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RESEARCH ARTICLE

Haemostatic and Haematological Parameters among Type 2 Diabetes Patients in A Tertiary Health Facility in Ondo State, Nigeria: A Cross-sectional Study

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Abstract:

Background:

Type 2 diabetes mellitus (T2DM) remains one of the non-communicable metabolic disorders associated with serious thrombotic outcomes and risk of cardiovascular disease, which can be fatal.

Aim:

This study was therefore aimed at comparing the levels of haemostatic and haematological parameters of T2DM and non-diabetic subjects. The study also determines the relationship between haemostatic parameters with haematological parameters among the T2DM subjects.

Methods:

Total of 150 participants, comprising "75" of those with diabetes and those without diabetes, were recruited for the study. Blood samples were collected for the analysis of full blood count, Factor V, VII, and tissue plasminogen activator inhibitor-1 (TPA I-1). Test of significance of means was carried out using the One-Way Analysis of variance test, while relationships were tested using Pearson correlation and logistic regression.

Results:

The results revealed significantly higher levels of Factor V, VII, and TPA I-1 among participants with diabetes when compared with those without diabetes. However, significantly lower levels of red cell parameters and red cell indices were observed in the participants with diabetes. In addition, with the exception of lymphocyte and eosinophil levels, all other white blood cells(WBC), platelets, and differential leukocyte parameters were significantly higher in the subjects with diabetes. Moreover, there was a significant positive correlation between Factors V and VII, TPA I – 1 and Factor VII, TPA I-1 and platelets, Factor VII and Haematocrit (HCT) levels in diabetic subjects.

Conclusion:

Conclusively, the correlation between pro-coagulant and hypofibrinolytic factors may be accountable for the hypercoagulability and thrombotic events which characterize T2DM, thereby providing an insight into factor-specific management of the disease with haematological parameters assisting routinely predict factor levels thereafter increasing the ease of prognosis of T2DM.

Keywords: Type 2 diabetes mellitus, Tissue plasminogen activator inhibitor-1, Factor V, Factor VII, Haematological parameters, Hypercoagulability.

Article History	Received: January 09, 2023	Revised: June 19, 2023	Accepted: June 26, 2023

1. INTRODUCTION

The profound association of type 2 diabetes mellitus (T2DM) with a growing risk of thrombotic events cannot be overemphasized. Cardiovascular disease and thrombosis remain the major cause of death in 80% of patients with T2DM despite modern interventions, with diabetes having a prevalence rate of 4.3% in Nigeria [1 - 3]. In the world, generally, inflammation, insulin resistance, dyslipidaemia, thrombophilia, and obesity are higher in patients with T2DM, thereby marking the common risk factors for this disease [2, 4].

However, some additional factors of menace have been

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reportedly connected to the pathogenesis of cardiovascular disease in T2DM patients, thereby precipitating coagulation disruption and harassment of fibrinolysis, giving rise to an imbalance between haemostatic factors in plasma and endothelial cell surface, which is characterized by hypofibrinolysis [5 - 7]. The intervention of coagulation factors and co-factors can be molecularly marked by the assessment of some factors of the extrinsic and common coagulation pathway, which includes Factors I, II, V, VII, VIII and X [8 - 10].

Additionally, hypofibrinolysis may spring up by reason of a reduction in the expression of tissue plasminogen activator inhibitor – 1 (TPAI-1), an inhibitor and an important regulator of the fibrinolytic system which can as well serve as a molecular marker of the state of the same system [11, 12]. Previous investigations [13, 14] have reported numerous changes in haematological parameters among T2DM patients, and these include; structural and functional alterations alongside changes in the metabolism of platelets, white blood cells (WBC), red blood cells (RBC) and coagulation system, which manifest in various forms.

Although there have been various studies on the assessment of the effect of T2DM on the coagulation and fibrinolytic system, factor-specific studies are still few [15, 16] and inconsistent amongst the same population coupled with the fact that there is barely any information on the relationship between haematological parameters and coagulation/ fibrinolytic factors in T2DM subjects [17, 18]. This study was therefore aimed at comparing the levels of haemostatic and haematological parameters of T2DM and non-diabetic subjects. The study also determines the relationship of haemostatic parameters with haematological parameters amongst the T2DM subjects.

