Original Research Article

Study of Fibrinogen level and Platelets Indices in Type 2 Diabetes Mellitus and their relation with Microvascular Complications

Abstract

Background: Type 2 DM (T2DM), represents about 90% of all cases of diabetes mellitus (DM) and this is because of obesity and lack of exercise.It is marked by insulin resistance, high blood glucose, and a relative lack of insulin.The aim of this work was to assess the mean platelet volume, platelet distribution width, and platelet large cell ratio: (MPV, PDW, PL-cR) and fibrinogen in T2DM and their correlation with microvascular complications.

Methods: This case control study was carried out on 90 subjects who classified into three equal groups: Group (1) with type 2 diabetes mellitus without microvascular complications, group (2) with type 2 diabetes mellitus with microvascular complications. These complications are retinopathy, nephropathy and neuropathy, and group (3) as control group.All participants were subjected toserum fibrinogen evaluation, routine laboratory investigations and fundus examination

Results: Fibrinogen washigher significantly in the complicated group compared to the other studied groups ($p < 0.001$). Regarding fibrinogen, at cutoff level (301.5 mg/dL) the sensitivity, specificity, negative predictive value (NPV), andpositive predictive value (PPV) were (73.3%, 93.3%,77.8% and 91.6%), respectively. Concerning platelet distribution width (PDW), at cutoff level 17.65%, the sensitivity, specificity, NPV,and PPV of Platelet distribution width were (76.7%, 100%, 81.1%, and 100%), respectively. Additionally, platelet large cell ratio (PL-cr), at cutoff level 0.338 %, the sensitivity, specificity, PPV and NPV of Platelet distribution width were (76.7%, 100%, 100% and 81.1%), respectively.

Conclusions: Serum fibrinogen, platelet distribution width and platelet large cell ratio can be used as simple parameters to detect micro vascular complications in type 2 diabetes mellitus instead of ~~than~~ mean platelet volume.

Keywords: Fibrinogen;Platelets Indices;Microvascular Complications; Type 2 Diabetes Mellitus.

Introduction:

DM is a metabolic disorder with numerous etiologies, according to the World Health Organization (WHO), and is defined by chronic hyperglycemia and metabolic abnormalities of carbohydrate, lipid, and protein because of a fault in insulin production, action, or both [1]. Over 171 million individuals worldwide are impacted by DM and it will be expected to affect 366 million by 2030[2]. DM is divided into Type 1, 2, (T1DM and T2DM) and Other Specific types, including Gestational DM (GDM) [3].

Approximately 90% of all instances of diabetes are T2DM, which is caused by obesity and inactivity. It is marked by insulin resistance, high blood glucose, and a relative lack of insulin[4]. Chronic diabetes-related hyperglycemia is linked to long-term organ failure, dysfunction, and damage e.g. Kidney, eye, nerve, heart and blood vessels [5].

Diabetic microvascular problems include nephropathy, retinopathy, and neuropathy [6]. These three microvascular complications can lead to end-stage renal disease, blindness, and autonomic neuropathy and are lethal since they increase the cardiovascular diseases' risks (CVD) and premature mortality. Glycemic management and lifestyle changes should be made to avoid these consequences and CVD [7].

Hemostasis is a natural bodily process that aids in maintaining blood flow, closing off the damaged blood vessels when vascular injury occurs, and removing blood clots when vascular health has been restored [8].In diabetes, normal hemostasisis disturbed [9, 10] through hyperglycemia that has an impact on thrombus development and inhibition, fibrinolysis, and platelet and endothelial function, among other coagulation-related processes. The result is that DM has been characterised as a hypercoagulable condition with hypofibrinolysis.[11].

Diabetic patients, display increased platelet reactivity. Platelets are directly affected by hyperglycemiathrough increasing protein glycation. platelet reactivity increased by insulin resistance and deficiency [12].

