

Effect of Increase Duration of Type 2 Diabetes Mellitus on Von Willebrand Factor

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Abstract

Original Research Article

Diabetes mellitus, more in particular type 2, is a known causative factor of endothelial activation and resulting in the secretion of von Willebrand factor. This study was carried out to know the effect of duration of type 2 diabetes mellitus on von Willebrand factor level in Hausa/Fulani. The study was a cross sectional one carried out at Specialist Hospital, Sokoto from June to December 2018. The patients were assessed, the assessments include history (a questionnaire) and clinical examination. von Willebrand factor was determined in one hundred (100) diabetic subjects and one hundred (100) non-diabetic subjects using enzyme linked immunosorbent assay method. The diabetic patients were grouped into five groups. Group A1. Treatment naïve. Group A2. on treatment for less than a year (<1yr). Group A3. on treatment for one to less than two years (1 - <2yr). Group A4. on treatment for two to less than five years (2 - <5yr). Group A5. On treatment for five years and above (≥ 5 yr). The mean concentration of the Von Willebrand factor was significantly ($p < 0.05$) higher in group A5 on treatment for five years and above (≥ 5 yr) (42.09 ± 4.70 ng/L) and group A2 on treatment for less than a year (<1yr) (32.80 ± 8.40 ng/L) compared the controls. This present study revealed that, as the duration of treatment of diabetes mellitus increases, the plasma levels of von Willebrand factor also increases due to activation of the endothelium in Hausa/Fulani type 2 diabetic patients. Therefore, Von Willebrand factor should be included in the routine investigations for the management of diabetic patients as an adjuvant in predicting early vascular complication of diabetes mellitus as increased in plasma levels correlate with vascular injury.

Keywords: Type 2 diabetes mellitus, von Willebrand factor, Hausa/Fulani.

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INTRODUCTION

Type 2 diabetes mellitus (also known as non-insulin -dependent diabetes mellitus (NIDDM) refers to patients with diabetes mellitus characterized by insulin resistance or a state of relative insulin deficiency [1]. Increase in duration of type 2 diabetes mellitus post more risk of developing chronic complication [2]. Clinical studies often use diabetes onset after age of 30 years as an operational criterion for type 2 diabetes mellitus [1]. Type 2 diabetes mellitus is insidious and may be present for years before being diagnosed [3]. Approximately, a good percentage of all diagnosed cases

of diabetes mellitus is Type 2 and may be as many undiagnosed cases of Type 2 as diagnosed cases [3].

Von Willebrand factor (vWF) is a blood glycoprotein involved in hemostasis [4]. It is deficient or defective in Von Willebrand disease and is involved in a large number of other diseases, including thrombotic thrombocytopenic purpura, Heyde's syndrome, and possibly hemolytic-uremic syndrome [5]. Increased plasma levels in a large number of cardiovascular, neoplastic, and connective tissue diseases are presumed to arise from adverse changes to the endothelium, and may contribute to an increased risk of thrombosis in diabetic patients [6].

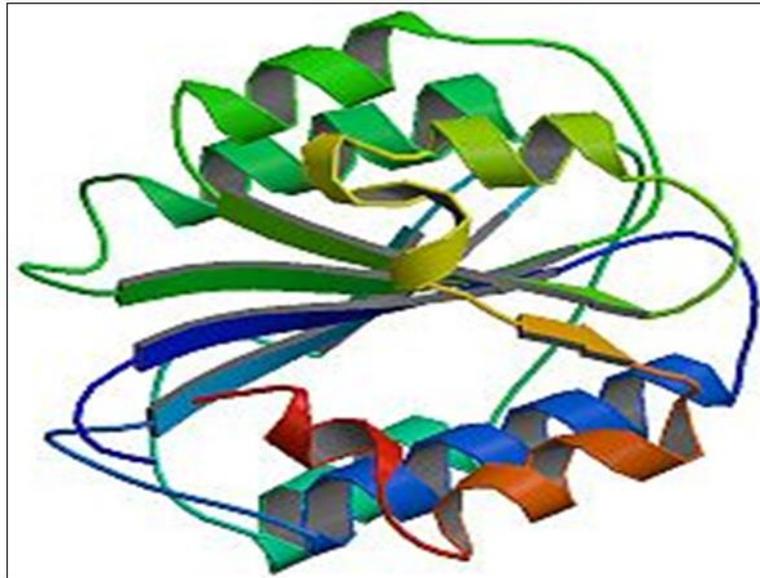


Fig-1: Structure of Von Willebrand factor [6]

