Original Article

DOI: 10.7860/JCDR/2018/36564.12188

Biochemistry Section

Relationship between Glycaemic Parameters and Mean Platelet Volume among Pre-Diabetics and Non-Diabetics in a Predominantly Tribal Population

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ABSTRACT

Introduction: Pre-diabetics are considered an important risk set within the population who though 'apparently normal' are at the highest risk of progression to clinical diabetes. Interventions in this subset can reduce or delay the onset of many dreaded complications of hyperglycaemia, especially cardiovascular complications, which are one of the leading causes of morbidity and mortality.

Aim: The study was designed and carried out to determine the relationship between Mean Platelet Volume (MPV) and glycaemic parameters in non-diabetics of predominantly tribal origin.

Materials and Methods: The study subjects were selected on the principle of convenient and consecutive sampling. Adult patients self-reporting to the Central Laboratory of a medical college hospital located in a predominantly tribal district of Odisha. Blood samples were collected for routine haematological and biochemical parameters. Based on the fasting plasma glucose, the patients were divided into normoglycaemics and pre-diabetics. The linear relationship between the quantitative variables was evaluated by computing the Pearson's correlation coefficients. The independent relationship between MPV and the other study variables was analysed by multiple linear regressions.

Results: The study was conducted with a total of 109 individuals (62 males and 47 females). Glycaemic parameters were significantly different between pre-diabetics and normoglycaemics with higher level in the pre-diabetics compared to normoglycaemics. Fasting Plasma Glucose (FPG) and Post Prandial Plasma glucose (PPPG) showed modest ($r<0.5$) positive correlation with MPV with variable statistical significance, but blood insulin level showed strong ($r>0.5$) positive correlation that was robustly significant. MPV was regressed on FPG, PPPG, insulin, cholesterol and total platelet count. The R square of the model varied between 0.415 and 0.637 for all the datasets with the highest value (0.637) for the pre-diabetics group. The strongest and statistically significant independent correlation was seen between MPV and insulin in all the datasets, with highest values in the pre-diabetics group (standardised beta coefficient=0.680).

Conclusion: The glycaemic parameters especially fasting blood glucose, PPPG, and insulin were found to be correlated with MPV in both normoglycaemics as well as pre-diabetics. The pre-diabetics showed higher levels than normoglycaemics. Thus, MPV may serve as an important marker in early detection of cardiovascular complications, in the non-diabetics.

Keywords: Cardiovascular, Insulin resistance, Platelet aggregation, Pre-diabetic

INTRODUCTION

Pre-diabetes is the pre-clinical stage of diabetes where the patients are at increased risk of developing diabetes. Such patients remain at risk of developing diabetes within 5-6 years or develop different macro and micro-vascular complications if not diagnosed early or do not adopt proper preventive measures. The pre-diabetics are sub-classified as Impaired Fasting Glucose (IFG) i.e., those who have a FPG between 100 and 125 mg/dL and Impaired Glucose Tolerance (IGT) if the plasma glucose is ≤200 mg% but more than 140 mg% after 75 gm Oral Glucose Tolerance Test (OGTT) [1-3]. Interventions in this subset can reduce or delay the onset of many dreaded complications of hyperglycaemia, especially cardiovascular complications, which is one of the leading causes of morbidity and mortality [4]. Research using a large multi-ethnic cohort has demonstrated that the risk of cardiovascular events or death in normoglycaemics and pre-diabetic subjects increases progressively with increasing FPG levels. One unit increase in FPG was associated with a 17% increase in risk of CVS events or death [4]. Thus, identification of the members of this subset who are at risk for cardiovascular complications due to the prothrombotic state remains an important public health priority.

