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Correlation of Mean platelet volume as an indicator of platelet hyperactivity in Diabetics and Non diabetic subjects

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Abstract: Diabetes mellitus is a global pandemic. The increased platelet activity may play a role in the development of vascular complications of this metabolic disorder. The Mean platelet volume (MPV) is an indicator of the average size and activity of platelets. Larger platelets are younger and exhibit more activity. Large platelets are more thrombogenic and thus put the patient at higher risk of Micro & Macro vascular complications. Mean platelet volume is a determinant of platelet functionality and increased MPV is associated with risk of Myocardial infarction, Stroke and Transient ischemic attack. This study was conducted to compare MPV in diabetic patients and non-diabetic controls.

Keywords: Diabetes Mellitus, Mean Platelet volume, Thromboxane, Thromboembolism, Ischemia, Platelet hyper activity

INTRODUCTION

The term Diabetes mellitus (DM) describes a group of metabolic disorders which is characterized by persistent hyperglycemia, with disturbance of carbohydrate, protein and fat metabolism resulting from defect in insulin secretion or insulin action or both [1]. DM is a leading public health problem with increasing incidence and long term complications such as diabetic nephropathy, diabetic neuropathy, diabetic retinopathy etc. These complications are mainly a consequence of macrovascular and microvascular damages of the target organs [2]. However, the major cause of morbidity and mortality in diabetes mellitus is macrovascular complications such as cardio vascular diseases. The patients with diabetes mellitus have two to four fold increased risk of coronary artery disease, peripheral arterial disease, and stroke compared with non-diabetic subjects [3].

Diabetes increases the risk of atherothrombotic phenomenon. Platelets in individuals with diabetes show increased activity, ultimately leading to increased aggregation [4]. The main physiological function of platelets is to maintain hemostasis by the initiation and formation of a hemostatic plug and by secretion of various biologically active factors leading to the repair of vascular injuries [5]. Increased expression of platelet surface adhesion molecules and receptors, enhanced production of Thromboxane and thrombin and disturbances in platelet Ca^{2+} homeostasis are well documented in diabetes mellitus [6]. It may be hypothesized that platelets, acting in concert with the vascular endothelium, leukocytes and coagulation play a key role in the development of diabetic angiopathy[7]. It has been reported that predominantly large platelets circulate in patients with diabetes mellitus. Larger platelets are more potent than smaller platelets and are hence chromogenic [8]. Larger and younger platelets are considered to be more reactive. The Mean platelet volume (MPV) is the indicator for platelet function [9]. Increase in MPV has been observed in patients with metabolic syndrome, stroke and diabetes mellitus. Increased MPV is one of the risk factor for myocardial infarction, cerebral ischemia and transient ischemic attacks. Patients with larger platelets can easily be identified during routine hematological analysis and could possibly benefit from preventive treatment.

METHODOLOGY

Mean platelet volume (MPV) test was conducted in 30 diabetic patients and 30 non-diabetic

subjects of age between 30-65 years after obtaining written and informed consent. The study was approved by institutional ethics committee. The following tests were performed to assess platelet hyper activity in diabetes mellitus:

Estimation of blood glucose

The blood glucose levels are estimated in diabetic subjects. Both fasting and post-prandial blood glucose levels are estimated in the Clinical Biochemistry laboratory with biochemical analyzer (Humalyser) by the method of GOD – POD (Glucose oxidase and peroxidase).2 ml of blood is taken into a tube which contains sodium fluoride which acts as an anticoagulant. It is mixed with anticoagulant and the tubes are centrifuged at 3000 RPM for 15 min to separate the plasma. 5 µl of plasma is mixed with GOD – POD reagent in a test tube and keep the tubes for 10 min in a water bath at 37^0C. After 10 min, the reaction mixture is aspirated by the analyzer and results were obtained.The analyzer is working on the principle of "Beer – Lambert's law".

