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Platelet Indices and Neutrophil/ Lymphocyte Ratio in Type 2 Diabetes Mellitus and their Correlation with Glycemic Control

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Abstract

Diabetes mellitus (DM) is the most challenging problem in today's world, it is a complex disease characterized by chronic hyperglycemia, metabolic abnormalities, and long-term macro and micro vascular complications. Type 2 diabetes mellitus (T2DM) accounts for over 80% of cases of DM. HbA1c is a more useful marker to determine mean blood glucose levels over a long time period. This study aims to assess changes in platelet indices and neutrophil / lymphocyte ratio in type 2 diabetes mellitus and their correlation with diabetic control. It is single center study, patients were selected from the outpatients and inpatients of the Endocrinology Department at Al-Zahraa University Hospital, through the period from February 2021 to July 2021. The study was conducted on 40 cases with type 2 diabetes mellitus which divided into two subgroups, group A (n=19) controlled diabetes (HbA1C <7%) and group B (n= 21) patients with uncontrolled diabetes (HbA1C >7%) in parallel with 40 apparently healthy individuals. For all subjects, platelet indices, and neutrophil/ lymphocyte ratio (NLR), prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin (PTT) time were investigated. In this study, a significant increase in mean platelet volume (MPV) and PTT were observed in the diabetic group in comparison to the control group. There was a significant increase in WBCs and lymphocyte count between controlled and uncontrolled diabetes. while there was no statistically significant difference of PLTs, MPV, PDW, PCT, NLR, PTT, PT, & INR between controlled and uncontrolled diabetes. Our study revealed that a significant increase in MPV in diabetic patients additionally there is a significant positive correlation between HbA1C and MPV , in addition, changes in coagulation profile (specially PTT) contribute to the thrombotic state in diabetes mellitus.

Keywords: Platelet Indices, Neutrophil/Lymphocyte Ratio, Type 2 Diabetes Mellitus, Glycemic Control.

1. Introduction

Diabetes mellitus is a group of metabolic disorders characterized by abnormal carbohydrate metabolism resulting in chronic hyperglycemia caused by defective insulin production [1]. Several studies have shown that T2DM predisposes to a multifactorial prothrombotic state, in which endothelial dysfunction, platelet hyper-reactivity, alterations of the coagulation cascade, impaired fibrinolysis, as well as chronic low-grade inflammation, are known to play a major role [2]. Platelets are essential for hemostatic plug formation and pathogenesis of arterial thrombosis [3]. Hence increased mean platelet volume (MPV) and platelet distribution width (PDW) might be associated with increased thrombotic potential. Larger platelets with altered morphology could be associated with an increased risk of vascular complications in diabetes. Diabetic patients have shown significantly higher MPV than the nondiabetic subjects [4]. The immune response to various physiological challenges is characterized by increased neutrophil and decreased lymphocyte counts, and NLR is often recognized as an inflammatory marker to assess the severity of the disease [5]. Neutrophil lymphocyte ratio (NLR) is an essential marker of systemic inflammation and an indicator of increased risk for cardiovascular events in patients with metabolic syndrome. In addition, increased NLR may be related to type 2 diabetes mellitus [6]. This study aims to assess changes in platelet indices and neutrophil /lymphocyte ratio in type 2 diabetes mellitus and their correlation with diabetic control.

2. Patients and Methods

2.1 Patients:

This study was a case-control, performed on 80 subjects. A total of 40 patients diagnosed with type 2 DM and 40 age and sex matched healthy subjects as control were included in this study. Their ages ranged from 25 to 70 years old. Those patients were selected from the outpatients and inpatients of the endocrinology department at Al-Zahraa University Hospital during the period from February 2021 to July 2021. The informed consent was obtained from the patients and controls before they participated in the study.

They were divided into 2 groups:

1- **Patients group**: Type 2 diabetes mellitus (T2DM) patients (n=40). They were 23 females and 17 males, their ages ranged from 36 to 65 years old. Based on HbA1C level, the patient group was divided into two subgroups, group A (n=19) controlled diabetes (HbA1C <7%) their age ranged from 39 to 65 years old and group B (n= 21) patients with uncontrolled diabetes (HbA1C >7%) their ages ranged from 36 to 62 years old.

2- **Control group:** Included apparently healthy individuals (n=40). They were 23 females and 17 males as a control group their ages ranged from 38 to 65 years old.