2. MATERIALS AND METHODS

2.1. Study Setting and Design

The study employed a cross-sectional approach and was carried out in a tertiary health facility in South West, Nigeria. A total of 150 participants, consisting of "75" participants with T2DM and "75" randomly selected participants without T2DM, were referred to as the control group.

For participants with diabetes, the inclusion criteria for the study were diagnosed patients with T2DM attending the diabetic clinic in the health facility who were willing to participate in the study. For the control group, the inclusion criteria for the study were supposedly healthy individuals that have no diabetes in the community where the health facility is located and who were willing to participate in the study. Patients on alcohol, antiplatelet, anticoagulant drugs for hypertension and coagulation disorders were excluded from the study.

2.2. Data Collection

Participants' socio-demographic data were collected using a structured questionnaire. To carry out heamotological and haemostatic analysis, a 9 ml blood sample was collected from the cubical vein of each participant using a 10 ml syringe. Following blood collection, the blood was divided into two portions, consisting of 4.5 ml dispensed into sample bottles with 0.5 ml of trisodium citrate and another 4.5 ml of EDTA (Ethylene Diamine Tetra Acetic Acid). The blood sample in EDTA bottles was used for full blood count using a blood cell count auto analyzer (Abbott Cell-DYN Emerald 22).

The blood sample in the trisodium citrate bottle was well mixed and centrifuged for 15 min at 2000 g, after which the obtained plasma was spun again for 15 min at 2000 g to obtain a platelet-poor plasma, which was separated and stored at -80°c until analysis of haemostatic factors (Factors V, VII, TPAI-1), using ELISA kits. Factors V and VII were estimated using Elabscience: E-EL-H0764 and Elabscience: E-EL-H0768, respectively; Elabscience: E-EL-H2104 was used for TPAI-1 estimation.

2.3. Statistical Analysis

All data were analysed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA) software. Data were presented using descriptive and inferential statistics. The generated data were presented as means ± standard deviation. A comparison of means was carried out using The One-Way Analysis of Variance (ANOVA), while relationships were tested using logistic regression and Pearson correlation. All analyses were carried out at a probability level of 0.05.

2.4. Ethical Considerations

Ethical approval for the study was obtained from the Research Ethics Committee of the Medical Facility used for the study with approval number: FMC/OW/380/VOL CXLIX/30; FMC/OW/380/VOL CXLIX/58. In addition, all procedures in the study were conducted in accordance with ethical regulations. Patients' anonymity and privacy were ensured throughout the study. Informed consent was obtained from all willing participants.

3. RESULTS

3.1. Socio-demographic Characteristics of the Subjects

Socio-demographic characteristics of the study subjects revealed that a greater number of participants with diabetes and those without diabetes span between ages 51- 60 years (41.3%) and 31-40 years (48.0%), respectively. Most of the participants in both categories had tertiary education. With respect to body mass index (BMI), the majority of participants with diabetes were classified as overweight (58.7%), while the majority of participants in the non-diabetic category had normal weight (76.0%). Generally, there was a preponderance of male participants in both categories. Amongst the participants with diabetes, 50.7% used a combination of Tablets, Antihypertensive (Amlodipine and Nifedipine) and STATIN (Rosuvastatin) drugs for treatment (Table **1**).

Table 1. Socio-demographic characteristics of the study subjects.

Socio-demographic		Number of Participants	
-	-	Participants' Categories	
-	-	With Diabetes	Without Diabetes
Age (years)	< 21	0 (0%)	2(2.7%)
	21-30	0 (0%)	25(33.3%)
	31-40	1 (1.3%)	36(48.0%)
	41-50	17 (22.7%)	10(13.3%)
	51-60	31(41.3%)	2(2.7%)
	61-70	19(25.3%)	0(0%)
	> 70	7(9.3%)	0(0%)
Gender	Male	42 (56.0%)	60(80.0%)
	Female	33(44.0%)	15(20.0%)
BMI	Underweight	0 (0%)	0(0%)
	Normal weight	16 (21.3%)	57(76.0%)
	Overweight	44 (58.7%)	18(24.0%)
	Obese	15 (20.0%)	0(0%)
Marital status	Single	0 (0%)	34(45.3%)
	Married	75(100%)	41(54.7%)
	Primary	2(2.7%)	0(0%)
Educational background	Secondary	12 (16.0%)	27(36.0%)
	Tertiary	61 (81.3%)	48(64.0%)
Duration (months)	< 2	5 (6.7%)	-
	2-3	17 (22.7%)	-
	6-7	14 (18.7%)	-
	8-9	1(1.3%)	-
	> 9	36(50.7%)	-
Hypertensive drugs	Patients on antihypertensive drugs	61(81.3%)	0(0%)
	Patients not on antihypertensive drugs	14(18.7%)	75(100%)
STATIN	Patients on STATIN	55(73.3%)	0(0%)
	Patients not on STATIN	20(26.7%)	75(100%)