Considered to be elevated in diabetes as a risk factor for cardiac disorders, the mean platelet volume (MPV) is a measurement of the average size and activity of the platelets. While theplatelet distribution width (PDW), a measure of platelet size variation that may indicate active platelet release. PDW and MPV have a clear correlation with platelet large cell ratio (PLCR) [12].

In the general population, fibrinogen is a major risk factor for cardiovascular disease, and those with T2DM have been reported to have higher fibrinogen plasma levels [13].

The aim of this work was to assess MPV, PDW, PLCR and fibrinogen in T2DM and their correlation with microvascular complications.

Patients and Methods:

This case control study included 90 individuals drawn from the out-patient clinic and in-patient wardsof Tanta University Hospital, Internal Medicine Department and Elmenshawy general hospital from January/2020 until January/2021.

After receiving clearance from Tanta University Hospitals' Ethical Committee, the research was carried out. The patient or his relatives provided written permission after being fully briefed.

Exclusion criteria were patients with Type1diabetes, hematological malignancies as leukemia,thrombocytopenia or thrombocytosis, receiving antiplatelet drugs eg. (asprin, Plavix), with hypercoagulable or bleeding disorders and taking anticoagulant drugs eg. (Heparin and warfarin).

The subjects were divided into three equal groups: Group (1) with T2DMwithout microvascular complications, group (2) with T2DMwith microvascular complications. These complications arenephropathy, retinopathy, and neuropathy, and group (3) as control group.

All patients had a comprehensive clinical examination, a detailed history, a serum fibrinogen assessment, and regular laboratory tests [complete blood count (CBC), fasting blood glucose

(FBG), and hour postprandial blood glucose(2-hrppbg), glycated haemoglobin (HbA1c), liver enzyme (ALT, AST), kidney function tests (serum urea, blood creatinine) and urine analysis], and fundus examination.

Neuropathy was examined by measuring light touch sensitivity with a 10-g monofilament, pain sensitivity with a pinprick, vibration sensitivity with a 128-Hz tuning fork, temperature sense and ankle jerk reflex.

-Nephropathy was evaluated by urine analysis through detection of albuminuria (macro- and microalbuminuria).

Platelet indices and fibrinogen method:

Three vacutainers held about (12–15 mL) of venous blood samples. The Dirui 3000 employed EDTA-filled containers to explore platelet indices, whereas a D10 analyzer used high performance liquid chromatography to determine HbA1c. Fluoride vacutainers were used to monitor blood sugar levels while fasting and after meals, while citrated blood was utilised to assess fibrinogen using a Coadata 4004 coagulation analyzer. Both the liver function test (LFT) and the kidney function test (KFT)were conducted using plainvacutainers ~~(KFT)~~. Blood samples for fasting blood and two hours after a meal were taken in the morning. All samples were obtained simultaneously.

Statistical analysis

Version 22 of SPSS Windows® performed the statistical analysis. In order to determine whether parametric or nonparametric statistical testing should be utilised, the distribution of quantitative data was tested using the Shapiro-Wilks normality test and histograms. The three groups' parametric variables were compared using the ANOVA test, with the post hoc (Tukey) test used to compare each pair of groups separately. Parametric variables were represented as mean and standard deviation (SD). Categorical variables were statistically examined using the Chi-square test and presented as frequency and percentage. Sensitivity,

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specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy estimations were derived at the ideal cut-off in a Receiver Operating Characteristic (ROC) analysis to evaluate the test's efficacy. The Pearson's correlation was used to determine if there was a correlation between two numerical variables in each group. Statistical significance was defined as a two-tailed P value of less than 0.05.