The patients were selected according to the following inclusion and exclusion criteria:

Inclusion criteria: Type 2 diabetes mellitus (T2DM) adults' patients, their ages ranging from (25 to 70) years old.

Exclusion criteria: Patients with, type 1 diabetes mellitus, idiopathic thrombocytopenic purpura, cardiac, stroke, liver cell failure, myeloproliferative neoplasm and patients on anticoagulant drugs or anti platelet drugs were excluded from the study.

Specimen collection and preparation: Five ml of peripheral venous blood were withdrawn from each individual under complete aseptic condition and divided into

two aliquots, 3 ml were collected in an EDTA tube for CBC analysis and HbA1C measurement, 2ml was collected in citrate tube for PT, INR, and PTT.

2.2 Methodology:

All Participants will be subjected to the following:

1) Complete history taking and full clinical examination.

2) Laboratory investigations including complete blood count and neutrophil lymphocyte ratio using (Cell Dyn Ruby, Germany), HbA1c% using (BIO-RAD D-10, France), PT, INR and PTT using (Stago Compact, France).

Statistical analysis

Data were analyzed using statistical program for social science (SPSS) version 24. Quantitative data were expressed as median and IQR as the data was abnormal distribution. Qualitative data were expressed as frequency and percentage. Mann–Whitney U test was used when comparing two means. Chi-square test was used when comparing non-parametric data. Pearson's correlation coefficient (r) test was used for correlating data. Probability (P-value) –P-value < 0.05 was considered significant. –P-value < 0.001 was considered as highly significant. P-value > 0.05 was considered non-significant.

3. Results

In this study 80 subjects aged (25-70) years old of both sexes, they were divided into 2 groups: the first group was patients' group: Type 2 diabetes mellitus patients (n=40). They were 23 females and 17 males. Their ages ranged from 36 to 65 years old. Based on HbA1C level, the patient group was divided into two subgroups, group A (19) controlled diabetes (HbA1C <7%) their ages ranged from 39 to 65 years old and group B (21) patients with uncontrolled diabetes (HbA1C >7%) their ages ranged from 36 to 62 years old. Another group is a control group: included apparently healthy individuals (n=40), they were 23 females and 17 males their ages ranged from 38 to 65 years. Table 1. shows a statistically significant increase (p-value < 0.05) between studied groups as regards MCHC, and MPV. No statistically significant difference (p-value > 0.05) between studied groups as regard RBCs, Hb, HCT, MCV and MCH. No statistical differences as regards, age and sex. No statistically significant differences (p-value > 0.05) between studied groups as regard WBCs, Neutrophil, Lymphocytes and NLR., PLTs, PCT, and PDW, no statistically significant difference (p-value > 0.05) between studied groups as regards PT and INR, while APTT showed a highly significant increase in the patient's group as compared to the control group (p-value < 0.05).

In patients' group there were statistically significant (p-value = 0.009) Positive correlation (r = 0.41) between HbA1C and MPV (fig.1), whereas not statistically significant (p-value > 0.05) correlation between HbA1C and other studied indices as shown in table (2).

Table. 3 shows a statistically significant increase (p-value < 0.05) between controlled and uncontrolled patients as regard WBCs and lymphocyte count while there are no statistically significant differences (p-value > 0.05) between controlled and uncontrolled patients as regard age and sex, Hb, RBCs, and RBCs indices, neutrophil count and NLR, PLTs, MPV, PCT and PDW. No statistically significant difference (p-value > 0.05) between controlled, and uncontrolled patients as regard PT, APTT, and INR.

In controlled patients' group there was not statistically significant (p-value > 0.05) correlations between HbA1C and other studied indices (Table4).

4. Discussion

Diabetes Mellitus (DM) is an important health problem affecting major population

worldwide. It is characterized by absolute or relative deficiency in insulin secretion and/or insulin action and is associated with chronic hyperglycemia and disturbances of carbohydrate, lipid and protein metabolism [7].

Table (1): Comparison between patient group and control group as regard age, sex, Hb, RBCs, RBCs indices, WBCs, neutrophil, lymphocytes, NLR, PLTs, MPV, PCT, PDW, PT, APTT and INR.