Table 2. Coagulation and antifibrinolytic factors in the study participants.

Concentration (ng/ml)	Participants' Categories		p-value
-	With Diabetes (n=75)	Without Diabetes (n=75)	-
Factor V	742.89 (± 10.13)	414.07 (± 7.91)	< 0.001
Factor VII	776.43 (± 9.12)	430.43 (± 8.54)	< 0.001
TPAI – 1	19.72 (± 0.57)	7.25 (± 0.18)	< 0.001

Note: All values are mean concentrations, while values in parentheses are standard deviations of means. TPAI-1 represents tissue plasminogen activator inhibitor-1.

3.2. Coagulation and Antifibrinolytic Levels of the Participants

Generally, the mean concentrations of all coagulation and antifibrinolytic parameters investigated were significantly higher ($p \leq 0.05$) in participants with diabetes than in those without diabetes (Table **2**).

Among participants with diabetes, significant positive correlations were observed between Factors V and VII ($r = 0.658$, $p < 0.01$) and between Factor VII and TPAI- 1 ($r = 0.260$, $p = 0.24$). Significantly weak positive correlations were observed between Factors V and VII ($r=0.832$, $p< 0.01$), between Factors V and TPAI-1 ($r= 0.270$, $p= 0.019$), and between Factor VII and TPAI-1 ($r= 0.232$, $p= 0.045$) among participants without diabetes (Table **3**).

Among participants with diabetes, significantly lower levels of white blood cell count, platelet count, and some other differential leucocyte parameters except for lymphocytes were observed ($p< 0.05$) compared to the non-diabetic participants with diabetes (Table **4**).

Table 3. Relationship between coagulation and antifibrinolytic factors among the participants.

-		Factor V	Factor VII	TPAI-1
Participants with Participants				-
Factor V	R	1	.658**	.149
	P	-	.000	.202
Factor VII	R	.658**	1	.260*
	P	.000	-	.024
TPAI-1	R	.149	.260*	1
	P	.202	.024	-
Participants without Diabetes				-
Factor V	R	1	.832**	.270*
	P	-	.000	.019
Factor VII	R	.832**	1	.232*
	P	.000	-	.045
	P	.260	.382	.341
TPAI-1	R	.270*	.232*	1
	P	.019	.045	-

Note: 'r' and 'p' represent the correlation coefficients and probability values, respectively. TPAI-1 indicates tissue plasminogen activator inhibitor-1.

Table 4. Haemotological characteristics of the study participants.

Concentration (ng/ml)	Participants' Categories		p-value
-	With Diabetes (n=75)	Without Diabetes (n=75)	-
Haematocrit (%)	35.97 ± 0.42	42.67 ± 0.39	< 0.01
Haemoglobin conc (g/dl)	12.11 ± 0.15	14.61 ± 0.09	< 0.01
Mean cell volume (fl)	82.30 ± 0.11	83.53 ± 0.15	< 0.01
Mean cell haemoglobin (pg)	27.17 ± 0.08	28.31 ± 0.07	< 0.01
Mean cell haemoglobin concentration (g/dl)	32.29 ± 0.05	32.92 ± 0.04	< 0.01
Red blood cell count ($x10^{12}$/L)	4.43 ± 0.05	5.02 ± 0.05	< 0.01
White blood cell count ($x10^{9}$/L)	7.752.0 ± 2.57	5.439.33 ± 1.74	< 0.01
Platelet count ($x10^{9}$/L)	302.440 ± 39.28	246.506 ± 51.02	< 0.01
Neutrophil count (%)	55.48 ± 0.10	52.24 ± 0.69	0.07
Lymphocyte count (%)	38.55 ± 1.09	44.12 ± 0.71	< 0.01
Monocyte count (%)	3.80 ± 0.16	1.93 ± 0.20	< 0.01
Eosinophil count (%)	0.75 ± 0.03	0.95 ± 0.11	0.83
Basophil count (%)	1.39 ± 0.03	0.12 ± 0.01	< 0.01

Table 5. Relationship of TPAI-1, Factors V and VII with haemotological characteristics of the two categories of participants.

