Original Article

Platelet Count, Mean Platelet Volume, Serum Creatinine And Delayed Clotting Time As Surrogate Markers Of Type 2 Diabetes Mellitus

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ABSTRACT

Diabetes Mellitus is a metabolic syndrome characterized by hyperglycemia resulting in complications affecting the nerves, kidneys, eyes and micro- and macrovascular structures. It has been suggested that abnormal platelet functions and endothelial damage may play a role in pathogenesis of microangiopathy in diabetes mellitus. Platelet size is predictor for recurrent myocardial infarction. Abnormalities of mean platelet volume have been observed in diabetics. Aims: This study evaluates platelet count and mean platelet volume correlated to fasting blood sugar, postprandial blood sugar, body mass index, serum creatinine and clotting time and duration of diabetes mellitus. This study been carried out prior to the onset of vascular complications and can be used as a diagnostic & prognostic test in the management of diabetes mellitus. Method: About 1000 diabetics were screened and 60 uncomplicated type 2 diabetes mellitus patients were selected & compared to 60 healthy subjects. Blood was drawn for estimation of blood sugar. The platelet count & mean platelet volume was estimated by using cell Dyne 1700 automatic cell analyzer. Result: The mean platelet volume was correlated to fasting blood sugar (r-0.6755 & p<0.0001) and post prandial blood sugar (r-0.5416 & p<0.0001) which is highly significant as compared to controls. There was significant increase in p value for clotting time (p<0.04254 & r 0.1048), serum creatinine (p 0.0333 & r-0.2757). Mean platelet volume showed no significant correlation with body mass index (p 0.0517 & r-0.2525) nor with duration of diabetes (p 0.731 & r-0.979). Platelet count from uncomplicated NIDDM showed no significant rise as compared to normal healthy controls. Conclusion: Mean platelet volume, serum creatinine and delayed clotting time can be taken as surrogate markers of type 2 diabetes mellitus.

1. Introduction

"Diabetes is a mysterious illness." This statement made in antiquity by Aerates of Cappadocia is still valid today that is 1900 years later, in the sense that the cause of complications of diabetes remains a mystery. There is a wi deviation of occurrence of type 2 non insulin dependent diabetes mellitus (NIDDM) and insulin dependent diabetes mellitus (IDDM). 80% of diabetes mellitus is due to type 2 diabetes mellitus in Asia whereas insulin dependent diabetes mellitus occurs in 3% of population. Type 2 diabetes mellitus is one of the most common noncommunicable diseases of the world [2]. It is associated with devastating complications which influences the quality of life, mortality and morbidity. Diabetes mellitus is associated with adverse effects throughout. The complications of diabetes are cardio vascular complications such as myocardial infarction, stroke, peripheral vascular disease, retinopathy, renal complications, and peripheral neuropathy. Microangiopathy leads particularly to accelerated coronary
arterial disease, cerebrovascular accident and peripheral arterial disease. The incidence of cardiovascular complications is two to four times higher in diabetic population than in nondiabetics. Cerebrovascular and peripheral vascular disease occurs two fold to three fold and two fold to five fold more frequently respectively [3].

The morbidity of microangiopathy in diabetes mellitus which causes disability and death has been going up these years [4]. Our knowledge and level of understanding in the area of pathophysiology of these complications is increasing but remains imprecise. The diverse manifestation is incompletely understood and hence demands for continuing investigations by the research scientists and clinicians.

It has been suggested that abnormal platelet functions and endothelial damage may play a role in pathogenesis of microangiopathy in diabetes mellitus [5]. Although platelets were discovered in 1842 their contribution to vascular complications in diabetic population remains unclear. In the past 10 years several studies done on platelet function have shown that there is increased platelet sensitivity to aggregating agents, and presence of activated state of platelets in diabetic microangiopathy [5]. However whether the abnormal functions of platelets is a cause or a consequence of underlying microangiopathy has not yet been confirmed. There remains some controversy about whether platelet changes occur before and therefore contribute to vascular complications or whether they are secondary to vascular disease.

Platelet size is a determinant of platelet function [6]. Larger platelets are more reactive per unit volume than smaller platelets. They produce more prothrombotic factors such as thromboxane A2. Increased mean platelet volume in diabetics has been demonstrated in few animal studies and in humans also. It is proved that platelet size is predictor for recurrent myocardial infarction.

Estimation of mean platelet volume (MPV) is a simple outpatient technique for determination of platelet function. A very few studies have been carried out on mean platelet volume in diabetics hence in this study we have tried to compare mean platelet volume in type 2 diabetes mellitus with non diabetic population. Studies on diabetic patients with vascular complications shows increase in mean platelet volume. There are only few studies on diabetic without any vascular complications hence this study has considered type 2 DM without any vascular complications. This study also evaluates mean platelet volume changes prior to the onset of vascular complications, and its implication as a diagnostic & prognostic test in the management of diabetes mellitus.