Determination of mean platelet volume (MPV)

The MPV is the determinant of platelet functionality. MPV is a measurement of average size of platelets. MPV is determined by using automated hematological analyzer. Here, we are using the Beckman colter 5 parts differential analyzer.For determination of MPV; we have to take 2 ml of blood by venipuncture by using aseptic conditions. Then the blood is mixed with the anticoagulant. The anticoagulant used here is ethyl diamine tetra acetate (EDTA) or sodium citrate. After mixing the blood with anticoagulant, sample will be aspirated by analyzer. In analyzer the blood sample is mixed with the diluent. The machine will count the number of platelets and measures their size and the MPV is reported as the average size of platelets on the display.

Determination of Platelet count

Determination of platelet count was done by using Beckman colter 5 parts differential analyzer. The blood was collected by veni puncture by using aseptic conditions and the blood was mixed with anti-coagulant. The anticoagulant used here is ethyl diamine tetra acetate (EDTA) or sodium citrate.

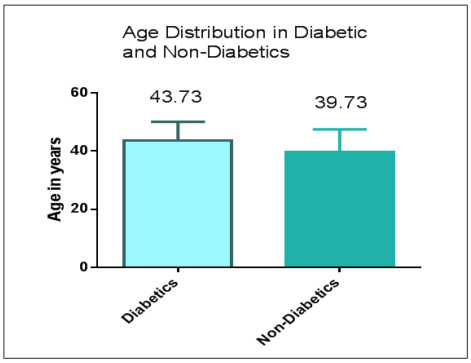
RESULTS

The results of the above tests were compared between the cases (diabetics) and healthy age matched controls (Non diabetics). Values are expressed as mean ± Std. Deviation in the tables.

Table-1: **Showing age Distribution in Diabetics and Non-Diabetics**

Status of Diabetes	Numbers	Mean(years)	Std.Deviation	P value
Diabetics	30	43.73	6.330	0.0325
Non-Diabetics	30	39.73	7.746	

Table 1: Age distribution in Diabetics and Non-Diabetics. The mean age for Diabetics is 43.73 and for Non-Diabetics it is 39.73

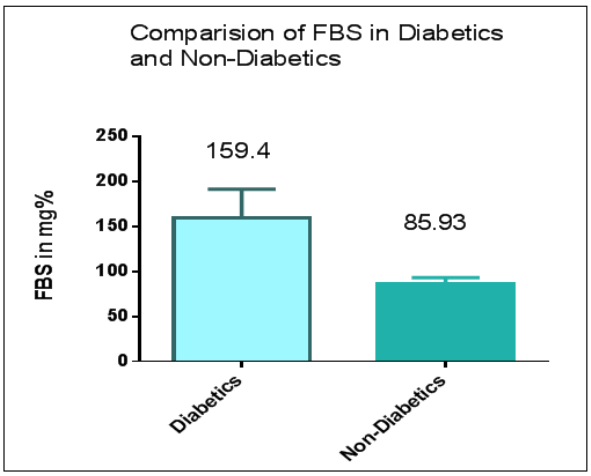


Graph-1: Age distribution in Diabetics and Non-Diabetics. The mean age for Diabetics is 43.73 and for Non-Diabetics it is 39.73.

Table-2: **showing FBS values in Diabetics and Non-Diabetics**

Status of Diabetes	**Number**	**Mean**	**Std. Deviation**	**P value**
Diabetic	30	159.4	32.214	<0.0001****
Non-Diabetic	30	85.93	7.386	

