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PLATELET INDICES AND DIABETIC NEPHROPATHY SEVERITY IN TYPE 2 DIABETES MELLITUS

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Abstract

BACKGROUND: Diabetes Mellitus is a chronic metabolic disorder that affects the entire world's population, with rates increasing in Asia and peaking in the Indian subcontinent. Indians are more susceptible to type 2 diabetes due to a genetic tendency to insulin resistance, which results in high incidence of DM; that is why India is known as the "Diabetes Capital of the World". Type 2 diabetes mellitus (T2DM) is characterised by insulin resistance in body tissues and impaired insulin excretion by the pancreas. Diabetes results in long-term diabetes-related complications in multiple organ systems due to persistent hyperglycemia and metabolic dysregulation. These complications cause the bulk of morbidity and mortality associated with the disease, reducing the patient's quality of life and imposing large financial costs on the patient, family, and healthcare system.

AIM: Correlation of platelet indices with severity of diabetic nephropathy in type 2 diabetes mellitus.

MATERIAL AND METHOD: This was an Observational cross-sectional study performed. All patients of T2DM visiting OPD as well as getting admitted in the department of medicine were selected randomly and screened for nephropathy. And only the patients developing nephropathy were considered as the study population Informed consent was secured from the patients for participation in the study. At the same time, Venous samples were also drawn for the evaluation of fasting blood sugar, HbA1C, serum creatinine and other routine investigations like serum Urea, serum electrolytes and liver function tests. CBC which includes haemoglobin, thrombocyte counts, Platelet indices like MPV, PCT, PDW, P-LCR; were assessed by the device – Sysmex XN 1000 automated hematology analyser.

RESULTS: In all patients of diabetes, developing nephropathy, anemia is more prevalent and it occurs early in the course of development of complication. Association of hypertension in diabetes patients, increases the risk of developing microvascular complications. Platelet indices like MPV, PDW, PCT, PLCR are significantly raised in all diabetic patients developing nephropathy. As well when associated with other microvascular complications like retinopathy and neuropathy, MPV and PDW are found to be elevated. The platelet indices correlated with the progression of nephropathy stages. MPV, PDW, PLCR and PCT were significantly higher as there was increase in severity of nephropathy.

CONCLUSION: Thus, changes in platelet indices are found to be statistically associated with diabetes and its microvascular complications and being cost effective, noninvasive and being easily available in peripheral blood counts; these platelet indices can be used as a surrogate marker to predict the presence and the progression of diabetic nephropathy much earlier in life, as well, MPV and PDW can be also used as marker for the presence of other microvascular complications of diabetes.

KEYWORDS: Microvascular, Diabetic nephropathy, Diabetes mellitus and Platelet Indices

Introduction

"Diabetes Mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both", leading to long term microvascular complications like nephropathy, retinopathy, neuropathy and macrovascular complications like coronary artery disease, peripheral artery disease, cerebrovascular accidents along with increased susceptibility to infections.[1]

Type 2 diabetes mellitus is the final stage of a chronic and progressive syndrome characterised by various

combinations of insulin resistance and impaired pancreatic-cell activity resulting from both genetic and acquired defects.[2] Type 2 diabetes mellitus is currently diagnosed when the underlying metabolic abnormalities of insulin resistance and decreased cell function cause an increase in plasma glucose of more than 126 mg/dl (7 mmol/L) in the fasting state and/or more than 200 mg/dl (11.1 mmol/L) 120 minutes after a 75-g glucose load and/or HbA1C levels > 6.5%.[3]

Due to changes in platelet morphology and function in diabetes mellitus, platelets contribute to the vascular complications of diabetes. The prothrombotic state of platelets is a hallmark of DM, which results from prolonged hyperglycaemia and insulin resistance, causing injury to pericytes and endothelium. Increased platelet activity is thought to play a key role in the development of vascular complications associated with this metabolic disorder.[4]

Platelets contribute to homeostasis mainly in three ways: adhesion, activation, and aggregation, which results in the creation of a platelet plug in the endothelium. Platelets attach to vascular endothelium and aggregate more readily in type 2 diabetics than in healthy patients.[5]

