Effects of Oral Hypoglycemic Agent and Physical Activity on Some Haemostatic and Haemorheological Parameters in Nigerian Diabetic Subjects

Article · April 2020

CITATIONS
0

READS
699

3 authors:

Momodu Imoru
Aminu Kano Teaching Hospital
42 PUBLICATIONS **216** CITATIONS
SEE PROFILE

Jessy Medugu
University of Maiduguri
51 PUBLICATIONS **94** CITATIONS
SEE PROFILE

Mamza Yusuf Palnam
University of Maiduguri
20 PUBLICATIONS **62** CITATIONS
SEE PROFILE

Effects of Oral Hypoglycemic Agent and Physical Activity on Some Haemostatic and Haemorheological Parameters in Nigerian Diabetic Subjects

Imoru Momodu*[1], Medugu Jessy[2], Mamza Yusuf[2]

1.Department of Haematology, Aminu Kano Teaching Hospital, Kano, Kano State.
2.Department of Medical Laboratory Science, College of Medical Sciences, University of Maiduguri, Maiduguri, Borno State

ABSTRACT

Background: Metformin and physical exercise have been associated with unaltered rheological parameters and lowering of whole blood clogging rate, blood coagulation factor VII, plasminogen activator inhibitor type-1 (PAI-1) apart from the prevention and control of diabetes mellitus. The aim of this study was to determine the levels of haemostatic and haemorheological parameters in patients with type 2 diabetes mellitus on metformin and who also engaged in physical exercise.

Materials and methods: Eighty-four diabetic patients, aged 30-69 years, and 84, age- and sex-matched healthy, non-diabetic subjects were studied in the University of Maiduguri Teaching Hospital, Borno State, Nigeria between January and December, 2018. Samples for prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen assay, protein C concentration, antithrombin III and d-dimer levels, platelet count, platelet indices, relative plasma viscosity (RPV) and whole blood viscosity (WBV) were analyzed using standard techniques.

Results: The values of platelet count, platelet indices, PT, APTT and d-dimer in diabetic patients with respect to physical exercise, oral hypoglycemic agent and combined treatment compared to that of non-diabetic subjects showed no statistically significant differences ($P>0.05$). There were no significant changes in protein C, fibrinogen, RPV, WBV and antithrombin III levels with respect to types of treatment in diabetic patients ($P>0.05$), but showed significantly lower values of protein C and antithrombin III and significantly higher values of fibrinogen, RPV and WBV compared to non-diabetic subjects ($P<0.05$).

Conclusion: There were significantly lower values of protein C and antithrombin III, and significantly higher values of fibrinogen, RPV and WBV in diabetic patients irrespective of the treatment option. Therefore, patients with type-2 diabetes mellitus could be prone to thrombotic conditions.

Keywords: Effects, treatment, exercise, haemostasis, haemostasis, diabetes
***Corresponding author: E-mail:** imorumomodu67@yahoo.com; Phone: 08033174997
ORCID; https://orcid.org/0000-0001-6954-758X
Author's contributions: This work was carried out and approved in collaboration between all the authors, and take responsibility for its accuracy and integrity. IM and MJ designed the study; IM, MJ and MY sourced for funding; IM and MJ wrote the protocol; IM and MJ contributed in literature search; MJ did Lab experiments; IM and MJ statistical data analysis; IM and MY contributed in discussions; IM drafted the manuscript; IM supervised the study; IM wrote the final manuscript; IM proofread the final version for publication.

Received: March/06, 2020**; Accepted:** April/06, 2020**; Published:** April/25, 2020**.**

Citation: Imoru M, Medugu J, Mamza Y. Effects of Oral Hypoglycemic Agent and Physical Activity on Some Haemostatic and Haemorheological Parameters in Nigerian Diabetic Subjects**. J Med Lab Sci, 2020; 30 (1): 96-106**

INTRODUCTION

Diabetes mellitus has acquired a character of epidemic in recent decades due to the increasing number of diabetics. In 2000, the number of diabetics worldwide was approximately 151 million and it has been estimated that in 2025, it would be 324 million (1).