Table 2: Fasting blood glucose (FBS) values in Diabetic and Non-Diabetics

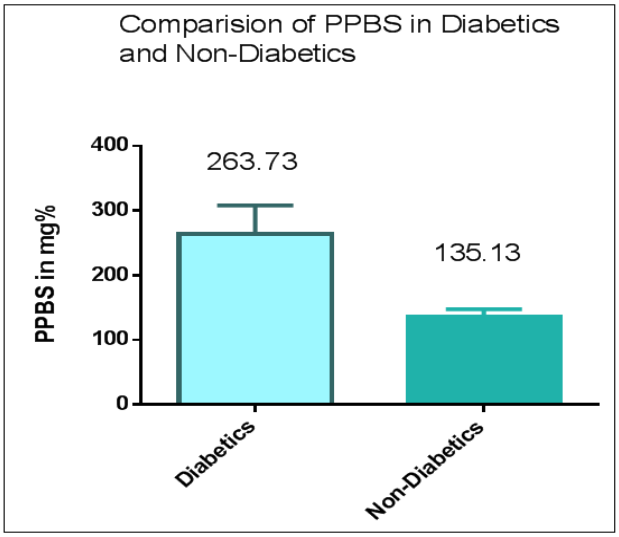


Graph-2: FBS values in Diabetics and Non-Diabetics. FBS values are more in Diabetics and the values are statically significant. (p value = <0.0001)

Table-3: showing PPBS in Diabetics and Non-Diabetics

Status of Diabetes	Number	Mean	Std.Deviation	P value
Diabetics	30	263.73	44.268	<0.0001****
Non-Diabetics	30	135.13	12.230	

Table 3: Post prandial blood glucose (PPBS) in Diabetics and Non-Diabetics

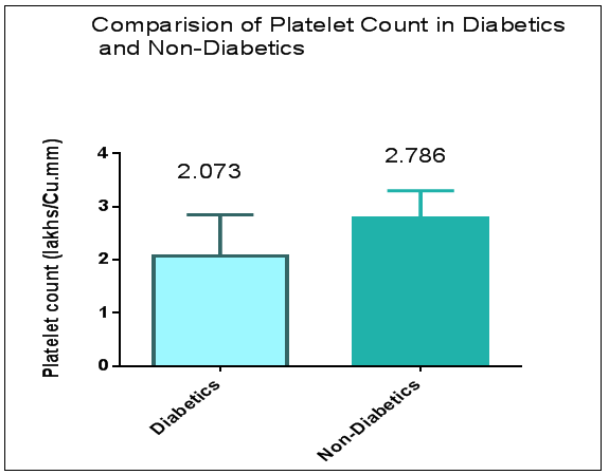


Graph-3: PPBS in Diabetics and Non-Diabetics. The PPBS values are high in Diabetics and the values are statistically significant (p value =<0.0001)

Table-4: showing Platelet Count in Diabetics and Non-Diabetics

Status of Diabetes	Number	Mean	Std.Deviation	P value
Diabetics	30	2.073	0.777	0.0001***
Non-Diabetics	30	2.786	0.519	

Table 4: Platelet Count in Diabetics and Non-Diabetics

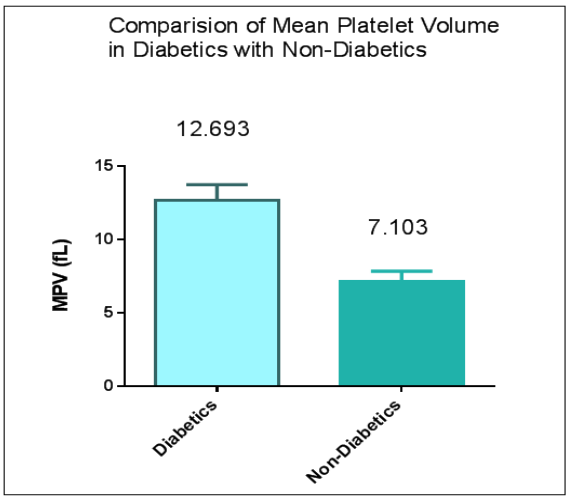


Graph-4: Platelet Count in Diabetics and Non-Diabetics. Platelet Count is high in Non-Diabetics and the values are statistically significant (p value =0.0001).