The prothrombotic state in the diabetic and pre-diabetic group is attributed to several factors such as increasing coagulation, impaired fibrinolysis, endothelial dysfunction and platelet hyperactivity [5]. MPV and total platelet count are important markers and determinants of platelet function [6]. Thus, platelets with bigger volume are functionally more active and expected to produce more Thromboxane A2 and B2 and express adhesion molecules P selectin, Glycoprotein IIb/IIIa and thromboglobulin, which increases the propensity to thrombosis [7]. Studies have established the role of MPV as an independent risk factor for thromboembolism, stroke and myocardial infarction in type 2 diabetes mellitus [8,9]. It has been shown that patients with type 2 diabetes mellitus tend to have higher levels of MPV compared to their normoglycaemic counterparts [6]. Platelet dysfunction in diabetes may be found even before the development of visible damage to the blood vessel wall. However, various contrasting results are obtained in several studies and no clear cut results can be established in the relationship between MPV and various haemoglycaemic parameters in the pre-diabetics. The few studies done till date are of varying ethnicities like Japanese, etc, but none on Indian tribal population in particular [6,10].

Insulin binds to platelet membrane receptor and has direct inhibitory effect on platelet aggregation. Previous studies have revealed

diabetic patients being less sensitive to this inhibitory effect of insulin [11]. The status of serum insulin and insulin resistance in pre-diabetics needs to be explored to prevent the micro and macro-vascular complication.

The present study was designed and carried out to determine the relationship between the haematological and biochemical parameters in pre-diabetics and normoglycaemic persons of predominantly tribal origin and correlate the level of serum insulin and insulin resistance with these parameters.

MATERIALS AND METHODS

Study Design

The study was designed as a prospective cross-sectional study. The study subjects were selected on the principle of convenient and consecutive sampling. Adult patients self-reporting to the Central Laboratory of Pandit Raghunath Murmu Medical College and Hospital, Baripada, for various investigations in a fasting state were the intended study subjects. The medical college has been established recently (April 2017) with joint efforts of both the state and national governments. The study assumes special significance since the medical college is located in the Mayurbhanj district of Odisha state which is an underdeveloped and backward district, with a predominantly tribal population (58.7% as per 2011 census). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Inclusion and Exclusion Criteria

A total of 109 patients, age between 18 to 75 years of both sexes who self reported to the Central lab after being referred from the medicine OPD between May 2017-December 2017 and willing to participate were included in the study. From among them, 52 patients were found pre-diabetic and 57 were normoglycaemics after routine fasting blood sugar examination. Persons with self reported history of the following conditions were excluded from the study viz.,

- Use of medications affecting platelet function (aspirin, ticlopidine, warfarin or heparin);
- Use of lipid lowering agents;
- Essential hypertension;
- Hepatic and renal diseases;
- Anemia (Haemoglobin <12 g; both sexes);
- Thrombocytopenia (<1.5 L) or Thrombocytosis (>4.5 L);
- Diabetes Mellitus under treatment with oral hypoglycaemic agents and /or subcutaneous insulin;
- Pregnancy;
- Polycystic Ovarian Disease (PCOD);
- Surgery within previous 30 days.

All eligible individuals were explained the purpose and design of the study and consent was sought from each of them before enrollment in the study. Ethical aspects of the study design and protocol were approved by the institutional authorities prior to commencement of the study. Based on the FPG level, the study subjects were divided into two groups i.e., normoglycaemics (FPG<100 mg/dL) and pre-diabetics (100≤FPG≤126 mg/dL) as per the American Diabetic Association (ADA) criteria [12].

Laboratory Protocol

Venous blood samples were collected for routine haematological and biochemical parameters. Since they were in a fasting state, the blood samples were collected in the first visit itself along with the socio-demographic parameters. Patients who were not in the fasting state were advised to come the following day after fasting for 8-10 hours for fasting blood sugar and lipid profile test. Blood for complete blood count {including Haemoglobin (Hb), Total Red Cell Mass (TRBC), Total White Blood Cell Count (TWBC), Mean Corpuscular Volume (MCV)} was collected in EDTA tubes and analysed in Sysmex CBC analyser. The routine biochemical parameters such as FPG, PPPG, Insulin, and Lipid Profile (Serum Cholesterol, Triglyceride, HDL, LDL and VLDL) were collected in fluoride and plain vials analysed in Erba 360 Auto-analyser. FPG and PPPG were estimated by Glucose Oxidase-Peroxidase (GOD-POD), Serum Cholesterol by Cholesterol Oxidase-Peroxidase (CHOD-POD), Serum Triglycerides by Glycerol Phosphate Oxidase-p-aminophenazone (GPO-PAP) method, HDL by Direct measure, Immunoinhibition method. Serum LDL and VLDL were calculated parameters. Serum Insulin was estimated by Chemiluminiscent immunoassay method in Abbott Immunoassay system. Homeostasis Model Assessment (HOMA) was used to determine insulin sensitivity index with the formulae: HOMA IR=Fasting Insulin (μU/mL) X Fasting Glucose (mg/dL)/405 [13].