-	Constant	HCT	HBG	MCV	MCH	MCHC	RBC	WBC	PLT	NEU	LYMP	MON	EOS	BAS
Participants with Diabetes														
TPAI-1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Beta	-	0.116	-0.309	0.028	0.031	-0.045	0.215	-0.328	0.524	0.037	-0.537	-0.087	-0.01	0.018
Sig.	0.931	0.696	0.234	0.851	0.864	0.667	0.191	0.074	0	0.96	0.516	0.635	0.931	0.862
Factor V	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Beta	-	0.299	-0.366	-0.116	0.048	0.171	0.016	0.127	0.113	0.801	1.156	0.4	0.063	0.075
Sig.	0.735	0.439	0.276	0.548	0.834	0.209	0.94	0.59	0.514	0.402	0.282	0.095	0.674	0.584
Factor VII	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Beta	-	0.765	-0.505	-0.289	-0.391	0.093	0.317	-0.104	0.092	0.965	0.811	0.077	0.073	0.144
Sig.	0.202	0.034	0.103	0.104	0.069	0.455	0.105	0.63	0.563	0.273	0.41	0.725	0.597	0.252
TPAI-1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Beta	-	-0.176	0.048	-0.376	0.19	-0.142	0.244	-0.293	0.228	0.41	0.369	0.085	-0.164	0.084
Sig	0.061	0.585	0.879	0.019	0.219	0.297	0.204	0.013	0.144	0.187	0.186	0.56	0.22	0.521

(Table 5) contd.....

-	Constant	HCT	HBG	MCV	MCH	MCHC	RBC	WBC	PLT	NEU	LYMP	MON	EOS	BAS
Participants with Diabetes														
Factor V	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Beta	-	0.106	0.061	-0.078	0.202	-0.054	-0.004	0.017	0.536	-0.052	-0.072	0.075	-0.094	-0.034
Sig.	0.915	0.701	0.821	0.562	0.128	0.641	0.98	0.859	0	0.845	0.761	0.549	0.411	0.765
Factor VII	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Beta	-	-0.222	0.194	0.17	0.009	-0.009	0.137	0.089	0.396	0.009	-0.114	0.074	-0.168	0.049
Sig.	0.469	0.456	0.508	0.244	0.949	0.943	0.437	0.404	0.007	0.976	0.657	0.584	0.175	0.686

Note: Beta and Sig. represent correlation coefficient and significant values, respectively. HCT: haematocrit (%), haemoglobin concentration (g/dl), mean cell volume (fl), mean cell haemoglobin (pg), mean cell haemoglobin concentration (g/dl), red blood cell count (10^{12}/l), white blood cell (10^{9}/l), platelet count ((10^{6}/l), neutrophil (%), lymphocyte (%), monocyte (%), eosinophil (%) and basophil (%). TPAI-1: tissue plasminogen activator inhibitor-1.

There was a significant positive correlation between levels of TPAI-1 and platelet count (Beta = 0.524, $p < 0.001$), Factor VII, and Haematocrit level (Beta = 0.765, $p = 0.034$) among the participants with diabetes (Table **5**).

4. DISCUSSION

In the present study, a greater proportion of the participants with T2DM were within the age group of 51-60 years. This was marginally higher than the observation of earlier researchers with similar studies [19, 20]. In a recent study in Ekiti State, Nigeria, a slightly higher age range of 60-69 years was reported to be dominant among individuals with T2DM [21]. It is opined that a change in metabolism has been associated with age in most diseases that are non – communicable, without the exclusion of diabetes. The tilt of the age trend toward adulthood is not farfetched from the fact that aging reportedly initiates a reduction in insulin sensitivity. Hence, glucose tolerance gradationally declines with age [22]. With regard to BM1, the majority of the study participants with diabetes were observed to be overweight as against the high record of normal weight observed among participants without diabetes. Previous researchers have also observed a similar trend [23, 24].