		Patients (N = 40)	Control (N = 40)	Stat test/ MW	P-value
Age (years)	**Median**	50.5	52	MW = 676	0.232 NS
	IQR	44 - 59.8	48 - 60		
Sex	**Male**	17(42.5%)	17(42.5%)	X^2 = 0.0	1.0 NS
	Female	23(57.5%)	23(57.5%)		
RBCs (10^6/uL)	**Median**	4.6	4.7	741	0.569 NS
	IQR	4.32 - 5.1	4.3 - 4.9		
Hb (g/dl)	**Median**	13.05	12.7	717	0.424 NS
	IQR	11.9 - 13.9	12. - 13.5		
HCT (%)	**Median**	39	38.9	764	0.729 NS
	IQR	36.2 - 41.7	37.4 - 41.2		
MCV (fL)	**Median**	82.8	84	623	0.088 NS
	IQR	79.2 - 85.6	79.9 - 89.8		
MCH (pg/cell)	**Median**	27.9	27.4	783	0.870 NS
	IQR	25.1 - 29.3	25.9 - 29.3		
MCHC (g/dl)	**Median**	33.3	32.5	**582**	**0.036 S**
	IQR	31.9 - 34.6	31.5 - 33.1		
WBCs and differential count					
WBCs ($x10^9$/L)	**Median**	6.35	6.1	719	0.435 NS
	IQR	4.9 - 8.4	5.3 - 7.4		
Neutrophil ($x10^9$L)	**Median**	3.25	3	748.5	0.620 NS
	IQR	2.3 - 4.2	2.1 - 3.8		
Lymphocytes ($x10^9$/L)	**Median**	2.6	2.5	698.5	0.328 NS
	IQR	1.9 - 3.2	2 - 2.7		
NLR	**Median**	1.22	1.27	787.5	0.904 NS
	IQR	0.8 - 1.66	0.85 - 1.62		
PLTs indices					
PLTs ($x10^9$/L)	**Median**	233	257.5	708	0.376 NS
	IQR	184.3 - 314	234.8-287.3		
MPV (fl/cell)	**Median**	10.1	9	**497**	**0.004 S**
	IQR	8.5 - 10.9	8.1 - 9.57		
PCT (%)	**Median**	0.24	0.23	771	0.780 NS
	IQR	0.19 - 0.29	0.19 - 0.27		
PDW (%)	**Median**	16.2	15.5	652	0.154 NS
	IQR	13.02 - 21.2	13.5 - 18.2		
PT, APTT and INR					
PT (sec)	**Median**	13.2	13	692.5	0.3 NS
	IQR	12.5 - 13.7	12.5 - 13.3		
APTT (sec)	**Median**	34.9	31.2	**469.5**	**0.001 HS**
	IQR	31.4 - 37.5	29.3 - 33.8		
INR	**Median**	1	1	767	0.631 NS
	IQR	1 - 1	1 - 1		

X^2: Chi-square test; HS: p-value < 0.001 is considered highly significant; MW: Mann-Whitney U; NS: p-value > 0.05 is considered non-significant; S: p-value < 0.05 is considered significant.

Table (2): Correlation study between HbA1C and (PLT indices & NLR, PT, PTT, INR) in patients' group and control group.

Variables	Patients		Control	
	r	p-value	r	p-value
HbA1C vs PT	- 0.15	0.332 NS	0.16	0.305 NS
HbA1C vs PTT	0 -039	0.814 NS	0.1	0.515 NS
HbA1C vs INR	- 0.240	0.135 NS	- 0.02	0.9 NS
HbA1C vs PLTs	-0.02	0.881 NS	-0.08	0.617 NS
HbA1C vs MPV	**0.41**	**0.009 S**	0.05	0.771 NS
HbA1C vs PCT	0.17	0.3 NS	-0.07	0.667 NS
HbA1C vs PDW	-0.11	0.509 NS	-0.01	0.956 NS
HbA1C vs NLR	-0.02	0.923 NS	-0.15	0.345 NS

(r): Pearson correlation coefficient. **S: p-value < 0.05 is considered significant.**
NS: p-value > 0.05 is considered non-significant

Table (3): Comparison between patient's sub-groups as regard age, sex, Hb, RBCs, RBCs indices, WBCs, Neutrophil, Lymphocytes, NLR, PLTs, MPV, PCT, PDW, PT, APTT and INR.

