hypoplasia. Abnormally low MPV values correlate with thrombocytopenia when it is due to impaired production as in aplastic anemia. In addition, low MPV can correlate with abnormally small platelet size, sometimes a symptom of a spectrum referred to as Wiskott-Aldrich Syndrome (WAS), caused by a genetic mutation of the WAS gene. Sample for MPV testing is obtained in a Lavender-Top EDTA tube. A typical range of platelet volumes is 9.4–12.3 fL (femtolitre), equivalent to spheres 2.65 to 2.9 μm in diameter [12].

Mean Platelet Volume (MPV) is an indicator of the average size and activity of platelets. Larger platelets contain more dense granules and hence are more potent and thrombogenic. This suggests a relationship between the platelet function especially MPV and diabetic vascular complications thus indicating changes in MPV reflect the state of thrombogenesis. The data of MPV value in diabetics and their association with vascular complications are scarse in India. Hence based on above findings the present study was planned for clinical evaluation of the mean platelet volume in patients diagnosed with type 2 diabetes mellitus and correlation with the condition.

Methodology:

The present study was planned in Anugrah Narayan Magadh Medical College, Gaya, Bihar from jan 2017 to July 2017. Total 100 cases of diabetes and 50 cases of the normal patients were enrolled in the present study. In the 100

diabetes patients were divided as per the with complication and without complications. MPV and platelet counts were measured in the above subjects using an automated blood counter. The blood glucose (fasting, post-prandial) levels and HbA1c levels were also measured along with urine for microalbuminuria.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: Patients already diagnosed with Type 2 DM and Non-diabetic patients without known coronary artery disease, cerebrovascular disease, peripheral vascular disease; Age between 20 – 80 yrs.

Exclusion Criteria: Male patients with hemoglobin below 13g% and female patients below 12g% (nutritional anemia can be a reason for reactive thrombocytosis and hence increased MPV); Patients with abnormal haematocrit and/or abnormal white blood cell count and/or abnormal platelet number; Non diabetics with coronary artery disease, cerebrovascular disease, peripheral vascular disease and diabetics on antiplatelet drugs like aspirin and clopidogrel; Subjects diagnosed with any malignancy.

Results & Discussion:

The vascular complications in DM patients pose higher risk of morbidity and mortality. Patients with type 2 DM usually develop early interruption of endothelial functions, hyper-activation of platelets and progressive atherosclerosis [13]. This is one of the suggested mechanisms of atherosclerosis among diabetics. Increased platelet reactivity leads to enhanced platelet volume [14] due to altered platelet size and density. MPV refers to the average of the size of the platelets in the blood [15].

The MPV and platelet counts are not only indicators of thrombotic potential, but also risk factors for microvascular complications in diabetics [16-18]. Such platelets synthesize more thromboxane A2, are able to aggregate better, and are able to secrete more serotonin and β- thromboglobulin than regular platelets [19-20].

Diabetic patients have an increased risk of developing micro- and macrovascular disease, and platelets may be involved as a causative agent with respect to altered platelet morphology and function.[21] DM is characterized by the prothrombotic state of platelets which owes to the persistent hyperglycemia and insulin resistance, causing injury to pericytes and endothelium. The increased platelet activity is believed to play a vital role in the development of vascular complications of this metabolic disease.[22]

Microvascular complications, retinal lesions, microalbuminuria, and proteinuria have been described as factors that are predictive of cardiovascular and cerebrovascular morbidity and mortality among diabetic subjects.[23] Hence, if detected early, microvascular complications would alert us regarding the increased risk of cardiovascular and cerebrovascular complications. Thus, microvascular complications were chosen to be studied in this study.

In the present study diabetics group had significantly higher MPV than the non-diabetic group. This is similar to findings seen in studies done by Hekimsoy *et al*, Demirtunc *et al*., Zuberi *et al*., Ates *et al*., Jindal *et al*., Papanas *et al*., and Kodiatte *et al*. [24-26] Higher values of MPV were observed in our study among the diabetic subjects with microvasular complications such as Retinopathy and Microalbuminuria which was statistically significant.