A nationwide population estimate of diabetes mellitus (DM) was undertaken in Nigeria during the 1992 Nigeria National Non-communicable Diseases (NCD) survey and it was put as 2.2% of population (2). However, the current prevalence of DM among adults, aged 20-69 years, was reported to be 1.7% (3).

Two types of diabetes mellitus are the most prevalent. Type-1 diabetes mellitus is characterized by auto-immune destruction of pancreatic beta cells resulting in an absolute deficiency in insulin while type-2 diabetes (T2DM), which is approximately 90% of the cases of diabetes worldwide, is characterized by insulin resistance and/or reduced production of insulin (4).

Metformin monotherapy is recommended as an initial therapy for newly diagnosed patients with an haemoglobin A1c (HbA1c) level of $\leq$ 7.5% or first-line therapy in subjects with T2DM (5-8). Metformin has been shown to lower FVII and PAI-1, and also to decrease the concentration of both blood coagulation factor XIII (FXIII) A- and B- subunits as well as a sustained reduction in FXIII cross linking activity (8).

The alternative choices for metformin include dipeptidyl peptidase 4 (DPP4) inhibitors, sodium- glucose cotranspoter-2 (SGLT2) inhibitors, thiazolidinediones (TZDs), glucagon-like peptide 1 receptor agonists (GLP - IRAS), sulphonylureas (SUs) and glinides (meglitinide) (9).

Sulphonylureas such as gliclazide have been shown to reduce clot permeability, creating a pro-thrombotic clot structure that is resistant to fibrinolysis (10) while glipizide is associated with fall in PA1-1 level, thereby enhancing fibrinolysis (11).

The use of metformin has been associated with unaltered rheological parameters except for the whole clogging rate which decreased significantly (12).

Physical exercise, along with a proper diet are central factors in the prevention and control of diabetes mellitus, since their effects include appropriate values of blood pressure, glycaemia and lipidemia (13). Currently, the guidelines to physical exercise prescription by the American diabetes association to type 2 diabetes mellitus provided general information such as exercise daily and accumulate 150 minutes of exercise in a moderate intensity or 75 minutes of high intensity per week (13).

Despite the importance of oral antihyperglycaemic drugs and physical exercise in the management of patients with type 2 diabetes, there is still paucity of information on the effects of antihyperglycaemic treatment and physical exercise on some haemostatic and haemorheological parameters in diabetic patients in Nigeria. Therefore, this study aimed to determine the levels of platelet count, platelet indices, PT, APTT, fibrinogen, D-dimer, protein C, antithrombin III, relative plasma viscosity (RPV) and whole blood viscosity (WBV) in diabetic patients on oral hypoglycemic agent (OHA) and physical activity.

MATERIALS AND METHODS

A total of 168 participants were studied in Borno State of Nigeria and out of which 84

subjects with uncomplicated type 2 diabetes mellitus, aged 30-69 years, were recruited from the metabolic clinic of the University of Maiduguri Teaching Hospital Borno State between January and December, 2018. These recruited diabetic subjects were controlled by oral hypoglycemic agent (metformin) and physical exercise with moderate intensity of about 150 minutes per week (walking for 30 minutes in each of the three sessions of exercise in a week) (14). The remaining 84, age-and sex-matched, non-diabetic subjects resident in Maiduguri served as controls.

Diabetic and non-diabetic subjects with bleeding disorders, pregnancy and hypertension were excluded from the study.

Informed written consent and ethical approval were obtained from all the participants for the study and University of Maiduguri Teaching Hospital Maiduguri, respectively. Venous blood of 8.5ml was collected from each participant and out of which, 4.5ml of the blood sample was mixed with 0.5ml 3.2% trisodium citrate solution in a container and centrifuged at 2500 revolutions per minute for 15 minutes while the plasma separated into plastic plain container was used for the determination of PT, APTT and the concentration of protein C, antithrombin III and d-dimer. However, the remaining 4ml of blood was dispensed into dipotassium ethylene diamime tetra-acetic acid (EDTA) bottle to the final concentration of 1.5mg/ml for the determination of platelet count and indices, relative plasma viscosity and whole blood viscosity.

Prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen were determined using Diagen kits with catalogue numbers CRBT000, KAPS051 and FIBC440 respectively, manufactured by Diagnostic reagents limited, United Kingdom while platelet count and platelet indices were determined using Human count 30^{TS}, a 3-part analyser produced by Gesellschaft for Biomedica and diagnostic mbH, Germany. Antithrombin III, protein C and d-dimer levels were determined using Sunlong Human Kits with catalogue numbers SL0263Hu, SL1472Hu and SL0598Hu respectively, manufactured by Sunlong Biotech Company Limited, China according to the manufacturers' instructions. Whole blood viscosity and relative plasma viscosity were determined by Reid and Ugwu methods (15).

Statistical Analysis

Data were expressed as mean±standard deviation while student's t-test and one-way analysis of variance (ANOVA) were used to compare the differences among groups. P value ≤ 0.05 was considered statistically significant.

RESULTS

Table 1 shows effects of treatment types on some coagulation parameters in diabetic subjects attending metabolic Clinic in Maiduguri Teaching Hospital. The result reveals no significant changes in platelet count, platelet indices, PT and APTT in diabetic subjects based on treatment types and when compared to control group ($P>0.05$).

Influence of treatment types on antithombin III, D-dimer and protein C levels in diabetic subjects attending metabolic Clinic n Maiduguri Teaching Hospital is revealed in table 2. The values of protein C and antithrombin III were significantly lower in diabetic subjects irrespective of the treatment types compared to control subjects ($P<0.05$) while d-dimer levels showed no significant changes in diabetic subjects

based on treatment types and when compared to control group (P>0.05).

Table 3 has shown the effects of physical exercise and oral hypoglycemic agent on haemorheological parameters in diabetic patients. The values of fibrinogen, RPV and WBV were significantly higher in diabetic subjects irrespective of the treatment types compared to control group (P<0.05).

Table 1: Effects of treatment types on some coagulation parameters in diabetic subjects attending metabolic Clinic in Maiduguri Teaching Hospital.

Parameter	Control subjects (Non-diabetics)	Diabetic Patients: Physical activity only	Diabetic Patients: Oral Hypoglycemic (OHA) only	Diabetic Patients: Physical activity and OHA	P-value
Number	84	2	14	68	
Platelet count ($X10^9$/L)	299.0±90.17	257.0 ±70.17	286.43±90.26	309.56±114.22	0.7549
Plateletcrit %	0.26± 0.07	0.23± 0.08	0.25±0.08	0.27±0.10	0.7500
MPV (fl)	8.66±0.73	9.15±0.64	8.69±0.84	8.54±097	0.6412
PDW (fl)	12.53±1.69	12.9±0.14	12.68±2.08	12.22±2.24	0.5821
P-LCR (%)	37.49±6.53	43.21±5.35	37.48±7.86	36.03±8.3	0.3946
PT (seconds)	12.69±1.15	12.75±1.2	12.73±1.61	12.47±1.2	0.6986
APTT (seconds)	33.86±4.63	36.9±3.25	33.63±5.9	33.51±4.07	0.7483

Table 2: Influence of treatment types on antithrombin III, D-dimer and protein C levels in diabetic subjects attending metabolic Clinic in Maiduguri Teaching Hospital.

Parameter	Control subject (Non-diabetics)	Physical activity only	Oral Hypoglycemic (OHA) only	Physical activity and OHA	P-value
Number	84	2	14	68	
Protein C (ng/ml)	47.67±22.45	11.89±7.42*	7.83±1.96**	9.76 + 4.95**	0.000
Anthrombin III (mg/dl)	95.01±66.54	66.72±63.9	20.91±12.35**	31.03±28.5**	0.000
D-dimer ng/ml	88.73±47.03	143.76± 79.15	121.27±70.07	118.04±93.91	0.0533

*: P<0.001, compared to control group
**:P<0.0001, compared to control group

TABLE 3: Effects of physical exercise and oral hypoglycemic agent on some haemorheological parameters in diabetic subjects attending metabolic Clinic in Maiduguri Teaching Hospital.