Table-5: **showing Mean Platelet Volume (MPV) in Diabetics and Non-Diabetics**

Status of Diabetes	Number	Mean	Std.Deviation	P value
Diabetics	30	12.693	1.069	< 0.0001***
Non-Diabetics	30	7.103	0.746	

Table-5: Mean Platelet Volume in Diabetics and Non-Diabetics.



Graph-5: Mean Platelet Volume in Diabetics and Non-Diabetics. The Mean Platelet Volume is high in Diabetics and the values are statistically significant (p value = < 0.0001).

DISCUSSION

Diabetes Mellitus is a complex metabolic syndrome characterized by chronic hyperglycemia resulting in complications affecting the peripheral nerves, kidneys, eyes, and micro and macro vascular structures. The prevalence of all types of diagnosed diabetes in most western societies is 3-7%. Kodiatte TA, *et al*. reporting Countries with the highest absolute number of diabetics are India (19million), China (16million), and the United States (14million). The prevalence of diabetic micro vascular complications is higher in people with poor glycemic control, longer duration of diabetes mellitus, associated hypertension, and obesity [10]. Zimmet P. *et al*. shows this leads to increased morbidities and mortalities in diabetes mellitus. Diabetes and its vascular complications can cause a financial havoc; become a burden to a country's national economy and its growth. India, having the highest number of diabetics, faces such issues [11]. Ferroni P *et al.* reporting mean platelet volume canbe used as a simple economical test in the monitoring of DM and thereby help to decrease the morbidity and mortality. Sustained hyper glycemia leads to a series of inter related alterations that can cause evident endothelial dysfunction and vascular lesions in diabetic complications [12]. Formation of advanced glycation

end products and activation of protein kinase C are the possible mechanisms by which increased glucose induces vascular abnormalities.

Stegner D, *et al*. Platelets are small discoid blood cells that circulate and participate in hemostasis. Primary plug formation due to platelets seals the vascular defects and provides the required phospholipid surface for the recruited and activated coagulation factors[13]. In response to stimuli generated by the endothelium of blood vessels, platelets change shape, adhere to sub endothelial surfaces, secrete the contents of intracellular organelles, and aggregate to form a thrombus. These pro aggregator stimuli include thrombin, collagen, epinephrine, ADP (dense storage granules), and thromboxane A2 (activated platelets). Thus, platelets may assume an important role in signaling of the development of advanced atherosclerosis in diabetes. MPV is an indicator of the average size and activity of platelets. Larger platelets are younger, more reactive and aggregable. Hence, they contain denser granules, secrete more serotonin and β-throm boglobulin, and produce more thromboxane A2 than smaller platelets. All these can produce a pro-coagulant effect and cause thrombotic vascular complications. High MPV is emerging as a new risk factor for the vascular complications of DM of which atherothrombosis plays a major role. Thus, DM has been considered as a "prothrombotic state" with increased platelet reactivity. Platelet hyperactivity has been reported in diabetics.

Platelet hyper reactivity and increased baseline activation in patients with diabetes is multi factorial. Kakouros N, *et al.*[14] It is associated with biochemical factors such as hyperglycemia and hyper lipidemia, 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 is directly regulated by insulin via a functional insulin receptor (IR) found on human platelets. 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. Tousoulis D *et al.* shows inflammation of superoxide increases intra platelet release of calcium after their activation, thus enhancing platelet reactivity. Furthermore, superoxide limits the biologic activity of nitric oxide (NO) because the oxidative stress impairs endothelial function that reduces production of NO and prostacyclin[15]. Decreasing the effect of NO brings about increased platelet reactivity. Platelets from patients with diabetes express more surface P-selectin and glycoprotein (GP) IIb/IIIa receptors and are more sensitive to agonist stimulation than platelets from patients without diabetes. Platelets in DM have dysregulated signaling pathways that lead to an increased activation and aggregation in response to a given stimulus (platelet hyper-reactivity). 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 neo vascularization of lens in diabetic retinopathies.

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