Does von Willebrand Factor Have an Effect on the Occurrence of the Diabetic Complications?

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ABSTRACT

It has been reported that von Willebrand factor (vWf) plays a role in the development of complications of diabetes mellitus. The relationships between vWf and polyneuropathy, nephropathy, and retinopathy were investigated in the patients with type 2 diabetes mellitus. 58 patients with type 2 diabetes mellitus (22 men and 36 women, mean age 54 ± 9) and 30 healthy nondiabetic controls (12 men and 18 women, mean age 40 ± 11) were admitted to this study. They were examined by an internist, a neurologist and an ophtalmologist for complications of diabetes mellitus. Electromyography was performed to all the patients. The mean vWf levels of the patients and control group were 1.48 ± 0.55 and 1.25 ± 0.32 IU/mL respectively. There was no significant difference between the two groups (p= 0.146). Diabetic retinopathy in 18 patients (31%), polyneuropathy in 20 patients (34.5%), trap neuropathy in 5 patients (8.6%), microalbuminuria in 9 patients (15.5%), macroalbuminuria in 2 patients (3.5%) and normoalbuminuria in 47 patients (81%) were detected. The difference between vWf levels of the patients with retinopathy and without retinopathy were not statistically significant (p= 0.913). There was no significant difference between patients with polyneuropathy and without polyneuropathy group (p= 0.737). There was also no difference between trap neuropathy and without trap neuropathy (p= 0.431), and between polyneuropathy and trap neuropathy (p= 0.246) patient subgroups. The vWf levels in normoalbuminuric, microalbuminuric and macroalbuminuric patient groups were not different (p values: 0.526, 0.392 and 0.759 respectively). vWf levels between patients with complications of diabetes mellitus and control group were not different (p> 0.05). There was not a significant correlation between the vWf level and body mass index, serum glucose, triglycerides, total cholesterol, HDL-C, LDL-C, VLDL-C, platelet counts, fibrinogen levels, prothrombin and activated thromboplastin times in 33 patients with any complication of diabetes mellitus (p> 0.05). We conclude that, vWf has not an effect in the development of complications in patients with diabetes mellitus.

Key Words: Diabetic complications, von Willebrand factor (vWf).

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INTRODUCTION

Diabetes mellitus is a disease characterised by chronic hyperglycemia and effecting the kidneys, eyes, peripheral nerves and micro and macrovascular systems. In diabetes mellitus, the development of vascular complications is one of the most important factors effecting both morbidity and mortality[1,2]. Endothelial dysfunction or damage has been reported as an essential factor in the etiology of diabetic microangiopathy[3,4]. von Willebrand factor (vWf) is a multimeric glycoprotein synthesized by vascular endothelium, platelet a-granules and megacaryocytes. vWf plays roles in platelet adhesion, aggregation, coagulation as a carrier of factor VIII in plasma and in the development of endothelial dysfunction. It is suggested that increased level of vWf reflects endothelial damage. In recent years, although some authors have reported increased levels of vWf in patients with diabetic microangiopathy and atherosclerosis, vWf level is increased in all patients with diabetic complications[3-7].

In this study, we analyzed the effect of vWf on the development of complications of diabetes mellitus.

MATERIALS and METHODS

Patients

58 patients with type 2 diabetes mellitus (22 men and 36 women, mean age 54 ± 9) and 30 healthy nondiabetic controls (12 men and 18 women, mean age 40 ± 11) were admitted to this study. The patients with hypertrigliseridemia (> 200 mg/dL), hypercholesterolemia (> 160 mg/dL), hypertension (> 140/90 mmHg), haemorrhagic diathesis were excluded from the study. An elevated plasma glucose level above 126 mg/dL was accepted for the diagnosis of diabetes mellitus[8]. All the patients and controls were examined by an internist, a neurologist and an ophtalmologist. Nihon Kohden Neuropak II was used for Electromyography (EMG).

Laboratory Study

Complete blood counts were assayed by using Coulter counter. Prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen levels were measured by photocoagulometric assay. vWf levels (vWf: Ag) were obtained by Radial immunodiffusion assay. Microalbuminuria was measured by chemiluminescent method. The patients who had bacteriuria, hematuria and marked proteinuria were excluded from the study. Proteinuria in the range of 30-300 mg/24 h. and above 300 mg/24 h. were regarded as microalbuminuria and macroalbuminuria respectively. Serum glucose, total cholesterol, HDL-C, LDL-C, VLDL-C, and triglyceride levels were measured by spectrophotometric method.