Higher values were also seen in studies done by Papanas *et al* and Ates *et al*. [28-29] This suggested a role for the increased platelet activity in the pathogenesis of vascular complications. On the contrary, in the studies done by Hekimsoy *et al* and Demirtunc *et al*., [25-29] MPV was not significantly different in subjects with diabetics complications. Their possible explanation was centered on the rapid consumption of activated platelets in diabetic without complications.

Table 1: Demographic Details

Parameter	Summary
Age	42 – 68 years
Males Females	96 54
Duration of diabetes	3 – 6 years
Diabetes History	
· Known Case	85
· Recently Diagnosed	65

Table 2: Platelet Volume in Different Groups

Group	DM with complication	DM without complication	Normal Cases
No. of Cases	50	50	50
Mean platelet volume	11.5 ± 1.6	9.81 ± 1.7	8.35 ± 1.2
Platelet distribution width	14.8 ± 3.6	13.5 ± 3.2	15.2 ± 2.4
Platelet large cell ratio	25.6 ± 5.6	23.9 ± 4.5	24.02 ± 4.2

Table 3: Complications Observed

Group	No. of Cases	Mean platelet volume (MPV)	Platelet distribution width (PDW)	Platelet large cell ratio (PLCR)
Diabetic retinopathy	20	11.3 ± 1.5	14.8 ± 3.5	26.8 ± 4.5
Nephropathy	9	11.3 ± 1.8	15.5 ± 3.8	25.9 ± 6.3
Neuropathy	8	11.5 ± 2.1	14.3 ± 3.5	24.3 ± 5.2
Coronary Artery Disease	14	10.8 ± 1.6	15.1 ± 2.9	27.9 ± 3.9
Peripheral Vascular Disease	1	10.9 ± 1.7	12.8 ± 3.9	24.2 ± 6.8
Diabetic foot	2	12.1 ± 2.1	14.5 ± 3.6	29.5 ± 5.7

Sustained hyperglycemia leads to a series of interrelated alterations that can cause evident endothelial dysfunction and vascular lesions in diabetic complications. Formation of advanced glycation end products, activation of protein

kinase C and disturbances in polyol pathways are the possible mechanisms by which increased glucose induces vascular abnormalities. [30]

Kakouros N *et al* suggested that hyperglycemia causes to generate larger platelets and abnormal platelet-endothelial interactions have been identified as an essential pathogenic mechanism in the development of atherosclerosis. [31] The patients with type 2 DM have larger platelets that are more reactive and agreeable. Some authors speculated that vascular complications in diabetes should be consequence of increased platelet activity. Activated platelets tends to be larger in diameter resulting in elevation in MPV. [32] MPV is found to be significantly higher in diabetic patients, thereby playing role in the micro- and macro vascular complications. Although several measurements of platelet activity have been emerged as potential contributors to athero thrombosis, many of these measurements are time-consuming, expensive, uses high sample volume, or require speciality training. [33-34] Alternatively Mean Platelet Volume (MPV), a marker of platelet size is easily determined on routine automated hemograms and routinely available at a relatively low cost. [35-36] MPV is a simple and cost effective tool which can be explored for predicting the acute vascular events in patients suffering from diabetes mellitus.

The platelet function and its size are said to be related to each other. Larger platelets are highly active and have more dense granules, secrete more prothrombotic factors e.g. thromboxane A2, thromboxane B2, platelet factor 4, serotonin, and platelet-derived growth factor than smaller sized platelets and hence cause increased tendency to thrombotic events. [37-41] Platelet hyperactivity in DM is also attributed to hyperglycemia as it is postulated that large sized platelets may form because of persistent and unregulated blood sugar levels. This seems to occur through certain mechanisms such as nonenzymatic protein glycation of these platelets and also osmotic effect of glucose and protein kinase C activation.

Regarding the limitations of our study, the lack of controls and a relatively smaller sample might lessen the significance of the findings observed in the study population. Also assessing the patients from a single institution might limit the generalizability of the study findings.

Conclusion:

The data generated from the present study concludes that MPV is increased in Diabetes mellitus (DM) and that platelets become more reactive and agreeable. The increased platelet size may be a risk factor for atherosclerosis associated with DM and its vascular complications. Hence, MPV would be a useful prognostic marker of cardio-vascular complications in Diabetes mellitus (DM).

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