STATISTICAL ANALYSIS

Quantitative data were expressed as mean and standard deviation. Categorical data were expressed as counts. Chi-square test was used to compare the categorical variables and Student t-test was used to compare continuous variables. The linear relationship between the quantitative variables was evaluated by computing the Pearson's correlation coefficients. The independent relationship between MPV and the other study variables was analysed by multiple linear regressions. HOMA-IR was computed from the fasting plasma glucose and insulin. All the statistical analysis was done by using SPSS version 11.0 (SPSS Inc., Chicago, Ill., USA). Probability (p) values less than 0.05 were considered as statistically significant.

RESULTS

The study was conducted with a total of 109 individuals consisting of 62 males and 47 females, meeting the inclusion and exclusion criteria. The distribution of males and females in the two study groups was similar (p>0.05). The demographic and haematological characteristics of the study subjects enrolled into either of the two groups i.e., normoglycaemics (n=57) and pre-diabetics (n=52), showed no statistically significant differences (with the exception of MPV and total platelet count). However, the glycaemic parameters were different in both the groups [Table/Fig-1]. The FPG, PPPG, Total Platelet Count (TPC) and blood insulin level were all significantly different in both the groups with higher mean level in the pre-diabetics compared to normoglycaemics. The serum cholesterol, TG and HDL were also higher in the pre-diabetics compared to the normoglycaemics.

The linear association between the various quantitative study parameters was assessed by computing the Pearson's' correlation coefficient 'r' in the whole group (n=109) as well as independently in both the study groups. The correlation coefficients between MPV and the various haematological and biochemical parameters are shown [Table/Fig-2]. The glycaemic parameters FPG and PPPG showed modest (r<0.5) positive correlation with MPV with variable statistical significance. However, blood insulin level and HOMA-IR both showed strong (r>0.5) positive correlation that was robustly significant across both the study groups. Non-significant p-values obtained for FPG in normoglycaemics and significant p-values were obtained for pre-diabetics. However, two of the three blood lipid parameters i.e., triglycerides and HDL did not show any statistically significant correlation. In order to ascertain the independent relationships between MPV and the important

Variables	Comparison of demographic and haematological parameters		
	Normal (n=57)	Pre-diabetic (n=52)	p-value
Demographic details			
Age	46.96±11.8	49.44±11.0	0.261
Sex			
Male	30	32	
Female	27	20	0.439
Haematological Parameters			
Hb (g/dL)	13.40±1.1	13.46±1.0	0.754
TRBC (mill/µL)	5.03±0.8	5.17±0.8	0.392
TWBC (per cu mm)	8496.49±3708.0	8046.15±1445.8	0.399
MCV (fL)	83.35±7.3	82.58±8.5	0.615
TPC (lac/cu.mm)	2.76±0.7	3.16±0.8	0.009*
MPV (fL)	8.14±1.3	9.03±2.1	0.012*
Biochemical parameters			
FPG (mg/dL)	89.56±7.7	110.04±6.6	0.000**
PPPG (mg/dL)	128.86±20.0	151.13±17.8	0.000**
Insulin (µ IU/mL)	7.53±4.0	10.22±4.2	0.001*
HOMA_IR	1.67±0.9	2.78±1.1	0.000**
Cholesterol (mg/dL)	137.63±20.2	150.38±24.1	0.004*
TG (mg/dL)	88.56±30.7	102.06±34.5	0.034*
HDL (mg/dL)	45.32±7.9	46.67±5.6	0.304
LDL (mg/dL)	74.60±16.9	83.30±19.7	0.015*

[Table/Fig-1]: Comparison of demographic and haematological parameters.