vWF is a large multimeric glycoprotein present in blood plasma and produced constitutively as ultra-large vWF in endothelium (in the Weibel-Palade bodies), megakaryocytes (α -granules of platelets), and subendothelial connective tissue [6].

The basic vWF monomer is a 2050-amino acid protein [7]. Every monomer contains a number of specific domains with a specific function, elements of note are [7]. The D¹/D₃ domain, which binds to factor VIII (Von Willebrand factor type D domain). The A1 domain, which binds to: Platelet GP1b-receptor, Heparin and Possibly collagen. The A2 domain, which must partially unfold to expose the buried cleavage site for the specific ADAMTS13 protease that inactivates vWF by making much smaller multimers [8]. The partial unfolding is affected by shear flow in the blood, by calcium binding, and by the lump of a sequence-adjacent “vicinal disulfide” at the A2-domain C-terminus. The A3 domain, which binds to collagen (Von Willebrand factor type A domain). The C1 domain, in which the RGD motif binds to platelet integrin $\alpha_{IIb}\beta_3$ when this is activated (Von Willebrand factor type C domain). The “cysteine knot” domain (at the C-terminal end of the protein), which vWF shares with platelet-derived growth factor (PDGF), transforming growth factor- β (TGF β) and β -human chorionic gonadotropin (β HCG, of pregnancy test fame). (Von Willebrand factor type C domain) [7]. Monomers are subsequently N-glycosylated arranged into dimers in the endoplasmic reticulum and into multimers in the Golgi apparatus by crosslinking of cysteine residues via disulfide bonds. With respect to the glycosylation, vWF is one of only a few proteins that carry ABO blood group system antigens [9]. Multimers of VWF can be extremely large, >20,000 kDa, and consist of over 80 subunits of 250kDa each [10]. Only the large multimers are functional. Some cleavage products that result from vWF production are

also secreted but probably serve no function [11]. The interaction of vWF and GP1b alpha. The GP1b receptor on the surface of platelets allows the platelet to bind to vWF, which is exposed upon damage to vasculature. The vWF A1 domain (yellow) interacts with the extracellular domain of GP1ba (blue) [12]. Von Willebrand factor’s primary function is binding to other proteins, in particular factor VIII, and it is important in platelet adhesion to wound sites. It is not an enzyme and, thus, has no catalytic activity [12]. vWF binds to a number of cells and molecules, the most important ones are: Factor VIII is bound to vWF while inactive in circulation; factor VIII degrades rapidly when not bound to vWF. Factor VIII is released from vWF by the action of thrombin. In the absence of vWF, factor VIII has a half-life of 1-2hours; when carried by intact vWF, factor VIII has a half-life of 8-12 hours. vWF binds to collagen, e.g. when it is exposed in endothelial cells due to damage occurring to the blood vessel. Endothelium also releases vWF which forms additional links between the platelets’ glycoprotein 1b/IX/V and the collagen fibrils. vWF binds to platelet gpIb when it forms a complex with gpIX and gpV; this binding occurs under cell circumstances, but is most efficient under high shear stress. vWF binds to other platelet receptors when they are activated, e.g. by thrombin (i.e. when coagulation has been stimulated) [13]. vWF plays a major in blood coagulation. Therefore, vWF deficiency or dysfunction (Von Willebrand disease) leads to a bleeding tendency, which is most apparent in tissues having high blood flow shear in narrow vessels. From studies it appears that vWF uncoils under these circumstances, decelerating passing platelets. Recent research also suggests that Von Willebrand factor is involved in the formation of blood vessels themselves, which would explain why some people with Von Willebrand disease develop vascular malformation (predominantly in the digestive tract) that can bleed excessively [13].

