Some Markers Of Coagulation Activation And Glycemic Control In Type 2 Diabetic Mellitus Patients Based On ABO And Rhesus D Blood Group

Alphonsus Ogbonna Ogbuabor[1], Mathew Chibunna Igwe[2], Nkiruka Millicent Amadi[1,2]
Department of Medical Laboratory Sciences, Faculty of Basic Medical Sciences, College of Medicine Enugu State University of Science and Technology, Enugu State, Nigeria.
Correspondence : ogbuaborao@yahoo.com

***Abstract*—The burden of type 2 diabetes mellitus is increasing worldwide and raising concern.It is a leading cause of death and reduced lifespan globally. Due to lack of funds and poor healthcare system, sub-Saharan Africa is the worst affected with Nigeria bearing the greatest burden for the region. A major factor underlying the development of complication in type 2 diabetes is poor glycemic control and coagulation activation. The aim of the present study is to determine the impact of the ABO/RhD blood group system on glycemic and coagulation control in type 2 diabetes mellitus. This was an observational cross sectional study involving 100 type 2 diabetic mellitus patients (52 males and 48 females) aged 40-80 years. Subject's blood group was determined using the hemagglutination technique and commercial antisera obtained from Fortress Diagnostic Ltd, UK. The activated partial thromboplastin time, prothrombin time, and the International normalized ratio were determined by manual method using kits obtained from Fortress Diagnostic Ltd, UK. The fasting blood sugar and the two hour post prandial glucose level were determined by the glucose oxidase enzymatic method with commercial kits obtained from Biologo Co. Ltd, France while the glycated hemoglobin levels were determined by the Ion exchange chromatography method with reagents obtained from Fortress Diagnostic kits, UK. The fibrinogen von willebrand factor antigen and D-dimer levels were determined by ELISA with kits obtained from Shanghai Huirui Chemical Technology Co. Ltd, China. Data was analyzed using SPSS version 20 (IBM Statistics, Armok, USA). Differences were determined by Student Test and One Way Analysis of Variance. Result were presented as mean + SD. P < 0.05 was considered significant. The activated partial thromboplastin time, prothrombin time and the international normalized ratio were significantly increased for the subjects with blood type O (P = 0.003, 0.007 and 0.04) respectively compared to the A, B, and AB individuals.The von willebrand factor, fibrinogen and D-dimer levels were significantly decreased for the subjects with blood type O (p = 0.001, 0.006, 0.011) respectively compared to the A, B and AB subjects. There was no significant differences (P > 0.05) in these parameters between the RhD (+) and RhD (-) subjects. These findings suggests that individuals with blood type O may have a better glycemic and coagulation control and lower risk for developing complications due to type 2 diabetes mellitus. This also suggests that the RhD blood type may not have influence on the glycemic and coagulation control and the risk for developing complications for type 2 diabetes mellitus.**

Keywords—blood group, diabetes mellitus, complications, glycemia, coagulation, control

Introduction

Diabetes mellitus is a group of metabolic disorders characterized by abnormal carbohydrate metabolism resulting in chronic hyperglycemia caused by defective insulin production, action or both[1,2].Type 2 Diabetes mellitus (T2DM) is the most prevalent type of diabetes and accounts for about 90-95% of diabetes cases[3,4,5]. It's global prevalence has increased from 4.7% (108 million) in 1980 to 9.3% (463 million) in 2019 and postulated to increase to 10.2% (578 million) by 2030 as well as 10.9% (700 million) by 2045 as well [6,7] It is also estimated that 15.5% (9.8-27.8 million) people in the Sub-Saharan Africa have type 2 diabetes with Nigeria having the highest burden of cases[8]. As type 2 Diabetes mellitus is emerging as a modern epidemic, studies of T2DM are also ever increasing to predict its risk and causative factors to improve the prognosis and treatment outcomes[9].The blood group systems represents polymorphic traits inherited among individuals of a population[10].They refer to all the genes, alleles, genotype and phenotypes that exist for a particular set of blood antigen. The ABO blood group system defines individuals by the presence of "A", "B", both "A" and "B" or by the absence of these antigens "O" in their red blood cell membranes whereas the Rhesus "D" blood group system defines the expression of the "D"-antigen" on the red blood cell membranes as Rhesus positive and its non expression as Rhesus negative[11]. Studies have reported the relationships between blood group systems, coagulation activation and glycemic control in patients with type 2 diabetes

mellitus with coagulation activation and poor glycemic control in some blood groups suggested as the common underlying factor to the development of complications[12].However, there are currently a paucity of data on the relationship between the ABO/Rhesus D blood group and glycemic control as well as coagulation activation in individuals with T2DM for the Nigerian population. The present study was designed to determine the relationship between ABO/Rhesus D blood group to glycemic control and coagulation activation.