biochemical parameters, statistical modelling was done using multiple linear regressions. Thus, the MPV was regressed on FPG, PPPG, insulin, cholesterol and TPC. Low values for HOMA_IR signifies insulin sensitivity where as higher values indicate insulin resistance or low insulin sensitivity. In our study, we found a strong correlation of HOMA_IR with insulin r=0.972, 0.988 and 0.986 in all the three comparison datasets i.e. total group, normal and prediabetics, respectively. Hence, HOMA IR was excluded from the model based on the principle of statistical co-linearity since it already had FPG and insulin factored in it. Thus, addition of HOMA-IR would not provide any additional explanation to the variability of MPV. The other parameters were not included in the final model because they failed to demonstrate a robust and statistically significant linear correlation with MPV [Table/Fig-2] and successive alterations failed to increase the adjusted r^2 for the model. The model was fitted independently using the dataset of both the individual study groups as well as total study group and the regression diagnostics were compared. The adjusted R-square of the model varied between 0.415 and 0.637 for all the three datasets with the highest value (0.637) for the pre-diabetics group. The model was statistically significant for all the three datasets. Standardised β coefficients (instead of raw coefficients) were used to compare the five model parameters since all have different units of measurement. After adjusting for confounders, the results of multiple linear regressions depicted in [Table/Fig-3] are for the three different datasets. Significant p-value and positive value for standardised β coefficient is appreciated for Insulin in total group (Standardised β co-efficient=0.591, p=0.001), PPPG (Standardised β co-efficient=0.237, p=0.052) and insulin (Standardised β co-efficient=0.469, p=0.001) in normoglycaemics group, FPG (Standardised β co-efficient=0.315, p=0.003) and insulin (Standardised β co-efficient=0.680, p=0.000) in pre-diabetics group. However, the strongest and statistically significant correlation was seen between MPV and insulin in all the three datasets, with strongest values in the pre-diabetics group (beta coefficient=0.680), with all the other parameters held constant [Table/Fig-3].

Variables	Total (n=109)		Normal (n=57)		Pre-diabetic (n=52)	
	Pearson's 'r'	p-value	Pearson's 'r'	p-value	Pearson's 'r'	p-value
Age	-0.054	0.577	0.191	0.154	-0.298	0.032*
Hb	-0.061	0.527	-0.158	0.241	-0.008	0.955
TRBC	0.013	0.897	-0.177	0.188	0.111	0.434
TWBC	0.101	0.294	0.289	0.029*	-0.095	0.503
MCV	0.028	0.774	0.189	0.158	-0.050	0.727
TPC	0.238	0.013*	0.252	0.058	0.151	0.287
FPG	0.335	0.000**	0.076	0.574	0.397	0.004*
PPPG	0.356	0.000**	0.393	0.003*	0.202	0.151
Insulin	0.668	0.000**	0.577	0.000**	0.706	0.000**
Homa_IR	0.697	0.000**	0.557	0.000**	0.755	0.000**
Cholesterol	0.288	0.002*	0.147	0.275	0.292	0.036*
TG	0.107	0.270	-0.245	0.065	0.254	0.069
HDL	0.026	0.792	-0.102	0.450	0.106	0.453
LDL	0.306	0.001*	0.313	0.018*	0.237	0.091

[Table/Fig-2]: Matrix of linear correlation coefficients of various study parameters vs. MPV.
*(p<0.05) **(p<0.001)

	Total (n=109)		Normal (n=57)		Pre-diabetic (n=52)	
Model 1^						
R square	0.488	0.000	0.415	0.000	0.637	0.001
Adj. R square	0.463		0.358		0.597	
	Standardised β		Standardised β		Standardised β	
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
TPC	0.123	0.097	0.203	0.071	0.127	0.165
FPG	0.060	0.474	-0.030	0.784	0.315	0.003
PPPG	0.016	0.846	0.237	0.052	-0.043	0.657
Insulin	0.591	0.000**	0.469	0.000**	0.680	0.001**
Cholesterol	0.130	0.097	0.014	0.901	0.074	0.468

[Table/Fig-3]: Standardised regression coefficients of multiple linear regression of MPV.
^MPV is the dependent; TPC, FPG, PPPG, Insulin and Cholesterol are independent variables
*(p<0.05) **(p<0.001)

DISCUSSION

The natural history of type 2 Diabetes mellitus is a continuum of hyperglycaemia, which begins in the pre-clinical stage called pre-diabetes. Persons with pre-diabetes are at a high risk of progressing to development of clinical diabetes mellitus [3]. They are also at a high risk of adverse cardiovascular events (myocardial infarction, stroke or cardiovascular death) in later life [14,15].