MATERIALS AND METHODS

The research was carried out in the Department of Chemical Pathology and Immunology, College of Health Sciences (CHS) and Department of Medicine Specialist Hospital Sokoto. A total of 200 participants were consecutively selected for the study. Only diabetic and apparently healthy individuals who fulfilled the inclusion criteria and agreed to participate in the study were selected. Diabetic subjects were selected from diabetic clinics in the Department of Medicine Specialist Hospital, Sokoto. Preliminary information such as age, sex, height, weight of the patients, duration of the disease and medications were obtained using a questionnaire. Patients that were only dieting as means of diabetic controls were also noted. The control subjects were 100 apparently healthy individuals, of both genders. Those with history of liver diseases and cigarette smoking were excluded from the study. Type 2 diabetic patients and apparently healthy individuals aged 18 years to 60years were recruited into the study. Type 1 diabetic patient, Hypertensive patient, Diabetic patient with coexisting other endocrine disorders and Diabetic patient that consume alcohol were excluded from the study. Individuals who were non-diabetic and who have never had any family history of diabetes were included in the study as controls. Participants (Diabetics patients and apparently healthy controls) were fully informed, and their consent were obtained before the commencement of the research. Participants were allowed to withdraw from the study at any time and for any reason. Approval was obtained from the Ethics and Research Committee of the Specialist Hospital Sokoto. The study was a descriptive cross-sectional study, which was performed on Diabetic subjects attending Diabetic Clinic at Specialist Hospital Sokoto, for a period of 12 months. The research was carried out on diabetic subjects and apparently healthy individual serve as controls. The diabetic patients were categorized into 2; group A based on duration of treatment and group B, which served as control. Group A was further subclassified into 5.

Group A1. Treatment naïve

Group A2. on treatment for less than a year (<1yr)

Group A3. on treatment for one to less than two years (1 - <2yr)

Group A4. on treatment two to less than five years (2 - <5yr)

Group A5. On treatment for five years and above (≥ 5 yr).

Three milliliter (3ml) of whole blood was collected from each diabetic subjects and controls. The three milliliter (3ml) was placed in EDTA bottles for von Willebrand factor assay and the EDTA samples was stored at 2°C.

STATISTICAL ANALYSIS

The data obtained were analyzed using Microsoft Office Excel 2007 and SPSS software version 20.0 of 2016. The results of plasma von Willebrand factor obtained from diabetic subjects were compared with the controls using pair two-tailed student's t-test for matched samples, while analysis of variance (ANOVA) was used to for comparisons of three (3) or more mean values of the parameters in the various groups. In each case where there was significant difference, a post-hoc analysis was carried out using Bonferroni multiple comparisons test. A p-value of less than or equal to 0.05 ($P \leq 0.05$) was considered as statistically significant.

RESULTS

A total of two hundred (200) subjects participated in this study. Of this number, 100 were diabetic patients, 45 males (45%) and 55 females (55%) with their age ranged between 20 and 60years and mean age and standard error of mean of (49.53±0.92). The remaining 100 were age and sex matched apparently healthy individual comprised of 48 males (48%) and 52 female (52%) who served as controls.

The anthropometric data of the diabetic subjects were summarized in table 1, the age, body weight, BMI and diastolic blood pressure of the diabetic were found to be similar with the control ($p > 0.05$). However, the systolic blood pressure and height of the diabetic subjects was significantly higher than the control ($p < 0.05$).