Parameter	Control subjects (Non-diabetics)	Diabetic patients			P-value
		Physical activity only	Oral Hypoglycemic (OHA) only	Physical activity and OHA	
Number	84	2	14	68	
Fibrinogen (g/l)	2.23±0.60	2.7±1.49	2.9±0.6*	2.53±0.89	0.0053
RPV (mPa.s)	1.19±0.18	1.30±0.26	1.25±0.15	1.28±0.18*	0.0209
WBV (mPa.s)	2.67±0.44	3.33±1.03	3.11±0.55*	2.89±0.59	0.0032

*: P<0.001, compared to control group

DISCUSSION

Physical exercise, along with a proper diet are central factors in the prevention and control of diabetes mellitus (DM), since their effects include appropriate values of blood pressure, glycaemia and lipidemia (13). Physical activity has also been associated with reduction of thrombotic risk by stimulating endogenous fibrinolysis, (16,17) as expressed by high levels of tPA activity (18).

The study has shown that the platelet counts in diabetic patients on oral hypoglycemic agent and physical exercise showed no significant differences when compared to the non-diabetic subjects. However, earlier studies have shown that acute exercise results in a transient increase in platelet count due to haemoconcentration and by platelet release from the liver, lungs and most importantly, the spleen (19-21).

MPV and PDW values for diabetic subjects on oral hypoglycemic agent and physical activity showed no significant differences compared to control subjects in this study. These findings are similar to the previous reports (22,23) but at variance with other studies which showed significantly higher values of MPV and PDW in diabetic subjects (24,25). However, increased value of PDW has been associated with accelerated production of platelets in patients with T2DM, leading to qualitative changes such as different sizes of platelets (26).

PT, APTT and P-LCR values in diabetic patients on oral hypoglycemic agent and physical exercise in this study showed no significant differences compared to the control subjects. This observation on P-LCR is comparable to the earlier report (27). However, divergent views have been expressed by previous researchers on PT and APTT in diabetic subjects (28,29) as Hilberg et al. (29) reported prolonged value of PT and shorter level of APTT after exercise in insulin-dependent diabetic mellitus while Kahraman et al. (28) observed significantly prolonged value of PT value and normal APTT level after the submaximal exercise in young sedentary males. Discordant PT results by various authors could be

associated with different sample sizes used, improperly defined types and periods of physical exercise among other factors.

Our study has further confirmed the previous findings which showed no significant difference after exercise in d-dimer levels (28,29). This therefore shows that there is no significant change in fibrinolytic activity after exercise.

The study has shown that the values of protein C and antithrombin III in diabetic subjects did not show significant differences based on treatment types (physical exercise, oral hypoglycemic agent and combined treatment). These findings are in agreement with the previous studies (30,31). Significantly lower values of protein C and antithrombin III level were observed in diabetic subjects compared to the control groups irrespective of the use of oral hypoglycemic agent and physical exercise in this study. However, divergent views have been expressed by previous authors who reported lower levels of protein C in diabetic subjects (32,33) as against higher protein C level documented by other researcher (34) while Patrassi et al. (35) and Gandolfo et al. (36) reported that there was no significant difference in antithombin III level in diabetic subjects but significantly higher values of antithrombin III were observed in type 1 and type 2 diabetics by Hamulu et al. (31) Varying levels of protein C and antithrombin III in diabetic subjects reported by various researchers could be associated with different analytical techniques such as spectrophotometric assay using chromogenic substrate Chromozym TH, immunochemical method and Statclot assay as against ELISA technique used in this study. The sensitivities of the various reagents to the analytes and disproportionate samples' (patients and control groups) sizes used by the authors could still contribute to disagreeing results of protein C and antithrombin III levels.

This present study also revealed a non-significantly higher value of d-dimer in diabetes mellitus subjects with respect to treatment types compared to the control group and these are in conformity with earlier reports (37,38). However, elevated d-dimer level may be due to increased fibrinolysis as a result of thrombotic event (39).