Excess weights have been reported as a risk factor for T2DM, thus predisposing patients to an increment in the production of some cytokines and adipokines, which contribute to insulin resistance and reduction in levels of adiponectin. It also leads to the deposition of ectopic fat in some body parts, most especially the liver [25, 26]. In addition, the study observed a higher number of male participants among those with diabetes. A similar observation has been reported by earlier investigators [27, 28]. Increased prevalence of T2DM in middle age/elderly men in which smoking has reportedly played a significant role, as has been reported earlier [29]. However, some studies have reported a high prevalence of diabetes among females, which is incongruous with the present study [30, 31].

In the present study, significantly higher levels of Factors V and VII were observed among the participants with diabetes. A similar observation has been reported by earlier investigators [18, 32]. The study findings, however, negated the observation of Erem *et al*. [17], who revealed no significant change in the levels of Factors V and VII in participants with diabetes when compared with those without diabetes. Generally, modification of coagulation factors has been reportedly associated with metabolic disorders, including diabetes mellitus. Thus altering the physiological mechanisms, which results in a prothrombotic state [6]. A significantly higher level of TPAI–1 was observed among the participants with diabetes in this study. A similar observation has also been reported elsewhere [33, 17]. Oxidative stress, which is pivotal in T2DM, has been attributed to a spike, a 3–fold rise in the level of TPA I – 1 by acting on Activator Protein – 1 (AP-1) binding site at s- 60/52 of the promote, which is a normal observation in the mutational analysis [34].

Results of the haematological parameters revealed significantly lower levels of red cell parameters were observed among the participants with diabetes. This observation corroborates the trend reported by Arkew *et al*. [35]. Generally, oxidative stress, which is connected with diabetes mellitus, does affect the antioxidant enzymes of the red blood cells. In this case, glutathione reductase level is affected, which results in a reduction in the red cell parameters, majorly haemoglobin [14, 36]. However, significantly lower levels of white blood cell count, platelet count, and some other differential leucocyte parameters, except for lymphocytes, were observed among the participants with diabetes in this study. A similar observation has been reported by other workers [37, 38].

In addition, the present study revealed a significantly positive correlation between factors V and VII in both categories of participants. A similar trend has been reported by other researchers [5, 39, 40]. It is indicated that platelets can accommodate a high proportion of TPAI-1 found in the blood. Diabetic platelets have reportedly been big and over-reactive. This might have resulted in the correlation increment observed between TPAI-1 and platelets in T2DM subjects [41]. Similarly, there was a positive correlation between the haematocrit levels and factor VII levels in diabetic subjects, which was not recorded in the non-diabetic counterpart. It has been indicated RBCS maintains a great involvement in haemoglobins both physiologically and pathologically. This is exposed by its contribution to thrombotic events through RBC and RBC precipitated microvesicle surface phosphatidylserine association with the coagulation cascade [42].

CONCLUSION

This study revealed a significant correlative increment between Factors V and VII, TPAI-1 and Factor VII in diabetic subjects. This has further established the claim that hypercoagulability is associated with T2DM. Moreover, the positive correlation observed between TPAI-1 and platelets, Factor VII and HCT, can perhaps make platelets and HCT serve as routine predictors of TPAI-1 and Factor VII levels, respectively. Hence, a definitive and easy approach toward

achieving the goal of factor-specific therapy in the management of T2DM becomes more realistic. The limitation of this research is the difficulty in getting information from some illiterate subjects.

LIST OF ABBREVIATIONS

T2DM	=	Type 2 diabetes mellitus
WBC	=	White blood cells
RBC	=	Red blood cells

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval for the study was obtained from the Research Ethics Committee of the Medical Facility used for the study with approval number: FMC/OW/380/VOL CXLIX/30; FMC/OW/380/VOL CXLIX/58.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committees and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants of this study.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

STANDARDS OF REPORTING

STROBE guidelines were followed.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors are grateful to Afe Babalola University, Ado-Ekiti, for providing facilities for the study.

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