Results:

There was significant difference among all studied groups as regard platelet large cell ratio**,** platelet distribution widthmean platelet volume, fibrinogen, serum creatinine, blood urea, glycated haemoglobin, 2-hour post prandial blood glucose and fasting blood glucose(P< 0.001). Complicated group showed higher significant level of platelet large cell ratio, platelet distribution width mean platelet volume, fibrinogen, serum creatinine, blood urea, when compared with uncomplicated and control group, while uncomplicated group showed insignificant difference when compared with control group. There was insignificant difference among the studied groups as regard age, sex, (ALT) and (AST). Complicated group showed higher significant level of fasting blood glucose, 2-hour post prandial blood glucose, glycated haemoglobin, when compared with uncomplicated & control group. Moreover, Uncomplicated group showed higher significant difference when compared with control group.

Table 1: Comparing the analysed groups' characteristics in terms of age, sex, mean platelet volume, platelet distribution width, platelet large cell ratio, fibrinogen, serum creatinine, blood urea, liver enzymes, glycated haemoglobin, 2-hour postprandial blood glucose, and fasting blood glucose.

		Group 1 (uncomplicated)	**Group 2** (complicated)	**Group 3** (control)	**P-value**	
Age (years)		52±7.06	52.3±6.99	48±8.57	0.054	
Sex	**Female**	19(63.3%)	18(60.0%)	16 (53.3%)	0.725	
	Male	11(36.7%)	12(40.0%)	14(46.7%)		
Routine laboratory investigations						
Fasting blood glucose (Mg/dl)		169.83±30.68	199.37±43.36	80.33±7.62	P<0.001*	P1<0.001*
						P2<0.001*
						P3<0.001*

2-hour postprandial blood glucose (Mg/dl)	257.53±41.09	304.67±60.09	109.17±8.23	P<0.001*	P1<0.001* P2<0.001* P3<0.001*
Glycated hemoglobin (%)	7.59±1.65	9.53±1.55	5.28±0.45	P<0.001*	P1<0.001* P2<0.001* P3<0.001*
Alanine transaminase (IU/L)	23.27±6.87	25.2±9.66	21.7±6.01	0.215	
Aspartate transaminase (IU/L)	27.47±6.43	28.23±8.74	25.77±6.44	0.410	
Blood urea (mg/dL)	22.63±5.85	30.87±12.93	20.7±5.83	P<0.001*	P1=0.002* P2=1.000 P3<0.001*
Serum creatinine (mg/dL)	0.85±0.17	1.05±0.32	0.76±0.14	P<0 .001*	P1=0.002* P2=0.414 P3<0.001*
Fibrinogen (mg/dl)	253.37±37.76	325.5±40.59	251.73±31.22	P<0 .001*	P1=0.002* P2=1.000 P3<0.001*
Mean platelet (FL)	8.7±1.02	11.05±2.89	9.43±1.44	P<0 .001*	P1<0.001* P2=0.449 P3=0.005*
Platelet distribution width (%)	15.05±1.67	21.25±4.89	16.46±2.1	P<0 .001*	P1<0.001* P2=0.282 P3=0.002*
Platelet large cell ratio (%)	0.24±0.06	0.45±0.16	0.29±0.09	P<0 .001*	P1<0.001* P2=0.311 P3<0.001*

Data are presented as mean ± SD or frequency (%), P 1: complicated vs uncomplicated group, P 2: uncomplicated vs control group, P 3: complicated vs control group, *: significant P value

Table 2 shows micro vascular complications in the complicated group.

Table 2:Micro vascular complications in the complicated group (group2)

		Complicated diabetic group (group 2)	
		Number	**%**
Neuropathy	**yes**	25	83.3%
	no	5	16.7%
Nephropathy	**yes**	6	20.0%
	no	24	80.0%
Retinopathy	**yes**	30	100.0%
	no	0	0.0%