Among all the factors in the web of causation of cardiovascular diseases, platelets have been the primary focus. Altered platelet function is an essential contributor in the aetio-pathogenesis of most, if not all, adverse cardiovascular events. MPV and TPC are two surrogate markers of platelet dysfunction (and reactivity). In the current study, both of these parameters were found to be significantly higher in the pre-diabetic patients in comparison to the normoglycaemic individuals (MPV-8.14±1.3 fL vs. 9.03±2.1, p-value-0.012, TPC-2.76±0.7 vs. 3.18±0.18, p-value-0.009. Also, the MPV had a significant positive association with FPG in the entire study population and pre-diabetic patients. MPV have also been found to be positively correlated with fasting glucose in diabetic subjects [16,17]. Shimodaira M et al., [10] conducted a study on Japanese subjects were subdivided into three groups: Normal Glucose Tolerance (NGT) group; impaired fasting glucose group (IFG) and impaired glucose tolerance group (IGT) [10]. The relationship between MPV, FPG, and post challenge glucose levels after 1 hour

(1 h-PG) and 2 hour (2 h-PG) were analysed. Multiple correlation analyses showed that FPG levels significantly correlated with MPV in the NGT and IGT groups. In addition, 1 h-PG and 2 h-PG levels correlated with MPV in the NTG and IGT groups, respectively.

Similar result was obtained in a study conducted by Kurt H et al., in which patients were subdivided into 7 groups according to OGTT results and their MPV values were estimated [18]. Both the diabetic and pre-diabetic had a higher MPV value as compared with the patients with normal glucose tolerance. Individuals with FPG between 100-109 mg/dL had a higher MPV value than NGT. They concluded that OGTT need to be planned for patients with high MPV values with blood sugar less than 110 mg/dL. Coban E et al., [16] in his study also got similar findings [15]. His study comprised of 48 patients with impaired glucose tolerance and 48 age and sex matched healthy controls. The MPV values were 9.06±1.5 fL vs. 8.28±0.8 fL, p=0.002. Also, MPV was positively correlated with 2 hours plasma glucose concentration in IGT group (r=0.39, p=0.006). They concluded that subjects with IGT tend to have increased platelet activation. Increased platelet activity could contribute to increasing the risk of cardiovascular disease in IGT.

Ozder A et al., in their study measured blood fasting glucose, complete blood count and LDL-cholesterol and compared the results between NGT, IFG and diabetic-201 subjects in each group [19]. In the patients with diabetes and subjects with IFG, MPV was significantly higher (10.66±0.94 fL and 10.49±0.96 fL, respectively) as compared to the non-diabetic group (10.04±1.01 fL) (p<0.001). Among the diabetic subjects, a positive statistical Pearson correlation was seen between MPV and HbA1c levels (r=0.357; p<0.001) and FBG levels (r=0.306; p<0.001). The mean MPV in patients having HbA1C <7.5% was 10.17±0.83 fL and significantly lower than that of patients with HbA1c ≥7.5% (10.80±0.92 fL) (p=0.001). They concluded that MPV could be used as a simple and cost-effective tool to monitor the progression and control of Type 2 Diabetes Mellitus (T2DM) and thereby, in preventing vascular events in primary health care.

In another study conducted by Kodiatte TA et al., [20] the mean platelet counts and MPV were higher in diabetics compared to the non-diabetic subjects {277.46±81 X 10^9/l vs. 269.79±78 X 10^9/l (p=0.256)}, 8.29±0.74 fL versus 7.47±0.73 fL (p=0.001), respectively [20]. MPV showed a strong positive correlation with fasting blood glucose, postprandial glucose and HbA1C levels (p=0.001). Significant higher MPV values were found in diabetic patients as compared to healthy individuals which indicates that elevated MPV could be either the cause for or due to the effect of the vascular complications. Hence, platelets may play a role and MPV can be used as a simple parameter to assess the vascular events in diabetes.