The debate whether glycemic control of diabetes mellitus influences secondary sequelae of the disease has been going on for years. Abnormalities of mean platelet volume have been observed in diabetic patients [7, 8]. The correlation of platelet count and mean platelet volume with fasting blood sugar, postprandial blood sugar, body mass index, serum creatinine clotting time and duration of diabetes mellitus has not yet been done. Platelet activity and aggregation potential are essential components of thrombogenesis and atherosclerosis and may affect clotting time. Serum creatinine level reflect the volume of skeletal muscle. A lower volume of skeletal muscle would mean fewer target sites for inulin and may play significant role in pathogenesis of type 2 diabetes.

These facts gave us an impetus to analyze platelet count, mean platelet volume, serum creatinine and clotting time in patients of type 2 diabetes mellitus and observe their suitability to be surrogate markers for type 2 diabetes.

Aims and objectives of the study:

To estimate the platelet count in uncomplicated type 2 diabetes mellitus and compare with thenormal subjects.

To estimates the mean platelet volume in patients of uncomplicated type 2 diabetes mellitus and compare with age matched normal controls.

To correlate the mean platelet volume with fasting blood sugar, postprandial blood sugar, body mass index, serum creatinine and clotting time and duration of diabetes mellitus in patients of uncomplicated type 2 diabetes mellitus.

MATERIALS AND METHODS:

The study was conducted at the diabetic clinic of Victoria hospital, Bangalore after obtaining institute ethical committee clearance. A total of one thousand patients were screened for diabetes mellitus out of which thirty males and thirty females non insulin dependent diabetics in the age group of 30-60 years were selected for the study. These non insulin dependent diabetes mellitus patients were having no clinical evidence of any other illness nor had any signs of any microvascular complications neither were on any medications other than oral hypoglycemic agents. The patients of anemia (hemoglobin level <12 g/dl in females and < 14 g/dl in males), hypertension, those with past history of blood transfusions, pregnant females, females consuming oral contraceptives or in menstrual phase, smokers and alcoholics were all excluded from the study. The thirty age matched controls who were selected for study were healthy males and females, non diabetic, nonsmokers, nonalcoholic, normotensive with no clinical evidence of any illness. The parameters selected for study were Body Mass Index, fasting and post prandial blood sugar, serum creatinine, clotting time, bleeding time, fasting & post prandial urine sugar, albumin, ketone bodies, urine microscopy, electrocardiogram (ECG) and fundoscopy.

Informed consent was obtained from the subjects who participated in the study. After recording complete history of present and past health status of controls and patients, physical examination was carried out and anthropometric measurement of the height and weight were recorded [9]. Body mass index was calculated by using Quetlet’s Index, i.e., weight in kilograms / by square of the height in centimeters. Haemoglobin and mean platelet count and mean platelet volume was estimated by using cell dyne 1700 automatic cell analyzer. The fasting and post prandial
This study was undertaken to assess the role of platelets and mean platelet volume in uncomplicated type 2 diabetes mellitus. Students unpaired ‘t’ test and ‘p’ value were applied to find out statistical significance for changes of mean platelet volume, Fasting Blood Sugar (FBS), Post Prandial Blood Sugar (PPBS), Body Mass Index (BMI), serum creatinine, clotting time, and platelet count in diabetics with controls. Mean platelet volume was correlated to Fasting Blood Sugar, Post Prandial Blood Sugar, Body Mass Index and duration of diabetes, serum creatinine, clotting time, and platelet count in type 2 diabetes mellitus.

The mean age in patients of diabetes mellitus was 48.86±10.34 & controls was 48.85±10.07. The mean of duration of diabetes was 4.30 ± 1.89.

In Table 1 Comparison of means, standard deviations & p value of fasting blood sugar (FBS), post prandial blood sugar (PPBS), platelet count, serum creatinine, clotting time, body mass index (BMI) MPV in type 2 Diabetics & controls.

Table 2 Correlation coefficient MPV of FBS, PPBS, BMI & duration of diabetes in type 2 Diabetics.

Table 1. Comparison of means, standard deviations & p value of BMI, FBS, PPBS, platelet count, serum creatinine, clotting time, MPV in type 2 Diabetics & controls.

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>Type2dm (n=60)</th>
<th>controls (n=60)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>25.26±4.10</td>
<td>22.11±1.69</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PPBS</td>
<td>223.92±82.38</td>
<td>103.42±11.8</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>FBS</td>
<td>27.92±7.18</td>
<td>140±24.14</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Platelet count K/ml</td>
<td>27.42±5.44</td>
<td>7.38±0.51</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>MPV</td>
<td>8.44±0.74</td>
<td>0.77±1.22</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.17±0.13</td>
<td>3.56±0.96</td>
<td></td>
</tr>
<tr>
<td>Clotting time</td>
<td>6.71±1.22</td>
<td>2.77±0.40</td>
<td></td>
</tr>
</tbody>
</table>

*P value <0.001 Highly Significant, # P value <0.01 Significant. FBS- Fasting blood sugar in mgs %, PPBS- post prandial blood sugar in mgs %, MPV-mean platelet Volume in femtoliters, Serum creatinine in milligrams % and clotting time in minutes.