The study further showed significantly higher value of fibrinogen in diabetic subjects on oral hypoglycemic agent compared to the control group. These observations agree with the previous documentations (40,41). However, increased fibrinogen level could make the diabetic subjects be prone to increased fibrin formation. Juhan-Vague et al. (42) has associated increased fibrinogen plasma level with an interdependent risk factor for cardiovascular disease.

Furthermore, the study revealed that there was no significant change in the values of relative plasma viscosity in diabetic patients on oral hypoglycemic agent and physical exercise. However, diabetic patients on combined physical exercise and oral hypoglycemic agent showed significantly higher RPV compared to the control group (non-diabetic subjects). These findings are in support of the previous work (43,44). However, Brun et al. (45) and Osei-Bimpong and Burthem (46) reported that plasma viscosity depends on the blood pressure and concentration of plasma proteins such as fibrinogen. The value of whole blood viscosity in diabetic subjects on oral hypoglycemic agent was significantly higher than the control group. This finding is in line with the previous reports (43,44). However, increase in blood viscosity has been associated to maximal and sub-

maximal exercise, resulting in a rise in plasma and haematocrit by Brun et al. (45) while the Gorodeski et al. (47) attributed it to increase in red cell mass, increased red cell deformity, increased plasma level of fibrinogen and coagulation factors and dehydration.

In conclusion, there were no statistically significant differences in the values of platelet count, platelet indices, PT, APTT and d-dimer in diabetic subjects irrespective of treatment types (physical exercise and oral hypoglycemic agent) compared to control subjects. However, significantly lower values of protein C and antithrombin III, and significantly higher values of fibrinogen, RPV and WBV were observed in diabetic patients. Subjects with type-2 diabetes mellitus could be prone to thrombotic conditions and therefore, it is advisable to include protein C, antithrombin III, RPV and WBV among other laboratory investigations for the management and monitoring of diabetic patients to avoid complications related to thrombosis.

Conflict of Interest: None

Acknowledgement: We wish to acknowledge the members of Haematology and Chemical Pathology staff of the University of Maiduguri Teaching Hospital for their cooperation throughout the period of study.

REFERENCES

1. Cheng D. Prevalence, predisposition and prevention of type II diabetes. Nutr Metab (Lond) 2005;2:29

2. Akinkugbe OO. Non-communicable disease in Nigeria. Final Report of National Survey, Lagos: Federal Ministry of Health and Social Services 1997; 64-90.

3. International Diabetes Federation (IDF). IDF Diabetes Atlas. 8th Edition, International Diabetes Federation, Brussels 2017.

4. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001; 414 (6865): 782-787.
5. UK Prospective Diabetes Study Group (UKPDS). Effect of intensive blood glucose control with metformin on complications in overnight patients with type-2 diabetes. Lancet 1998; 352: 854-865.

6. Maruthur NM, Tseng E, Hutfless S, Wilson LM, Suarez-Cuervo C, Berger Z, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type-2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2016; 164:740-751.

7. Palmer SC, Mavridis D, Nicolucci A, Johnson DW, Tonelli M, Criag JC et al. Comparison of clinical outcome and adverse events associated with glucose-lowering drugs in patients with type-2 diabetes: a meta-analysis JAMA 2016; 316: 313-324.

8. Standeven KF, Ariens RA, Whitaker P, Ashcroft AE, Weisel JW, Grant PJ. The effect of dimethylbuguanide on thrombim activity, FXIII activation, fibrin polymerization and fibrin clot formation. Diabetes 2002; 51: 189-197.

9. Ko S-H, Hur K-Y, Rhee SY, Kim NH, Moon MK, Park SO, et al. Antihyperglycemic agent therapy for adult patients with type 2 diabetes mellitus 2017: A position statement of the Korean Diabetes Association. Diabetes Metab J 2017; 41 (5): 337-348.

10. Dhall DP, Nair CH. Effects of gliclazide on fibrin network. J Diabetes Complications 1994; 8:231-234.

11. Cefalu WT, Schneider DJ, Carlson HE, Migdal P, Gan Lim L, Izon MP, et al. Effect of combination glipizide GITS/ metformin on fibrinolytic and metabolic parameters in poorly controlled type 2 diabetic subjects. Diabetes Care 2002; 25: 2123-2128.