Materials and Methods

Study Setting

This study was conducted at the Enugu State University of Science and Technology Teaching Hospital Parklane, Enugu State, Nigeria. The teaching hospital is a major tertiary health facility located at the centre of the State metropolis (Enugu) for easy accessibility to residents. Enugu State derived its name from its capital and largest city, Enugu. It has an area of 7,161km^2 with a population of 3,267,837 comprising mainly the Igbo tribe of the South Eastern Nigeria. It lies between longitudes 6^o 30$^{'}$E and 6^o 55$^{'}$E and latitude 5^o 15$^{'}$N and 7^o 15^{o}N. It consists of three senatorial divisions namely Enugu East, Enugu North and Enugu West and Seventeen Local Government Areas comprising 450 communities.

Study Design

This was a prospective analytical cross-sectional study conducted on patients with type 2 diabetes mellitus (T2DM) with ages between 40-80 years in the Diabetic Outpatient Clinic from January 2022 to February, 2023 using the convenient sampling technique. A total of 100 T2DM patients were recruited for the study.

Ethical Consideration

The ethical clearance to conduct this study was obtained from the Ethics Committee of the Enugu State University of Science and Technology Teaching Hospital (ESUT NP/C-MAC/RA/035/Vol.2/016), Enugu, with reference number. Informed consent was obtained from all participants before being recruited for the study.

Sample Size

The sample size was calculated using the cross-sectional sample formula as applicable to G-Power software version 9 (G Power, Dusseldorf, Germany) Power analysis for one-way analysis of variance was conducted to determine a sufficient sample size using an alpha of 0.05, a power of 0.95 and a large effect size (f = 0.40). Based on this, the calculated minimum sample size of 44 subjects gave a 95% power to detect a difference of 0.40 at a significance level of 0.05 based on 8.0% prevalence of T2DM in the South Eastern Nigeria and 58% prevalence of coagulation abnormality in T2DM patients[13,14].

Inclusion Criteria

- Only T2DM patients were recruited.
- Patients between the ages of 40-80 years were recruited.
- Both male and female patients were recruited.
- Patients with BMI (kg/m^2) between 18.5 – 28.5 were recruited.

Exclusion Criteria

- Those with history of blood coagulation disorders were excluded.
- Patients with current history of anticoagulant therapy and oral contraceptive pills were excluded.
- Pregnant and lactating mothers were excluded.
- Patients with signs and symptoms of any pathological condition such as thromboembolic events, liver disease, renal disease, psychiatric illness and malignancies were excluded.
- Smokers, prolonged immobilized patients and paralysed patients were excluded.

Data and Sample Collection

The medical history and clinical data of the subjects were obtained using administered questionnaires and information from subject's folder. Ten milliliters (10ml) of venous blood samples were collected from subjects following standard venipuncture technique. About 3.2ml was dispensed into EDTA bottles for the determination of patient's blood group. Another 1.8ml was dispensed into a trisodium citrate container. The plasma was separated by centrifugation of the samples at 5000 revolution per minute for 15 minutes for the determination of the PT, INR and APTT while the remaining was dispensed into plain sample bottles and allowed to clot at room temperature; the serum was separated by centrifugation of the samples at 5000 revolution per minute for 5 minutes and stored at about -20^{o}C for the determination of the fibrinogen, von willebrand factor and D-dimer levels. Subjects were also advised to observe overnight fast prior to collection of 2mls of blood for the estimation of FBS as well as another 2mls of blood immediately after 2 hours of eating for the estimation of 2HPPS while another random 2mls was collected for the estimation of HBAIC.

Determination of the Blood Group

The subjects blood group were determined using slide haemagglutination technique with commercially prepared antisera (namely anti-A, anti-B and anti-AB).