		HbA1C		Stat test	P-value
		Controlled <7% (N = 19)	Uncontrolled >7% (N = 21)		
Age (years)	**Median**	55	50	MW = 147.5	0.161 NS
	IQR	44 - 62	42 - 56.5		
Sex	**Male**	9(47.4%)	8(38.1%)	X^2 = 0.35	0.554 NS
	Female	10(62.6%)	13(61.9%)		
RBCs (m/mm³)	**Median**	4.5	4.8	145	0.145 NS
	IQR	4.3 - 4.8	4.5 - 5.3		
Hb (g/dl)	**Median**	12.6	13.4	163.5	0.333 NS
	IQR	11.8 - 13.6	12.6 - 13.9		
HCT (%)	**Median**	38.8	39.2	183	0.668 NS
	IQR	36.1 - 39.7	36.2 - 42.6		
MCV (fl/cell)	**Median**	85.5	80.3	129	0.057 NS
	IQR	79.3 - 89	78.5 - 84.7		
MCH (pg/cell)	**Median**	28	27.6	168	0.405 NS
	IQR	27.2 - 29.4	24.7 - 29.2		
MCHC (g/dl)	**Median**	33.2	33.5	196.5	0.936 NS
	IQR	32.2 - 34.6	31.6 - 34.7		
WBCs and differential count					
WBCs (x10³/mm³)	**Median**	5.2	7.4	122	**0.036 S**
	IQR	4.3 - 8.3	6.2 - 8.6		
Neutrophil (x10³/mm³)	**Median**	2.5	3.6	140.5	0.111 NS
	IQR	1.9 - 3.8	2.6 - 4.3		
Lymphocytes (x10³/mm³)	**Median**	2.3	2.8	124	**0.041 S**
	IQR	1.7 - 2.8	2.25 - 3.5		
NLR	**Median**	1.23	1.18	187	0.748 NS
	IQR	0.79 - 1.77	0.83 - 1.58		
PLTs indices					
PLTs (x10³/mm³)	**Median**	236	221	192	0.851 NS
	IQR	206 - 302	184 - 363		
MPV (fl/cell)	**Median**	9.8	10.4	133	0.074 NS
	IQR	8.1 - 10.2	8.75 - 11.85		
PCT (%)	**Median**	0.24	0.24	173	0.486 NS
	IQR	0.18 - 0.25	0.19 - 0.34		
PDW (%)	**Median**	16.5	15.9	186	0.728 NS
	IQR	12.8 - 21.2	13.2 - 21.6		
PT, APTT and INR					
PT (sec)	**Mean**	13.2	12.9	T = 1.2	0.235 NS
	±SD	0.7	0.9		
APTT (sec)	**Mean**	35.5	33.6	T = 1.3	0.192 NS
	±SD	4.2	4.6		
INR	**Median**	1	1	MW = 175.5	0.520 NS
	IQR	1 - 1	1 - 1		

MW: Mann-Whitney U; NS: p-value > 0.05 is considered non-significant; S: p-value < 0.05 is considered significant; T: independent sample T test; X2: Chi-square test

Table (4): Correlation study between HbA1C and (PLT indices & NLR, PT, PTT, INR) in studied patient's sub-groups.

Variables	Controlled patients		Un-controlled patients	
	r	p-value	r	p-value
HbA1C vs PT	-0.13	0.597	0.02	0.931
HbA1C vs PTT	-0.02	0.939	0.29	0.2
HbA1C vs INR	-0.14	0.563	-0.27	0.235
HbA1C vs PLTs	-0.08	0.753	-0.12	0.598
HbA1C vs MPV	0.30	0.217	0.34	0.13
HbA1C vs PCT	-0.03	0.919	0.13	0.568
HbA1C vs PDW	-0.18	0.463	-0.22	0.34
HbA1C vs NLR	0.10	0.686	-0.17	0.475

(r): Pearson correlation coefficient., S: p-value < 0.05 is considered significant, NS: p-value > 0.05 is considered non-significant