Such studies suggest that hyperglycaemia is known to increase atherogenecity by increasing the MPV values [19,20]. Moreover, a positive correlation was observed between MPV and FPG levels, only in pre-diabetics but not in normoglycaemics. When the confounding factors were controlled by regression, the association remained positive only in pre-diabetics and it was negative in normoglycaemics. It has been postulated that MPV can differ based on individual characteristics, including lipid profiles, alcohol intake, genetics, race/ethnicity and other population characteristics [21,22]. While lipid profile was evaluated for each of the study subjects in this study and also factored into the regression model as total cholesterol, alcohol intake was not studied.

Higher insulin levels in the pre-diabetic subjects were associated with insulin resistance. In patients with cardiovascular disease, MPV was significantly elevated in those with insulin resistance when compared to insulin sensitive subjects. There are very few reports regarding correlations between MPV and insulin level in the general population. The mean platelet volume was correlated with HOMA-IR (r=0.52, p<0.01) and insulin. Elsherby IA et al., conducted a study on 60 patients with slow coronary flow and 20 subjects with normal coronary arteries [23]. Slow coronary flow patients were again divided into 2 groups, insulin resistant (32 patients) and insulin sensitive (28 patients) according to the HOMA-IR. Patients with slow coronary flow had significantly higher mean platelet volume values (7.9±0.47 vs. 7.1±0.5, p<0.01), insulin level (10.8±3.2 vs. 8.2±1.4, p<0.01), and HOMA-IR scores (2.72±0.85 vs. 1.84±0.19, p<0.01). These parameters were significantly higher in insulin-resistant patients than in insulin-sensitive ones level (r=0.58, p<0.01). They concluded that increased mean platelet volume is a central process in the patho-physiology of coronary heart disease and increased platelet activation is due to insulin resistance. Nevertheless, MPV was positively associated with insulin levels in PCOD, which was used as an exclusion criterion in this study. In the present study, insulin levels were found to be higher in pre-diabetics than normoglycaemics. It was also found to be strongly correlated with MPV in both normoglycaemics and pre-diabetics as well. Even after controlling for possible confounders, the independent association between insulin level and MPV remained positive and robust. Thus, higher insulin levels (as would happen in insulin resistance) probably tend to make platelets more reactive and therefore bigger with consequently a higher MPV. Several studies have been carried out between MPV and plasma glucose values but its association with serum insulin and insulin resistance has not been much studied. However study conducted in diabetic patients revealed that platelets of these patients are less sensitive to the inhibitory effects of insulin-the receptor number and affinity both reduced leading to platelet hyperactivity [24].

LIMITATION

The present study was executed as a pilot study in a resource constrained set up (in a newly established medical college hospital's central laboratory). The ethnicity of the study subjects i.e., their tribal status could not be independently verified because of the sensitivity of such social issues. Likewise the alcohol intake status of the study subjects could not be ascertained with certainty and was kept out of the study design. The fasting state was presumed based on self declaration by the patient. The sample size was limited by various operational factors such as willingness to participate given the fact that most were tribal. Furthermore, it is a well-established fact that many people labelled as pre-diabetics by fasting plasma glucose levels may be diagnosed as diabetics if the standard of 75 g Oral Glucose Tolerance Test (OGTT) is applied. Thus, some of the pre-diabetics in the study sample may have been diabetics but due to constraints of feasibility and to keep the study design simple, that aspect was deliberately not factored into the study protocol.

CONCLUSION

The glycaemic parameters especially fasting blood glucose, post prandial plasma glucose, and insulin were found to be correlated with MPV in both normoglycaemics as well as pre-diabetics. The pre-diabetics showed higher levels than normoglycaemics. Both the former and latter were statistically significant in this study. The platelet abnormalities thus, start in the pre-diabetes stage, which is a clinically latent stage. These may have a role in the aetio-pathogenesis of progression from pre-diabetes to clinical type 2 diabetes mellitus and its associated thrombogenic complications. Thus, MPV may serve as an important marker in early detection of cardiovascular complications, in the non-diabetics.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Mar 28, 2018**
Date of Peer Review: **May 27, 2018**
Date of Acceptance: **Jul 18, 2018**
Date of Publishing: **Oct 01, 2018**