Determination of the Activated Partial Thromboplastin Time, Prothrombin Time and INR

The Activated Partial Thromboplastin Time and the Prothrombin Time were determined using the Manual method with plasma scann reagent obtained from Fortress Diagnostic Ltd, UK.

The INR was calculated using the formula

$$INR = \left(\frac{\text{Prothrombin time of subject}}{\text{Prothrombin time for laboratory reference plasma}} \right) ISI$$

Where

ISI stands for International Sensitivity Index for the plasmascann reagent.

Determination of the VWF, Fibrinogen and D-dimer

The VWF, fibrinogen and D-dimer levels were determined using the Sandwhich Enzyme Linked Immunosorbent Assay Protocol with kit obtained from Shanghai Huirui Chemical Technology Co. Ltd, China and the Microplate Reader, Mindray-96A, China.

Determination of Glucose

Glucose oxidase method was used to estimate the level of fasting plasma glucose and 2 hours post prandial plasma glucose with commercially available kit (Biologo, France) which has the standard for calibration measured at 500nm using spectrophotometer (SM 23A, England).

Determination of Glycated Hemoglobin

This was performed using the Ion Exchange Chromatographic Method with reagents obtained from Fortress Diagnostic Kits, England with values measured at 415mm using spectrophotometer (SMA 23A).

Statistical Analysis

Statistical analyses was performed using the statistical package for social sciences software SPSS for windows, version 22.0 Armonk, NY, USA). The variables were investigated using Kolmogorov-Smirnov Test to determine whether they were normally distributed. Data was presented using means and standard deviations from the means. One-way analysis of variance was applied to compare the markers of glycemic control and coagulation activation among the blood groups while the Student Test was used to compare between groups.

Results

The age of the subjects, Body Mass Index (BMI) and duration of diabetes was observed to be similar among the different ABO blood types (P = 0.116, 0.735, 0.888) respectively (Table 1). The fasting blood sugar (FBS), two hour post prandial sugar (2HPP) and the glycated hemoglobin levels were increased for the subjects with non-O blood groups (A, B, and AB) compared to the subjects with blood group O but this was not significant (Table 4.1). The Activated Partial Thromboplastin Time (APTT), Prothrombin Time (PT) and the International Normalised Ratio (INR) were significantly increased for the subjects with blood type O (P = 0.003, 0.007 and 0.014) respectively compared to the subjects with non –O blood types (A, B and AB) (Table 1). The Von Willibrand Factor (VWF), fibrinogen and D-dimer levels were significantly decreased for the subjects with blood type O (P = 0.001, 0.006, 0.011) respectively compared to the subjects with non –O blood type (A, B and AB).

The clinical data involving the age of the subjects, duration of diabetes, body mass index were similar for the subjects when they were compared based on the Rhesus D blood type similar result was also obtained for the markers of glycemic control involving the fasting blood sugar, two hours post prandial sugar and the glycated hemoglobin as well as for the markers of coagulation control involving the activated partial thromboplastin time, prothrombin time, International normalized ratio, von willebrand factor, fibrongen and D-dimer (Table2).

The age of the subjects, duration of diabetes and the body mass index were similar for the subjects when they were compared based on ABO and Rhesus d blood types together. The fasting blood sugar, two hour post prandial sugar and glycated hemoglobin were increased for the A^+, A^-, B^+, B^-, AB^+ and AB^- subjects compared to the O^+ and O^- though this was not significant. The activated partial thromboplastin time, prothrombin time and the international normalized ratio were significantly increased for the O^+ and O^- subjects (P = 0.002, 0.010, 0.007) respectively compared to the A^+, B^+, B^-, AB^+ and AB^- subjects. The von willebrand factor, fibrinogen and d-dimer levels were significantly decreased for subjects with O^+ and O^- (P = 0.038, 0.001, 0.006) respectively compared to the subjects with A^+, A^-, B^+, B^-, AB^+ and AB^- (Table 3).