12. Janssen M, Rillaerts E, Leeuw I. Effects of Metformin on haemorheology, lipid parameters and insulin resistance in insulin-dependent diabetic patients (IDDM). Biomed Pharmacother 1991; 45 (8): 363-367.

13. Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, et al. Exercise and type 2 diabetes : the American College of Sports Medicine and the American Diabetes. Diabetes care 2010; 33:2692-2696.

14. Umpierre D, Ribeiro PA, Kramer C K, Leitão CB, Zucatti AT, Azevedo MJ, et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. JAMA 2011; 305:1790–1799.

15. Reid HL, Uguw AC. A simple technique of rapid determination of plasma viscosity. Niger J physiol Sci 1987; 43-48.

16. Meade T. Exercise and haemostatic function. J Cardiovas Risk 1995; 2: 323-429.

17. Fernhall B, Sxymanski LM, Gorman PA, Milani J, Paup DC, Kessler CM. Fibrinolytic activity is similar in physically active men with and without a history of myocardial infarction. Arterioscler Thromb Vasc Biol 1997; 17: 1106-1113.

18. Eliasson M, Asplund K, Evrin PE. Regular leisure time physical activity predicts high activity of tissue plasminogen activator: the Northern Sweden MONICA study. Int J. Epidemiol 1996; 25: 1182-1187.

19. Chamberlain KG, Tong M, Penington DG. Properties of the exchangeable splenic platelets released into the circulation during exercise-induced thrombocytosis. American Journal of Haematology 1990:34(3):161-168.

20. Schmidt KG, Rasmussen JW. Exercise-induced changes in the in-vivo distribution of ^{111}In-labelled platelets. Scandinavian Journal of Haematology 1984; 32(2): 159-166.

21. Bakovic D, Pivac N, Eterovic D, Breskovic T, Zubin P, Obad A, et al. The effects of low-dose epinephrine

infusion on spleen size central and hepatic circulation and circulatory platelets. Clinical Physiology and Functional Imaging 2013; 33(1): 30-37.

22. Kratz A, Wood MJ, Siegel AJ, Heirs JR, van Cott EM. Effects of Marathon running on platelets activation markers. Direct evidence for in-vivo platelet activation. Am J Clin Pathol 2006; 125: 296-300.

23. Giovanetti TV, do Nascimento AJ, de Paula JP. Platelet indices: Laboratory and clinical applications. Rev Bras Hematol Hemoter 2011; 33(2): 164-165.

24. Alhadas KR, Santos SN, Freitas SMS, Viana SMSA, Ribeiro LC, Costa MB. Are Platelet indices useful in the evaluation of type 2 diabetic patients? J Bras Pathol Med Lab 2016; 52(2): 96-102.

25. Kodiatte TA, Manikyam UK, Rao SB, Jagadiish TM, Reddy M, Lingaiah HK, et al. Mean Platelet volume in type 2 diabetes mellitus. J Lab Physicians 2012; 4(1): 5-9.

26. Vadgatli E, Gounari E, Lazaridou E, Katsibourlia E, Tsikopoulou F, Labrianou I. Platelet distribution width: a simple, practical and specific marker of activation of coagulation. Hippokratia 2010; 14(1): 28-32.

27. Yilmaz T, Yilmaz A. Relationship between altered platelet morphological parameters and retinopathy in patients with type 2 diabetes mellitus. J Ophthalmol 2016; 2016: 9213623.

28. Kahraman S, Bediz CS, Piskim O, Aksu I, Topcu A, Yuksel F, et al. The Effect of the acute submaximal exercise on thrombin activatable fibrinolysis inhibitor levels in young sedentary males. Clinical and Applied Thrombosis/Hemostasis 2011; 17(4):414-420.

29. Hilberg T, Eicher E, Glaser D, Prasa D, Sturzebecher J, Gabriel HHW. Blood coagulation and fibrinolysis before and after exhaustive exercise in patients with IDDM. Thromb Haemost 2003; 90: 1065-1073.