Regarding fibrinogen, at cutoff level (301.5 mg/dL) the sensitivity, specificity, PPV and NPV were (73.3%, 93.3%, 91.6% and 77.8%), respectively. Regarding mean platelet volume (MPV), at cutoff level 94.5 FL, the sensitivity, specificity, PPV and NPV of mean platelet

volume were (70%, 80%, 77.8% and 72.7%), respectively. Concerning platelet distribution width (PDW), at cutoff level 17.65%, the sensitivity, specificity, PPV and NPV of Platelet distribution width were (76.7%, 100%, 100% and 81.1%), respectively. Additionally, platelet large cell ratio (PL-cr), at cutoff level 0.338 %, the sensitivity, specificity, PPV and NPV of Platelet distribution width were (76.7%, 100%, 100% and 81.1%), respectively. Figure 1

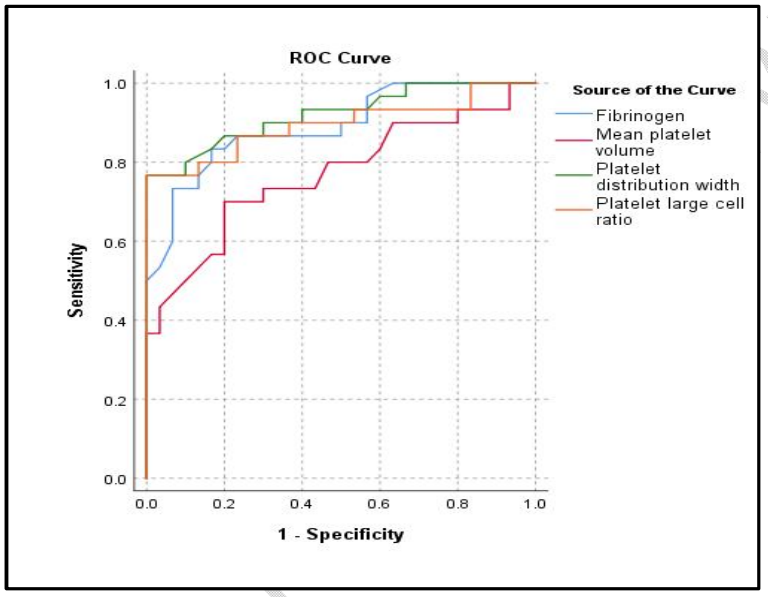

Figure 1: Roc curve for detection of microvascular complications using Fibrinogen and platelet indices (MPV, PDW, and PLcr)

Fibrinogen had positive correlation with MPV (r= 0.397, P= 0.03), but it had negative correlation with blood urea (r= -0.453, P= 0.012) and serum creatinine (r= -0.410, P= 0.025). Moreover, no significant correlation were detected between fibrinogen and other parameters (P>0.05). Mean platelet volume had positive correlation with fibrinogen (r= 0.397, p= 0.03. Additionally, Platelet distribution width had positive correlation with platelet large cell ratio (r= 0.896, P<0.001) and age (r= 0.388, p=0.034), but it had negative correlation with blood urea (r= -0.388, P= 0.034). Moreover, there was no significant correlation between platelet distribution width and other parameters (P>0.05). In addition, there was negative correlation

between platelet large cell ratio and blood urea (r= -0.389, P= 0.034). Meanwhile, there was no significant correlation between other parameters (P>0.05). Table 3

Table 3: Correlation between fibrinogen,platelet indices and different parameters in the complicated group (group 2):