Figure 1 compares the means of BMI, FBS, PPBS, Platelet count, serum creatinine, clotting time, mean platelet volume in type 2 DM and controls.

Figure 2 shows the correlation of FBS to MPV in type 2 DM.

Figure 3 shows the correlation of MPV to PPBS in diabetics.
DISCUSSION

The mean platelet volume of the sixty patients of diabetes were significantly increased as compared to controls and details of 'p' value are observed in Table 1. This is concurrent with findings of Sharpe PC [6], Goldberg RE [12] Erilseov [13] Saigo K [14], David bressman [15] Tschope.D [16] and A Knoeti roa [17]. The mean platelet volume is increased in type 2 diabetes mellitus. This increase can be due to increased number of younger platelets in diabetics. Younger platelets have increased platelet volume. Increased endothelial damage is seen in diabetes mellitus which reduces the survival of platelets and increases turnover of younger platelets in diabetes mellitus. Moreover MPV is an indicator of the average size and activity of platelets. Larger platelets are younger, more reactive and aggregable as they contain denser granules, secrete more serotonin and β-thromboglobulin, and produce more thromboxane A2 than smaller platelets. [8, 18] All these can produce a pro-coagulant effect and cause thrombotic vascular complications. This suggests a relationship between the platelet function especially MPV and diabetic vascular complications thus indicating that changes in MPV reflect the state of thrombogenesis. [8]

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. Platelet are hyperaggregable [19-25], they have increased sensitivity to aggregating agents in diabetes. Increased number of glycoprotein IIb/IIIa molecules is seen in diabetes [26-28] 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 [29]. The thrombin content is increased in diabetics which causes phosphorylation of light myosin chain leading to change in mean platelet volume.

The correlation coefficient MPV to FBS (R=0.6755 & P= P<0.0001) is highly significant. The correlation coefficient between MPV to PPBS in diabetics (R= 0.5416 & P<0.0001). The correlation coefficient is highly significant which is similar to that observed by Siage & Szeremeta M. [30,31]

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.

The correlation of MPV to BMI and duration of diabetics was not significant. Our finding correlates with their findings of Paton [31].

The platelet count in female diabetic’s verses female controls’ values were not significant. K.C. Malothra [32, 33] has also shown that the platelet count were normal in subjects as well as in diabetes mellitus.

The creatinine level was significantly lower in type 2 diabetes mellitus group than control and is attributed to lower volume of skeletal mass. Asians and Asian Americans have been reported to have a lower prevalence of obesity than Caucasians but a higher percentage of body fat at the same BMI [34]. These reports suggest that Asians and Asian Americans might have a lower percentage of total skeletal muscle mass than Caucasians at the same BMI level [34]. The lower serum creatinine level reflects a lower volume of skeletal muscle. Skeletal muscle is a major target tissue of insulin [35]. A lower volume of skeletal muscle would mean fewer target sites for insulin, and this may explain in part the pathogenesis of type 2 diabetes associated with lower serum creatinine.

The clotting time was increased in type 2 diabetics as compared to controls. It was found to be statistically significant and is attributed to the fact that haemostatic system is altered in diabetes secondary to changes in clotting factor levels. There is a general increase in plasma levels of procoagulant factors accompanied by decreased fibrinolytic capacity. The mechanisms for these alterations are complex with insulin resistance and hyperglycemia being clear culprits. Hyperinsulinemia due to setting of insulin resistance results in increased hepatic synthesis of prothrombotic factors including fibrinogen creating a thrombotic milieu. In addition to qualitative changes diabetes induces quantitative
modifications in clotting factors including glycation and oxidation, which also increase thrombosis risk. The net result of the above changes is an increased tendency to clot formation, with the fibrin network displaying a compact structure and resistance to fibrinolysis [36, 37].

CONCLUSION:

The mean platelets volume is significantly increased in the patients of diabetes mellitus and is attributed to the fact that thrombin content is increased in diabetic causing phosphorylation of light myosin chain leading to change in mean platelet volume.

The creatinine levels was significantly lower in type 2 diabetes mellitus group reflecting that type 2 diabetes mellitus patients have lower volume of skeletal muscle with few target sites for insulin

The clotting time was increased in type 2 diabetes mellitus and can be attributed to the fact that there is generalized increase in the plasma level of procoagulant with decrease in fibrinolytic activity

Hence mean platelet volume, serum creatinine and delayed clotting time can be taken as surrogate markers of type 2 diabetes mellitus.

References