For numerous years, platelet parameters have been available in the laboratory routine utilising blood cell counters. Mean platelet volume (MPV), Platelet Distribution Width (PDW), Plateletcrit (PCT), and Platelet Large Cell Ratio (PLCR) are some of them. Through these platelet parameters, the prothrombotic state of platelets can be recognised early utilising newer haematology analyzers. Metabolic syndrome, stroke, coronary artery disease, and diabetes mellitus have all been associated with increase in mean platelet volume (MPV). Platelet indices in diabetics are much higher than in nondiabetic individuals, according to a few studies.[6]

Among platelet indices, mean platelet volume indicates changes in platelet stimulation or platelet production rate, PDW is a measure of platelet heterogeneity, which can be caused by platelet ageing or heterogeneous megakaryocyte demarcation, and P-LCR is a measure of larger platelets. Platelet function is influenced by MPV. Platelet morphology and function have been discovered to be altered in diabetic individuals, and MPV levels have been found to be considerably greater in diabetic patients. They're probably associated with the pathological processes and elevated risk of vascular disease that these patients have.[7]

Once diabetes patients develop microvascular complications, the economic burden on any country and its citizens, as well as their families, is huge. Instead of screening all diabetic patients for all complications of diabetes, a target population of diabetic patients who are at risk might be examined and reviewed on a regular basis if the target population could be identified. In this context platelet indices seem to be a good marker to predict microvascular complications in Type 2 diabetic patients as this can be estimated even in basic care settings.[8]

Though there are some studies regarding association of platelet indices with microvascular complications of Diabetes Mellitus, not enough research on changes in platelet indices with severity of stages of Diabetic nephropathy is available in the literature. With this background the present study has been taken up to find out any correlation between the platelet indices and severity of nephropathy in Type 2 diabetes patients.[6]

MATERIAL AND METHODS

Study population: All patients of T2DM visiting OPD as well as getting admitted in the department of medicine were selected randomly and screened for nephropathy. And only the patients developing nephropathy were considered as the study population

Study duration: From September 2019 to march 2020.

Study design: Observational cross-sectional study.

Inclusion criteria:

- Age of the patients >= 18 years.
- All diagnosed cases of diabetes mellitus irrespective of treatment status.
- eGFR < 60 ml/min/1.73m2 (calculated by MDRD formula) and/or ACR > 30 mg/g.

Exclusion criteria

- Any diagnosed malignancy patients.
- Patients on antiplatelet drugs.
- Known case of quantitative and qualitative platelet disorder.
- Known case of thyroid disorder and rheumatic diseases.
- All patients with acute inflammation

Methodology: All the consecutive cases of T2DM, being admitted in the department of General Medicine, over a period of 2 years i.e from September, 2019 to March,2020; who were either newly diagnosed (as per ADA) or already on oral antidiabetic medication or parenteral insulin were taken into consideration. Patients were screened according to the inclusion and exclusion criteria as mentioned above. Patients were finally included in

the study after obtaining an informed written consent regarding the study from the conscious patients or their legal relatives. A detailed clinical history was obtained from the patients or their close relatives which included chief complains, history of present illness, past history, family history, personal history, drug history, allergy history. Detailed history regarding duration of Diabetes and medications taken for Diabetes and other underlying illness was noted. Any specific clinical signs and symptoms of illness were noted. A thorough general and systemic examination was conducted bedside and the findings were documented. Blood pressure was measured in mmHg by using Aneroid sphygmomanometer measured in right arm in seating position, and the mean of 2 consecutive readings taken within an interval of 5 minutes was considered.