	Fibrinogen		**Mean platelet volume**		**Platelet distribution width**		**Platelet large cell ratio**	
	r	**P-value**	**r**	**P-value**	r	**P - value**	r	**P-value**
Fibrinogen (mg/dl)	-	-	0.397	0.030*	0.100	0.597	0.136	0.474
Mean platelet volume(fl)	0.397	0.030*	-	.	0.037	0.846	0.205	0.278
Platelet distribution width (%)	0.100	0.597	0.037	0.846	-	-	0.896	0.0000*
Platelet large cell ratio(%)	0.136	0.474	0.205	0.278	0.896	<0.001*	-	-
Age (years)	-0.034	0.859	-0.293	0.116	0.388	0.034*	0.287	0.125
ALT (IU/L)	-0.180	0.342	-0.100	0.597	-0.095	0.619	-0.223	0.236
AST (IU/L)	-0.192	0.310	-0.026	0.891	-0.039	0.837	-0.118	0.535
Blood urea (mg/dL)	-0.453	0.012*	-0.185	0.328	-0.388	0.034*	-0.389	0.034*
Serum creatinine (mg/dL)	-0.410	0.025*	-0.206	0.276	-0.087	0.647	-0.076	0.691
Fasting Blood glucose (mg/dl)	-0.091	0.632	0.229	0.222	0.039	0.839	0.025	0.895
2-hour postprandial blood glucose (mg/dl)	-0.137	0.470	0.053	0.780	0.148	0.434	0.137	0.471
Glycated Hemoglobin (%)	-0.171	0.367	-0.013	0.945	0.177	0.350	0.030	0.874

*: significant p value, ALT: Alanine transaminase, AST: Aspartate transaminase

By using univariate analysis, it was found that a significant correlations existed between the occurrence of complications and fasting blood sugar (P=0.008), 2-hour postprandial blood glucose (P=0.003), glycated hemoglobin (P<0.001), fibrinogen (P<0.001), mean platelet volume (P=0.003), platelet distribution width (P=0.001) as well as platelet large cell ratio (P=0.035) separately. Meanwhile, multivariate analysis showed that there was significant association between presence of complications and 2-hour postprandial blood glucose (P= 0.047) as well as fibrinogen (P=0.008) and platelet distribution width (P=0.039). Table 4

Table 4:Univariant and multivariant logistic regression analysis

	Univariate	**Multivariate**

	P-value	Odd ratio	95% CI		P-value	Odd ratio	95% CI	
			Lower	Upper			Lower	Upper
Fasting Blood glucose (mg/dl)	0.008*	1.022	1.006	1.039	------	--	------	------
2 -hour postprandial blood glucose (mg/dl)	0.003*	1.019	1.006	1.032	0.047*	1.036	1.000	1.072
Glycated hemoglobin (%)	< 0.001*	2.190	1.411	3.400	------	------	------	------
Fibrinogen mg/dl	< 0.001*	1.044	1.022	1.065	0.008*	1.070	1.018	1.126
Mean platelet volume fl	0.003*	1.921	1.247	2.960	------	.------	------	------
Platelet distribution width %	0.001*	2.472	1.465	4.171	0.039*	2.946	1.054	8.230
Platelet large cell ratio %	0.035*	4.649	1.112	19.441	-----	------	------	------

*: significant p value

Discussion

DM is a metabolic disorder causing a significant health problem that is characterized by chronic elevated blood glucose causing complications affecting various organs; eyes, peripheral nerves, kidneys, with micro- and macrovessels affection [14].

The current study found significant difference between the 3 investigated groups as regard fibrinogen level (P < 0.001). Complicated group showed higher significant level of fibrinogen when compared with uncomplicated and control group (P1< 0.001, P3 < 0.001), respectively while, Uncomplicated group as compared to the control group, exhibited no discernible difference (P2 1.000).

In agreement with us, Khan et al.findings' [15]on diabetes patients with complications, plasma viscosity and fibrinogen levels were both markedly highercompared to those without complications and healthy control subjects. Elevation of plasma viscosity caused by the increase in the viscosity of the blood in diabetics is primarily attributed to a corresponding rise in fibrinogen content. It has been shown that hyperviscosity plays a significant role in diabetics' microcirculatory abnormalities[16].

In contrast, Abdeurahman et al.,[17] reported that the fibrinogen level was slightly elevated in cases with retinopathy than those who had not retinopathy, However, the difference was not

significant statistically. This might be attributed to diabetic retinopathy that was the only complication found in this study and its frequency was 14% only.