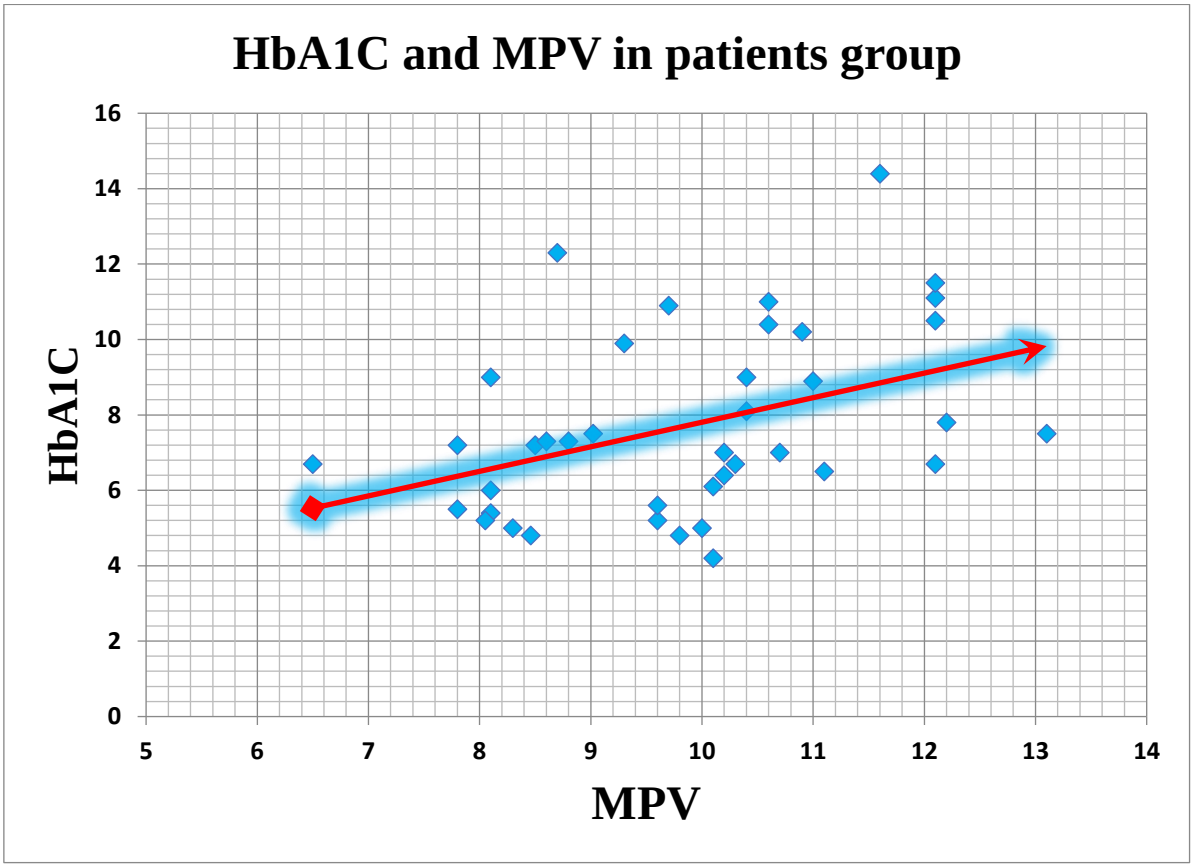

Figure (1): Positive correlation between HbA1C and MPV in patients' group.

In diabetes, several factors including impaired fibrinolysis, increased coagulation, endothelial dysfunction and platelet hyper reactivity, contribute to the prothrombic condition that describes patients with T2DM. Platelets are characterized by hyperactive with increased activation, adhesion and aggregation due to dysregulation of several signaling pathways in T2DM patients. Platelets involve in disease pathology by not only triggering thrombus formation but also by releasing oxidative, mitogenic and vasoconstrictive substances that induce the development of local vascular lesions. Furthermore, elevated baseline activation and platelet hyper reactivity in diabetic patients are associated with various metabolic conditions like hyperglycemia, insulin resistance, obesity, dyslipidemia, increased systemic inflammation and oxidative stress [8]. PLT and platelets indices such as MPV, PDW, and PCT

have emerged to be important markers for disease pathophysiology. Platelet activity is associated with the initiation of coagulation cascades. When a blood vessel is damaged, the sub-endothelial surface becomes the primary target site of platelet action, where it establishes hemostasis [9].