Investigations and procedures: After an overnight fasting of 12 hours, venous samples were drawn at a fixed time; at 8 AM from the antecubital vein under all aseptic measures. Samples were drawn with a 10 ml syringe disproven into dry and EDTA containing vials with amount of sample being 3 ml for the evaluation of complete blood count. At the same time, Venous samples were also drawn for the evaluation of fasting blood sugar, HbA1C, serum creatinine and other routine investigations like serum Urea, serum electrolytes and liver function tests. CBC which includes haemoglobin, thrombocyte counts, Platelet indices like MPV, PCT, PDW, P-LCR; were assessed by the device – Sysmex XN 1000 automated haematology analyser. Urine routine, microscopy tests were done and albuminuria was assessed by spot urine albumin creatinine ratio (UACR). Patients with UACR value >30 mg/g were considered for study

Procedure for sample collection: Patients were positioned in supine position comfortably. The skin of the inner angle of the elbow or the skin of dorsum of hand was selected where the vein was prominent, and was cleaned with alcohol or iodine for aseptic measures. A torniquet was applied to the area proximal to the vein to make the vein more visible and plumper, for the easy collection of blood sample. 3 ml of blood was then pulled from the vein via the needle by gently pulling the plunger on the syringe. Torniquet was then removed and the needle was taken out from the vein. The sample was then collected in an EDTA vial and was taken to the laboratory in a transport box within 15 minutes for assessment in the automated analyser.

Statistical analyses

Data collected under the study was scrutinized, codified and entered into the IBM SPSS Statistics, 24.0 software, www.spss.co.in for analysis. The following statistics procedure was used for analysis of data

RESULT: -

In order to analyses the correlation of platelet indices with severity of diabetic nephropathy in type 2 diabetes a sample of 150 cases have been studied

Table 1: Hemodynamic status, duration of diabetes and hypertension.

	Clinical profile	**No.**
Haemoglobin class	(<7mg/dl)	25
	(7-10 mg/dl)	50
	(>10 mg/dl)	75
	Mean ± SD	**8.3±1.7**
FBS group	≤100 mg/dl	20
	101-150 mg/dl	79
	151-200 mg/dl	23
	>200 mg/dl	28
	Mean ± SD	**155.3±75.8**
PPBS group	≤150 mg/dl	20
	151-200 mg/dl	30
	201-250 mg/dl	45
	251-300 mg/dl	25
	>300 mg/dl	30
	Mean ± SD	**238.9±84.5**
HbA1C group	<7.5 %	78
	7.5-10 %	35
	>10 %	37
	Mean ± SD	**7.8±4.9**

Duration of diabetes	≤1 year	10
	1-5 year	35
	6-10 year	75
	>10 year	30
	Mean ± SD	**7.1±4.6**
Hypertension	**NO**	43
	YES	107
Platelet group (in Lakhs)	Low (<1.5 Lakh)	30
	Normal (1.5 Lakh-4 Lakh)	100
	High (>4 Lakh)	20
	Mean ± SD	**228.5±109.7**

A little higher than ½ of the cases have hemoglobin level more than 10 mg/dl. Maximum cases have FBS level 101 – 150 mg/dl. and nearly a quarter have FBS level >200 mg/dl. Maximum, proportion of cases have HbA1C level. Nearly 1/6th cases have more than 10 years of diabetic history, 6 – 10 years. Majority of cases have hypertension. Nearly 1/5th have low platelet count.

Table 2: Classification of Platelet indices (N=150)

Platelet Indices	Range	No.
MPV	<7	5
	7-9.5	35
	>9.5	110
	Mean ± SD	**10.9±1.2**
PDW	<9	3
	9-17	104
	>17	43
	Mean ± SD	**14.6±4,7**
PCT	<0.17	30
	0.17-0.35	85
	> 0.35	35
	Mean ± SD	**0.25±0.09**
PLCR	<13	2
	13-43	100
	>43	48
	Mean ± SD	**28.4±10,4**

Majority of cases have MPV level > 9.5 and remaining have MPV in the range of >9.5. About 2/3rd cases have PDW level 9 -17. Majority cases have PCT level 0.17 – 0.35. Majority cases i.e. had PLCR level 13 – 43

DISCUSSION

Diabetes Mellitus is a chronic metabolic disorder that affects the entire world's population, with rates increasing in Asia and peaking in the Indian subcontinent. Indians are more susceptible to type 2 diabetes due to a genetic tendency to insulin resistance, which results in high incidence of DM; that is why India is known as the "Diabetes Capital of the World" (Radha and Mohan, 2007)[9]. Platelets in DM are larger, hyperactive, and produce more granules as a result of metabolic abnormalities, and they have a higher risk of thrombotic events, leading to both macrovascular and microvascular problems, which increases morbidity and mortality. Platelet indices, which are typically available from standard haematological examination, may provide useful information for early detection and evaluation of diabetes-related complications, allowing for earlier management.