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In the present study, we found a high significant difference between the three investigated groups as regard mean platelet volume (P- value < 0.001). Complicated group showed significant level of mean platelet volume incomparison with the uncomplicated and control group (P1< 0.001, P3 0.005), respectively. Meanwhile, when compared to the control group, the uncomplicated group didn't differ significantly from them (P2 0.449).

In agreement with us Citirik, et al., [18] conducted a study on diabetic patients with and without retinopathy to evaluate platelet volume indices; MPV, PDW and plateletcrit in diabetic retinopathy in comparison with the diabetic patients withoutretinopathy and those in healthy subjects as controls. It showed that MPV levels were significantly changed in the three groups of patients in comparisonto the controls (P<0.05).

In contrast, Akinsegun et al.,[19]Diabetes patients have reduced MPV compared to controls. However, as compared to healthy people, the MPV in diabetes was within the usual reference range. This finding may be explained by the fact that the vast majority of diabetics included in this research were using clopidogrel, an antiplatelet drug, for a variety of periods of time, which contradicts the findings of our investigation.

In our study we found a significant difference among the 3 studied groups as regard platelet distribution width PDW) (P-value < 0.001) Complicated group showed higher significant level of platelet distribution width when compared with uncomplicated and control group (P1< 0.001, P3 < 0.0018), respectively. However, when compared to the control group, the uncomplicated group didn't differ significantly from them (P 2 =0. 282).

Like our study Jindal et al. [20]discovered that PDW was considerably higher in T2DM patients. It was greater in microvascular complicated patients

PDW is a measure of platelet size variation that might be an indication of active platelet production and release. High values indicate greater creation of bigger reticulated platelets, which would be linked to the development of thrombi[21].

Conversely, Citiriket al., [18]discovered that no significant differences across patient groupsin PDW levels.

In our study,we found a significant difference among the 3 studied groups as regard PLCR (P-value < 0.001). Complicated group showed higher significant level of platelet large cell ratio when compared with uncomplicated and control group (P1< 0.001, P3< 0.001), respectively, while uncomplicated group showed a non-significant difference when compared with control group (P2 0.311). P-LCR reflected platelet morphology as well as it is crucial in vascular events including thrombosis and atherosclerosis. It shows the proportion of the youngest platelet group with the highest volume. [22].

Like our study, Jindal et al.,[20] ~~who~~ concluded a significantly higher P-LCR in diabetics patients compared to the non-diabetics.

T~~In t~~he current study, ~~it~~ also clarified some positive correlations between platelet distribution width, platelet large cell ratio and age, on one hand. on the other hand, platelet distribution width showed negative correlation with blood urea. Moreover, Fibrinogen had positive correlation with mean platelet volume.

The association between fibrinogen levels and hyperglycemiamay be caused by the fact that fibrinogen that has been glycosylated is less likely to be destroyed by plasmin or by the fact that differential protein synthesis is brought on by relative insulin insufficiency in DM patients, with albumin synthesis decreasing by 29% and fibrinogen synthesis increasing by 50% [23].

It's likely that hyperfibrinogenemia is just a side effect of atherosclerosis, which is characterised by persistent inflammation, or by the development of fatty plaques on blood

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vessel walls, which results in cardiovascular disease. Contrarily, hyperfibrinogenemia may consciously thickened the blood, influence platelet interactions, or activate other processes that proactively encourage the development of atherosclerotic plaques on walls of the arteries and veins [24, 25].

There has also been evidence between MPV and diabetes individuals' decreased glucose control. Increased PDW has reportedly been linked, like MPV, to vascular problems and diabetes [26], [27].

Like our study,Ateş et al.,[28]discovered a correlation between the average MPV levels and the degree of retinopathy. This discovery implies that platelets play a role in the development of vascular problems and that measuring mean platelet volume may help track the course of a disease.

Conclusions:

Instead of using mean platelet volume, basic indicators like serum fibrinogen, platelet distribution width, and platelet large cell ratio may be utilised to identify microvascular problems in type 2 diabetes mellitus.

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