Table.1: Comparison of clinical data, markers of coagulation and glycemic control for subjects based on ABO blood types

Parameter	A(n=25)	B(n=25)	AB(n=8)	O(n=42)	P-value
Age (years)	62.44±6.83	61.92±4.76	60.88±6.32	61.53±5.70	0.116
BMI (kg.m^2)	26.85±6.84	27.01±3.15	26.98±4.31	27.96±5.01	735
Duration (year)	3.20±1.1	3.31±1.6	3.13±2.0	3.08±1.9	0.888
APTT (secs)	33.6±2.21	33.9±2.28	32.90±3.43	41.7±1.16	0.003
PT (secs)	10.80±5.17	10.23±3.66	10.29±2.4	23.11±2.25	0.007
INR	0.38±3.93	0.41±2.61	0.39±5.82	1.02±8.31	0.014
VWF (ng/ml)	18.22±6.19	19.10±6.67	18.86±4.4	7.92±1.88	0.001
Fibrinogen (ng/ml)	7.6±10.4	8.10±9.6	7.94±9.25	3.11±1.31	0.006
D-dimer (ng.ml)	284±53.7	286±41.2	279±52.9	223±36.8	0.011
FBS (mg/dL)	159±5.4	160.3±5.9	161.8±4.87	156.6±5.28	0.658
2HPPS (mg/dL)	248±14.2	246±19.4	246±15.1	241±16.6	0.592
HBAIC (%)	8.31±1.7	7.79±1.4	8.1±2.22	7.4±3.25	0.358

APTT = Activated Partial Thromboplastin Time, PT = ProthrombinTume, INR = International Normalized Ratio, VWF = Von Willebrand Factor, BMI = Body Mass Index, FBS = Fasting Blood Sugar, 2HPPS = Two Hour Post prandial Sugar, HBAIC = glycated hemoglobin

Table.2 : Comparison of clinical data, markers of coagulation and glycemic control of subjects based on RhD blood type

Parameter	Rh (+) (n=193)	Rh (-) (n=7)	P-value
Age (years)	62.26±5.39	61.53±5.40	0.745
Duration (years)	3.25±1.17	3.12±1.22	0.572
BMI (kg/m^2)	25.91±5.33	26.02±4.77	0.346
APTT (secs)	34.06±1.31	33.57±1.55	0.813
PT (secs)	11.18±2.60	10.80±2.11	0.601
INR	0.39±1.82	0.36±1.50	0.594
VWF (ng/ml)	18.23±6.70	18.40±6.13	0.722
Fibrinogen (mg/ml)	8.11±10.20	7.81±9.77	0.209
D-dimer (mg/ml)	276±44.8	281±47.2	0.412
FBS (mg/dL)	162±8.90	159±8.38	0.503
2HPPS (mg/dL)	245±16.13	243.8±13.85	0.689
HBAIC (%)	8.01±2.2	8.32±1.44	0.714

APTT = activated partial thromboplastin time, PT = prothrombin time, INR = International normalized ratio, VWF = von willebrand factor, BMI = body mass index, FBS = fasting blood sugar, 2HPPS = two hours post prandial sugar, HBAIC = glucated hemoglobin

Table .3: Comparison of clinical data, markers of coagulation control and glycemic control fot the subjects based on both ABO and RhD blood types

Parameters	ARh(+)	ARh(-)	BRh(+)	BRh(-)	ABRh(+)	ABRh(-)	ORh(+)	ORh(-)	P-value
APTT (secs)	34.40±2.65	3.72±2.39	33.81±2.12	34.23±2.44	34.10±3.30	33.79±2.96	39.83±2.14	39.91±3.91	0.002
PT (secs)	9.88±1.4	10.4±1.37	10.11±1.28	1.00±1.31	10.26±1.39	10.16±1.11	22.51±2.27	21.84±1.82	0.010
INR	0.37±1.86	0.38±1.22	0.38±1.66	0.38±1.49	0.37±1.33	0.38±1.24	1.11±2.22	1.4±1.90	0.007
VWF (ng/ml)	20.02±6.48	18.53±5.39	20.31±4.88	19.86±6.12	19.21±6.87	20.44±5.53	8.03±1.66	8.22±1.34	0.038
Fibrinogen (ng/ml)	8.42±10.11	8.36±10.18	7.74±11.60	7.88±10.30	8.0±13.02	8.22±11.14	2.97±1.36	3.21±1.70	0.020
D-dimer (ng/ml)	288±67.1	285±62.9	287±66.4	286±59.5	287±38.3	286±60.2	220±33.4	228±41.2	0.006
Age (years)	61.94±6.67	61.86±5.52	62.03±4.58	61.7±6.60	60.88±5.49	62.12±5.36	61.72±4.46	62.01±5.30	0.576
Duration (years)	3.26±1.20	3.01±1.16	3.11±1.37	2.98±1.44	3.01±1.27	3.18±1.38	3.33±1.12	3.13±1.74	0.687
BMI (kg/m^2)	27.10±4.81	26.84±3.20	26.52±4.40	26.55±2.96	27.01±3.81	27.16±3.82	26.5±3.29	26.80±3.37	0.753
FBS (mg/dL)	160±2.66	161±2.73	159±1.98	160±2.20	160±2.63	161±2.29	136±4.02	157±3.50	0.102
2HPPS (mg/dL)	246±74.4	246±70.2	247±60.8	247±38	246±69.3	246±66.3	245±70.5	241±51.3	0.218
HBAIC (%)	8.43±1.9	8.10±2.11	7.79±1.80	8.01±2.32	8.16±2.53	7.86±2.49	5.9±2.80	6.4±2.99	0.071