Statistical Methods

Data were analyzed according to various parameters. The relationship between vWf and sex, body mass index (BMI), serum glucose, total cholesterol, HDL-C, LDL-C, VLDL-C, triglyceride, fibrinogen levels, platelet count, PT, APTT, retinopathy, microalbuminuria and neuropathy were investigated statistically. Correlations were analyzed according to Pearson's correlation test. In the comparisons of two and three groups, Mann-Whitney U and One way Anova tests were used respectively. p values < 0.05 were considered statistically significant.

RESULTS

The mean vWf levels of the patients and controls were 1.48 ± 0.55 IU/mL (0.46-3.32 IU/mL range) and 1.25 ± 0.32 IU/mL (0.54-2.00 IU/mL) respectively. These levels between two groups were not significantly different (p= 0.146). Characteristics of the patients were shown in Table 1. There was not a significant correlation between vWf levels and sex, BMI, serum glucose, triglyceride, total cholesterol, HDL-C, LDL-C, VLDL-C, fibrinogen levels, platelet counts, PT, APTT in 33 patients with diabetic complications (Table 2). There was also no significant correlations between the diabetic complications and vWf levels (Table 3). Diabetic retinopathy was detected in 18 patients (31%) and the vWf levels between patients with and without retinopathy was not statistically significant (p= 0.913). vWf leves of control group were not significantly different from those of the patients with retinopathy (p= 0.166). In neurological

Table 1. Characteristics of the patients

Characteristics	Average	Range
Age	54.22 ± 8.91	34-70
BMI (kg/m^2)	28.59 ± 5.09	18.90-45.20
Serum glucose (mg/dL)	188.60 ± 67.08	92-418
Total cholesterol (mg/dL)	221.26 ± 48.86	136-361
Triglycerides (mg/dL)	196.71 ± 120.45	49-559
HDL-cholesterol (mg/dL)	53.90 ± 14.10	33-117
LDL-cholesterol (mg/dL)	126.59 ± 37.72	67-277
VLDL-cholesterol (mg/dL)	38.47 ± 23.56	10-112
Platelet count (x 10^3/mL^3)	258.48 ± 75.25	90-500
PT (sec)	12.21 ± 3.42	9.50-15.60
APTT (sec)	25.52 ± 4.19	15.90-35.50
Fibrinogen (mg/dL)	271.45 ± 95.41	104-543
vWf (IU/mL)	1.48 ± 0.55	0.42-3.36
Microalbuminuria (mg/24 hour)	64.59 ± 290.02	2.16-2191

and EMG examinations, motor/sensitive polyneuropathy and trap neuropathy were detected in 20 (34.5%) and 5 (8.6%) patients respectively. vWf levels between the subgroups with and without polyneuropathy were not significantly different (p= 0.737). There was also no significant difference between the subgroups with and without trap neuropathy (p= 0.431) and between the subgroups polyneuropathy and trap neuropathy (p= 0.246). vWf levels between controls and the patients with polyneuropathy and trap neuropathy were not significantly different (p= 0.593 and p= 0.116 respectively). Microalbuminuria in 9 (15.5%) patients and macroalbuminuria 2 (3.5%) patients was detected. vWf levels between normoalbuminuric, microalbuminuric and macroalbuminuric groups, were not significantly different (p> 0.05). vWf levels of control group were not significantly higher than those of the patients with microalbuminuri and macroalbuminuri (p= 0.641 and p= 0.213 respectively).

DISCUSSION

It is known that there is a relationship between vWf level and atherogenesis/thrombogenesis. Although increased vWf level is an indicator of widespread endothelial dysfunction, it may be appraised as a marker of atherosclerosis in cerebral, coronary and peripheral arteries and of diabetic angiopathic conditions[3,9-13]. In the patients with type1 and type 2 diabetic retinopathy, increased vWf levels have been reported in several studies[3,7,14-16]. Increased levels of fibrinogen vWf may contribute to the development of diabetic retinopathy[17]. Increased vWf levels detected in both retina and blood even in early minimal retinopathy may indicate the damage of blood-retina barrier due to endothelial dysfunction. Increased vWf levels were reported when glucose had been added to retinal endothelial cells, obtained from media layer. This situation may be considered as a clue for the relationship between glucose and release of vWf[7]. But in our study, vWf levels were not significantly different between the patients with and without retinopathy. Some authors have advocated that increased vWf levels were not associated with diabetic retinopathy[5].