Table-1: Anthropometric Data of the Diabetic Subjects (Mean ± SEM)

Characteristics	Group A Diabetic Patients (n=100)	Group B Controls (n=100)	P value
Male	45	48	
Female	55	52	
Age (Years)	49.53 ± 0.92	45.9 ± 1.48	0.457
Sbp (mmHg)	115.59±0.84 ^b	111.30±1.54 ^a	0.009
Dbp (mmHg)	74.24±0.77	73.24±1.10	0.460
Body Weight (Kg)	68.11±1.70	65.98±2.62	0.485
Height(m)	1.62±0.01 ^b	1.72±0.01 ^a	0.000
BMI(Kgm ⁻²)	27.19 ± 0.63	25.14 ± 0.82	0.056

Values are expressed as Mean \pm SEM; Values of the group with superscript "a" are statistically significantly ($p < 0.05$) and different from group A. Values of the group with superscript "b" are statistically significantly ($p < 0.05$) and different from group B.

Table-2 shows the mean concentration of von Willebrand factor in diabetic subjects based on treatment duration and controls. The mean concentration of the Von Willebrand factor was significantly ($p < 0.05$) higher in group A3 (35.98 \pm 9.03ng/L), group A4 (40.55 \pm 6.64ng/L) and A5 (42.09 \pm 4.70ng/L) compared the controls.

Table-2: Effect of Treatment Duration in Diabetes Mellitus on Endothelial Function Biomarkers on Diabetic Subjects

Para meters	N	Von Willebrand Factor(ng/L)
Group A1	17	30.73 \pm 6.90 ^{eq}
Group A2	19	32.80 \pm 8.40 ^{eq}
Group A3	20	35.98 \pm 9.03 ^{eq}
Group A4	20	40.55 \pm 6.64 ^{eq}
Group A5	24	42.09 \pm 4.70 ^{abcdq}
Group C	100	13.12 \pm 4.60 ^{be}

Values expressed as Mean \pm SEM; Values with superscript "a" are significantly ($p < 0.05$) different from group A1. Values with superscript "b" are significantly ($p < 0.05$) different from group A2. Values with superscript "c" are significantly ($p < 0.05$) different from group A3. Values with superscript "d" are significantly ($p < 0.05$) different from group A4. Values with superscript "e" are significantly ($p < 0.05$) different from group A5. Values with superscript "q" are significantly ($p < 0.05$) different from group C.

DISCUSSION

Type 2 diabetes mellitus is one of the major non communicable diseases in Nigeria that is associated with vascular disease as a result of increases of secretion of von Willebrand factor [14]. Several reports have shown that diabetic patients tend to have higher tendency of developing atherosclerosis compared to non-diabetic patients as a result of excessive secretion of von Willebrand factor from endothelial activation [15]. In This present study, the mean concentration of the Von Willebrand factor was significantly higher in subjects living with diabetes mellitus for more than 5years compared to subjects with diabetes for less five years and also in controls. Also, in a similar study, type 2 diabetic patients with advance age had increased level of Von Willebrand factor compared to younger patients and also control [16]. Von Willebrand factor is procoagulant, produced by the endothelium due to injury and its levels increases to prolong activation of the endothelial cells [17]. This is in agreement with study carried out in china by Chen, Xia [18], which said there is positive correlation between the period of suffering from diabetes and Von Willebrand factor related parameters, indicating

that the duration of the diabetic process influences the endothelium and there by promotes VWF secretion [18]. Similar finding was also obtained in China, though, Von Willebrand factor was only used for the research, by Chen, Xia [18] it revealed that type 2 diabetic patients older than 60years of age had increased levels of VWF, VWF activation and VWF propeptide compared to younger patients who are non-diabetics. They also found that the total active VWF was associated with the time of being diagnosed with diabetes, indicating that probably the total active VWF is the best marker in this patient population for endothelial activation and endothelial damage [18].

CONCLUSIONS

This present study revealed that, as the duration of treatment of diabetes mellitus increases, the plasma levels of von Willebrand factor also increases due to activation of the endothelium in Hausa/Fulani diabetic patients. Therefore, Von Willebrand factor should be included in the routine investigations for the management of diabetic patients as an adjuvant in predicting early vascular complication of diabetes mellitus as increased in plasma levels correlate with vascular injury.

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