APTT = activated partial thromboplastin time, PT = prothrombin time, INR = International normalized ratio, VWF = von willebrand factor, BMI = body mass index, FBS = fasting blood sugar, 2HPPS = two hours post prandial sugar, HBAIC = glucated hemoglobin

Discussion

The blood group system has been reported to have direct effects on the susceptibility for several diseases (infectious and non-infectious) and the risk for developing complications. It is believed that blood group antigens serve as receptors and co-receptors for microorganisms such as viruses, parasites or bacteria and/or metabolites as well as oncogenic molecules which facilitate intracellular uptake and signal transduction pathways leading to the development of a disease condition[15]. The data on

the relationship between type 2 diabetes mellitus and blood group systems is still a puzzling issue due to differences in study populations and inconsistencies in study findings. In the present study, we evaluated the relationship between the ABO blood types, RhD blood types and glycemic control as well as coagulation activation which are the major risk factors for developing complications among patients with type 2 diabetes mellitus. An observed significant increase in the activated partial thromboplastin time (APTT), prothrombin time (PT), International normalized ration (INR), a significant decrease in the plasma von willebrand factor (VWF), fibrinogen and D-dimer levels for the blood group O subjects compared to the A, B and AB subjects suggests that blood group O subjects may have a lower risk for coagulation activation. This is not in agreement with the findings of some other studies who reported a lower risk for coagulation activation in blood group B individuals compared to A, AB and O in literature[16]. But is in agreement with the findings of another study which reported a lower risk for coagulation activation for individuals with blood group O compared to the non-O individuals and a large study in Bangladesh population which reported no relationship between ABO blood types and type 2 diabetes mellitus[17].

Similar results recorded for the subjects when the ABO and RhD blood types were assessed together suggests that individuals with either O^+ or O^- blood type may have a lower risk for coagulation activation and complications in type 2 diabetes mellitus. This is in agreement with the findings of some studies who reported that individuals with either blood type O^+ or O^- have the lowest risk for developing complications for type 2 diabetes mellitus[18]. An observed increase in the fasting blood sugar, two hours post prandial sugar and glycated hemoglobin though not significant for the non-O blood types (A, B and AB) is an indication for poor glycemic control for the subjects which suggests a link to increased levels of markers of coagulation activation namely the VWF, D-dimer and fibrinogen and the decrease in the INR, PT and APTT for the subjects. According to literature poor glycemic control is associated with increased activation of coagulation factors such as fibrinogen, FVII, FVIII, FXI, FXII, kallikrein, d-dimer, vonnwillebrand factor and decreased APTT, PT and INR due to protein glycation which results in dysfunction of the proteins[14]. This is not in agreement with the findings of a study in Iraqi which reported high blood glucose levels in blood type O subjects compared to A, B and AB individuals[19,20].

Our findings also suggest that the RhD blood type of an individual may not have any impact to the individuals' susceptibility for coagulation activation and poor glycemic control in type 2 diabetes mellitus.This is similar to the findings of a prospective study conducted in France which reported no relationship between RhD blood types of individuals with the risk of type 2 diabetes[18].

Conclusion

The findings of the present study suggests that individuals with blood group O has better glycemic control, and are less susceptible to coagulation activation and risk of developing complications for type 2 diabetes mellitus compared to non-O (A, B and AB) individuals. We also recorded that the RhD blood type has no influence on an individual's glycemic control, coagulation activation in type 2 diabetes mellitus.

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