In patients with peripheral and autonomic neuropathy, increased vWf levels have been found when compared to control groups[18-21]. In the biopsy of sural nerve, a relationship between the levels of vWf, fibrinogen and neural capillary basement membrane thickness and endoneural capil-

Table 2. Statistical results between vWf levels and clinical, laboratory variables

Characteristics		n	vWf: Ag level (IU/mL)	p value
	Female	35	1.51	
Sex	Male	23	1.44	0.152
	> 30	21	1.32	
BMI (kg/m^2)	< 30	37	1.58	0.184
Serum glucose	> 110	54	1.47	
(mg/dL)	< 110	4	1.69	0.443
Total cholesterol	> 200	37	1.50	
(mg/dL)	< 200	21	1.47	0.833
Triglyceride	> 130	37	1.53	
(mg/dL)	< 130	21	1.41	0.502
LDL-cholesterol	> 130	21	1.44	
(mg/dL)	< 130	37	1.51	0.935
HDL-cholesterol	< 35	4	1.20	0.571 (between 1-2. groups)
(mg/dL)	35-50	21	1.51	0.549 (between 1-3. groups)
	> 50	33	1.51	1.000 (between 2-3. groups)
VLDL-cholesterol	> 50	14	1.55	1.000
(mg/dL)	< 50	44	1.47	
Platelet count	< 150	1	1.32	0.082 (between 1-2. groups)
(x 10^3/mL)	150-400	55	1.51	0.472 (between 1-3. groups)
	> 400	2	1.00	0.090 (between 2-3. groups)
PT	> 12	5	1.15	0.188
(sec)	< 12	53	1.52	
APTT	> 33	3	1.36	0.739
(sec)	< 33	55	1.49	
Fibrinogen	< 200	16	1.44	0.969 (between 1-2. groups)
(mg/dL)	200-400	37	1.48	0.773 (between 1-3. groups)
	> 400	5	1.64	0.827 (between 2-3. groups)

lary lumen size changes and thromboxane B_2 production, had been found[19]. At EMG, negative relations between both motor and sensitive conduction velocity of sural, median, peroneal nerves and vWf, fibrinogen had been detected[21]. In patients with diabetic autonomic neuropathy, circadian rhythm of heart rate is damaged and increased vWf levels leading to, both prothrombic state and loss of nocturnal predominance may result in cardiovascular mortality of parasympathetic activity[20]. In this study vWf levels were not significantly different between patients with and without polyneuropathy. Also there was not significant difference between the subgroups with and without trap neuropathy and between the subgroups with polyneuropathy and trap neuropathy.

Microalbuminuria is an indicator of both increased mortality due to cardiovasculer system and development of nephropathy in diabetes mellitus. In patients with microalbuminuric diabetes mellitus, increased vWf levels have been detected in several studies[15,22-28]. Whereas no difference was observed between normoalbuminuric diabetic patients and nondiabetic controls[25,28]. On the other hand, increased vWf levels reflect generalized vascular endothelial damage in diabetic microalbuminuric patients but it is not attributed to kidney damage perse[28]. Another factor which effects the urinary albumin excretion is the elevation of fibrinogen level[26,27]. But in this study, vWf levels between normoalbuminuric, microalbuminuric and macroalbuminuric patient groups, were

Table 3. Relation between vWf levels and diabetic complications

Characteristics		n	vWf: Ag level (IU/mL)	p value
Diabetic retinopathy	Present (+)	18	1.48	0.913
	Absent (-)	40	1.49	
Diabetic neuropathy	Polyneuropathy (PNP +)	20	1.38	0.737 (between PNP + and PNP -)
	Polyneuropathy (PNP -)	33	1.50	0.246 (between PNP + and TN +)
	Trap neuropathy (TN +)	5	1.83	0.431 (between TN + and TN -)
Diabetic nephropathy	Normoalbuminuria	47	1.54	0.526 (between 1-2. groups)
	Microalbuminuria	9	1.32	0.392 (between 1-3. groups)
	Macroalbuminuria	2	1.02	0.759 (between 2-3. groups)

not significantly different. On the other hand, by Pearson's correlation test, there was no significant correlation between the vWf level and body mass index, serum glucose, triglyceride, total cholesterol, HDL-C, LDL-C, VLDL-C, fibrinogen levels, platelet counts, prothrombin and activated partial thromboplastin times in the patients with diabetic complications in this study.

We conclude that, although increased vWf levels especially have been accused in the development of endothelial damage in the previous studies, vWf was not found to have an effect on the development of the complications of diabetes mellitus in the patients with type 2 diabetes mellitus in our study. Concomitant with vWf, other possible mechanisms of endothelial damage include reduced synthesis or release of nitric oxide, hyperglycaemic pseudohypoxia, protein kinase-C activation, increased transforming growth factor-beta (TGF-ß), inhibition of fibrinolysis and activation of coagulation. Assays of parameters like nitric oxide, endothelin, TGF-ß, thromboglobulin, and fibrinolysis tests on extended number of patients may obtain more useful informations.

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