The clinical profile evaluated in our study showed Haemoglobin level of more than 10 mg/dl. Thus, very few participants had severe anemia. However, the mean Hb level is 8.3±1.7which suggests that majority of the participants have anemia. This occurrence of anemia in the study population can be explained by the fact that all the patients in the study are having diabetic nephropathy. This finding is in agreement with the findings of Inomata et al[10] in which 13 diabetic patients with overt nephropathy

and normal renal function were followed for 26 months and it was found that Haemoglobin (Hb), endogenous Erythropoietin (EPO) and Hb x EPO values gradually decreased with advancing age of nephropathy. Ozder A et al[11] and Ulutas et al[12], the mean FBS was 202.68±63.06 and 207.2±82.4 respectively. This shows that our study participants have a better glycaemic control.

The studies conducted by Arnetz et al[13] and Kilpatrick et al[14] showed increased duration of diabetes is associated with increased HbA1C values, which had similar findings with our study. But, in contrary to this, Kabadi et al[15] found no significant association between duration of diabetes and blood glucose levels.

M.M.Taderegew et al[16] and R.S. Walinjkar et al[17] the incidence of Hypertension among the study participants were 39.5% and 36% respectively. the studies conducted by Agarwal BK et al[18] having mean MPV of 11±2.2, which showed elevated mean MPV levels in diabetic groups compared to non diabetic groups. Similar studies conducted by – Kodiatte et al.[3], Jindal et al[6], Zuberi et al[5] with nondiabetic groups as controls had higher MPV values in diabetic groups as compared to nondiabetic controls. Many other studies[19,20] have also the similar findings**.**

study conducted by Schmidt et al[21], inflammatory markers are associated with the evolution of overt diabetes, which suggests that Diabetes mellitus is an inflammatory condition and MPV has been shown to be associated with a variety of inflammatory conditions in various studies. Also, Platelets that have been exposed to inflammatory conditions have shown an increase in size and the number of cytoplasmic granules in response to inflammation. Increased serum levels of inflammatory products in inflammatory diseases may interact with megakaryopoesis in the bone marrow, resulting in the formation of bigger platelets. Insulin levels rise in type 2 diabetic patients' serum, and animal studies demonstrate that insulin causes megakaryocytes to produce larger platelets. And larger platelets lead to elevated MPV.

the studies conducted by Jabeen et al[22] and Dalamaga et al[23] which had mean PDW of 15.02 and 16.4 respectively in Diabetic groups which was significantly higher when compared with non-diabetic control groups. Citirik et al[24] also found higher PDW values in patients with diabetics when compared with control groups, but this was not significant statistically. according to Vagdatli E et al[25] increase in PDW is attributed to abnormal activation of platelet leading to the formation of pseudophillias, seen in long standing uncontrolled diabetes. The study conducted by Jindal et al.[6] showed that diabetic people have higher values of PLCR but the difference was not significant. As of now, more research is required into this marker

CONCLUSION:

The study was conducted in context of finding any association of platelet indices with the progression of diabetic nephropathy as well as to find a better marker among the indices which correlates more with the severity of nephropathy. Thus, changes in platelet indices are found to be statistically associated with diabetes and its microvascular complications and being cost effective, noninvasive and being easily available in peripheral blood counts; these platelet indices can be used as a surrogate marker to predict the presence and the progression of diabetic nephropathy much earlier in life, as well, MPV and PDW can be also used as marker for the presence of other microvascular complications of diabetes.

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