In this study, analysis of the platelet indices demonstrated that mean platelet volume was significantly higher among both sexes in people with T2DM in comparison with control (p = 0.004). This is in corroboration with the studies conducted by, Shilpi et al. (2018) [10], Kodiatte et al. (2012) [11], Demirtas et al. (2015) [12], and Alhadas et al. (2016) [13] showed a significantly higher MPV in diabetic patients as compared with non-diabetic control. In contrast an earlier study Akinsegun et al., (2014) [14] showed lower MPV in diabetic cases compared to the controls with no statistically significant difference (p = 0.593) explained that the majority of diabetics utilized for this study had been on treatment and in particular antiplatelet medications like clopidogrel and vasoprin for varying durations. Also, our study showed higher MPV but not statistically significant difference (p= 0.07) between controlled and uncontrolled diabetes in agreement with the study conducted by Kshirsagar et al., (2019) [4] which showed there was no statistically significant difference in MPV between diabetics with and without complications. This indicates that elevated MPV could be either the cause for or due to the effect of the vascular complications. In agreement with Palella et al. (2020) [2], the current study demonstrated that there was a significant positive correlation (r = 0.41) between MPV and HbA1c between type 2 diabetics and control. In contrast to our study Kshirsagar et al., (2019) [4] showed there was no significant correlation between MPV and HbA1c for diabetics than for the controls. Elevated levels of MPV in people with T2DM of the present study may also be explained in terms of oxidative stress. Increased reactive oxygen species in diabetes induces non enzymatic glycation of proteins on the surface of the platelet [11], such glycation leads to over-accumulation of advanced glycation end products (AGEs) (15). Some of these AGE cause externalizations of platelet membrane phosphatidylserine that may cause changes in protein structure (conformation) and alterations of membrane lipid dynamics [16]. This may also explain the increased values of MPV in patients of the present study. In our study show there were no statistically significant difference in PDW, PCT between type 2 diabetics and control, also controlled and uncontrolled DM. Similar finding was observed in study done by Mowafy et al. (2015) [17]. However, in contrast to our study, Jinda et al. (2011) [16] observed a statistically significant difference higher PDW in diabetics with complications than without complications similar finding was observed in Shilpi et al. (2018) [10]. In this study, no statistically significant difference in PLTs count between the diabetic group and non-diabetic group, and between controlled and uncontrolled diabetes. In agreement with Kshirsagar et al., (2019) [4] showed there was no statistically significant difference in PLTs count between diabetics with and without complications. In contrast to our study Akinsegun et al., (2014) [14] revealed that significant higher mean platelet counts for diabetics than for the controls (p = 0.038). This study showed there were a statistically significant increase in WBCS & Lymphocyte count between controlled and uncontrolled diabetes. In (2021) Adane et al. [1] showed that WBC & lymphocyte count increased significantly in the DM patients compared with the control group. Incontrast to the currenet study Palella et al. (2020) [2] figured out there was no statistically significant difference in WBC & lymphocyte count between controlled and uncontrolled diabetes. NLR in

complete blood count is studied in many diseases as an inflammatory marker and is used to predict their prognosis [18]. Guo et al. (2015) [19] suggested that NLR, as an inflammatory marker, could accurately predict type 2 DM.

As regard neutrophil count and NLR, the current study showed , non-significant difference neither between the diabetic group and control nor the controlled and uncontrolled group of DM. In agreement with this study, Ciray et al. (2015) [20] found that NLR was not significantly different between patients with and without diabetic retinopathy. Another study conducted by Moursy et al. (2015) [21] figured out there was no statistically significant difference between T2DM without any microvascular complication and healthy control as regards the levels of NLR (p=0.65). In addition, similar finding was observed in Lee et al. (2014) [22] & Palella et al. (2020) [2] explained that NLR was close to, but did not reach a significant difference, probably due to small sample size. In contrast to the current study, Duman et al. (2019) [23] figured out that NLR is statistically elevated in the diabetic group compared with non-diabetic group. Diabetics have been shown to be in procoagulant state due to several plasma proteins in blood coagulation. Measurement of PT and activated partial abnormalities in APTT are usually done in patients with suspected retrograde nailing regarding functional outcome in distal half of femur fractures abnormal coagulation [24]. In our study, PTT showed statistically significant increase (p-value < 0.05) between diabetic group compared with non-diabetics (p = 0.001). In (2020) Mohammed OIA [24] study showed that significantly increased values of APTT, PT, and INR between diabetic patients and control. Similar findings were observed in Soltani et al. (2012) [25]. Explained that the reason was high glucose level causes incomplete activation of the coagulation cascade. It may be due to in vitro interference of fibrin clot by inhibitors. However, the hypercoagulable state in T2DM was probably due to the reduction of suppressive role of coagulation factors V, VIII. In agreement with studies by Ifeanyi et al. (2014) [26], the current study found that there was no significant change in PT diabetic group and control group. In our study there was no statistically significant difference in PT&PTT between controlled and uncontrolled diabetes in agreement with Ambelu et al (2018) [27] showed that there was no significant difference of the mean PT, PTT between treated diabetic and non-diabetic individuals ($P > 0.05$). This might be due to the effect of non-insulin hypoglycemic drugs on glucose level which in turn prevents the glycation process in treated DM patients. Also, some studies found no significant changes in coagulation studies among diabetic patients Mard-Soltani et al. (2011) [28].

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