30. Veglio M, Gruden G, Rosetto P, D'Este P, Cavallo-Perin P. Anticoagulant protein C activity in non-insulin dependent diabetic patients with normoalbuminuria and microalbuminuria. Acta Diabetol 1995;32(2):106-109.

31. Hamulu F, Centikalp S, Ozgen AG, Bayraktar F, Yilmaz C, Kabalak T, et al. The level of antithrombin III (ATIII) in Turkish diabetics. Turkish Journal of Endocrinology and Metabolism 1998; 4: 209-219.

32. Cereillo A, Qutraro A, Dello Russo P, March E, Barbanti M, Milani MR, et al. Protein C deficiency in insulin-dependent diabetes: a hyperglycemia- related phenomena. Thromb Haemost 1990; 64 (1): 104-107.

33. Aslan B, Eren N, Cigerli S, Muldur F, Yucel N. Evaluation of plasma

protein C antigen, protein C activity and thrombomodulin levels in type 2 diabetic patients. Turk J Med Sci 2005; 35:305-310.

34. Saito M, Kumabashiri I, Jokaji H, Asakura H, Uotani C, Otsuka M, et al. The levels of protein C and protein S in plasma of patients with type II diabetes mellitus. Thromb Res 1988; 52: 479-486.

35. Patrassi GM, Picchinenna R, Vettor R, Cappellato G, Coccarielli D, Girolami A. Antithrombin III activity and concentration in diabetes mellitus. Thromb Haemost 1985; 54(2):415-417.

36. Gandolfo GM, de Angelis A, Toressi MV. Determination of antithrombin III activities by different methods in diabetic patients. Haemostasis1980; 9:15-19.

37. Nwose EU, Richards RS, Jelinek HF, Kerr PG. D-dimer identifies stages in the progressive of diabetes mellitus from family history of diabetes to cardiovascular complications. Pathology 2007; 39(2): 252-257.

38. Coban E, Sari R, Ozdogan M, Akcit F. Levels of plasma fibrinogen and d-dimer in patients with impaired fasting glucose. Exp Clin Endocrinol Diabetes 2005; 113(1):35-7.

39. Riley RS, Gilbert AR, Dalton JB, Pai S, McPherson RA. Widely used types and clinical applications of d-dimer assay. Laboratory Medecine 2016; 47(2): 90-102.

40. Bembde AS. A study of plasma fibrinogen level in type-2 diabetes mellitus and its relation to glycemic control. Indian J Hematol Blood Transfus 2012; 28(2):105-108.

41. Odusan O, Raimi HT, Familoni OB, Olayemi O, Adenuga JO. A study of haemorrheological parameters as cardiovascular diseases in Nigeria type 2 diabetes mellitus patients. Nigerian Journal of Cardiology 2013; 28(2):72-76.

42. Juhan-Vague I, Alessi MC, Vague P. Thrombogenic and fibrinolytic factors and cardiovascular risk in non-insulin-dependent diabetes mellitus. Ann Med 1996; 28(4):371-380.

43. Cho YI, Mooney MP, Cho DJ. Hemorheological disorders in diabetes mellitus. J diabetes Sci Technol 2008; 2(6):1130-1138.

44. Awodu O, Famodu AA. Effects of exercise haemorheological parameters of young Nigerian smokers. Turkish Journal of Medical Sciences 2007; 37(1):11-16.

45. Brun J-F, Aloulou I, Varlet-Marie E. Type 2 diabetes with higher plasma viscosity exhibit a higher blood pressure. Clinical Hemorheology and Microcirculation 2004;30: 365-372.

46. Osei-Bimpong A, Burthem J. Supplementary techniques including blood parasite diagnoses. In: Dacie and Lewis Practical Haematology, 12th ed. 2017.p. 93-111.

47. Gorodeski EZ, Gorodeski GI. Epidemiology and risk factors of cardiovascular disease in postmenopausal women. In: Treatment of postmenopausal women. 3rd edition, 2007. p. 405-452.