

The Comparison of Different Risk Factors which Result in Endothelial Damage Leading to Diabetic Microangiopathy

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In this study, the effect of different risk factors (hyperglycemia, hypertension, hyperlipidemia, hyperuricemia) on endothelial damage was evaluated in 61 (two of them were type I, the other patients were type II) diabetic patients. von Willebrand Factor antigen (vWf Ag) was used as the marker of the endothelial damage. According to the risk factors patients were separated into five subgroups which were non-regulated diabetic patients (Group I, n:12), hyperlipidemic patients (Group II, n:9), hypertensive patients (Group III, n:15), hypertensive + non-regulated diabetic patients (Group IV, n:17) and hyperuricemic patients (Group V, n:8). Basal vWf Ag levels of non-regulated diabetic patients (Group I) were lower than those of the non-regulated + hypertensive diabetic patients (Group IV). While there was no significant decrease ($p>0.05$) in vWf level after the regulation of non-regulated diabetes, a significant decrease was determined in non-regulated and hypertensive diabetic patients after the improvement of the risk factors ($p<0.05$). Interestingly, besides the other risk factors, hyperuricemia also had a significant effect on endothelial damage. As a result, non-regulated diabetes alone has less effect than non-regulated diabetes plus other risk factors (particularly hypertension) on diabetic angiopathy.

KEY WORDS Diabetes mellitus, endothelial damage, von Willebrand Factor

Introduction

Chronic endothelial damage plays an important role in the development of angiopathy in diabetes mellitus (1). Since diabetic nephropathy is not determined in forty percent of patients with non-regulated type I diabetes mellitus, it is conceived that the role of hyperglycemia in angiopathy development is not very important. In addition to hyperglycemia, factors such as hypertension, hypercholesterolemia, hyperuricemia and genetics accelerate the development of angiopathy. Once diabetic nephropathy is developed, its progression

is not slowed down significantly by tight glucose regulation when compared to the regulation of hypertension (2).

von Willebrand factor (vWf) is reported as a marker of endothelial damage in many recent articles. An increase in the serum level of vWf was observed in diseases that cause endothelial damage such as vasculitis (3), SLE, rheumatoid arthritis (4-9), scleroderma (10), diabetes mellitus (4,11-13), glomerulonephritis (4,14), viral infections, toxemia of pregnancy, homocystinemia, myocard infarction and thromboembolic events (4). As microalbuminuria increases in diabetic nephropathy, vWf antigen level also increases (12,13,15).

Serum von Willebrand factor's synonyms are, VII R:Ag, VIII ag, VIII vWf and antihemophilic factor-

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like protein. von Willebrand factor (vWf) is a glycoprotein that is formed from sequenced high molecular weight (200000-240000) subunits. It has a large multimeric structure and an average molecular weight of 1200000 (1-30 million). It is synthesized in the endothelium, and megacaryocytes and is present in endothelial cells and platelets. It has a biological semi-life of 22-40 hours. von Willebrand factor antigen is an antigenic expression of vWf. It is measured with the immunoassay method using a heterolog antibody. Its synonyms are Factor VIII R:ag and Antihe-mophilic factor (AHF)-like antigen. Its normal serum value is % 43-150 mg (16).

In this study, we investigated the effect of hyperglycemia alone on the development of diabetic angiopathy among diabetic patients (type I or II), as well as the contribution of other risk factors such as hypertension, hypercholesterolemia and hyperuricemia together with hyperglycemia on endothelial damage and whether progression of the lesions can be stopped with the correction of these factors.

Materials and Methods

Sixty one patients (two of them were type I, the other patients were type II) with diabetes mellitus were included in the study. Patients were being followed up at I.U. Istanbul School of Medicine, Internal Medicine and Diabetes outpatient clinics. The age of the patients was over forty years. Their diabetes age was more than five years. None of them used cigarettes, alcohol or any other drug except insulin and/or oral antidiabetic agents. Absence of ischemic heart disease was proved with clinical evaluation and ECG. Platelet count was more than $10^5/\text{mm}^3$ in all of the patients.

Patients were divided into five different groups;

Group I, 12 non-regulated diabetic patients (mean age 51.33 ± 6.70) with normal blood pressure, lipidemia (cholesterol and triglyceride) and serum uric acid levels;

Group II, 9 regulated diabetic patients (mean age 53.66 ± 7.05) with normal blood pressure and

serum uric acid levels but who were hyperlipidemic (high cholesterol and/or triglyceride levels);

Group III, 15 regulated diabetic patients (mean age 50.00 ± 4.44) with normal lipidemia and serum uric acid levels but who were hypertensive (systolic and/or diastolic hypertension);

Group IV, 17 non-regulated diabetic patients (mean age 60.35 ± 6.32) with normal lipidemia and serum uric acid levels but who were hypertensive (systolic and/or diastolic hypertension);

Group V, 8 regulated diabetic patients (mean age 53.12 ± 8.35) with normal blood pressure and lipidemia but who were hyperuricemic.

Serum samples were obtained from each subject before and after the correction of the inappropriate parameter and the samples were stored at -20°C . All the samples collected from 61 patients were assessed by ELISA at the same time. AZFE01 Malakit Factor VIII R Ag ELISA kit with a % 40-200 mg as a normal for vWf was used. Glucose, triglyceride, cholesterol and uric acid were measured by Bayer Diagnostic Technicon DAX-72 auto-analyser. All of the results were evaluated statistically by the Wilcoxon paired two sample test.

Results

The results of our study are shown in the table. Diabetes regulation was established after six months by insulin or oral antidiabetic agent. Normalized $\text{HbA}_{1\text{C}}$ ($<7.2\%$) was accepted for diabetes regulation. Angiotensin converting enzyme inhibitors and calcium channel blockers were used for antihypertensive therapy. Hyperuricemia was controlled with allopurinol. Gemfibrozil and HMG-CoA reductase inhibitors were given for hyperlipidemia therapy. Blood pressure and serum lipid (cholesterol and/or triglyceride) and uric acid regulation were established respectively, after two, four and three months. As can be seen from Table 1, the serum levels of von Willebrand factor decreased significantly from the baseline values after the correction of risk factors in groups II, III and IV. In group I, where hyperglycemia was a risk factor, hyperglycemia and $\text{HbA}_{1\text{C}}$ values decreased whereas vWf levels increased significantly after the treatment. In all of the other four

groups, risk factors were corrected significantly after treatment. The decrease in the vWf level was more pronounced in group III where hypertension and in group IV where both hypertension and hyperglycemia were the risk factors.

Table 1.

		*BT	*AT	p
GROUP I	FBG (mg/dl)	280.58	150	p<0.01
	HbA _{1c} (%)	10.65	7.52	p<0.01
	vWF Ag (mg/dl)	71.75	78.5	p>0.5
GROUP II	Cholesterol (mg/dl)	311.5	187.7	p<0.01
	vWF Ag (mg/dl)	98.44	54.77	p<0.5
GROUP III	*SBP (mm Hg)	192	158.33	p<0.001
	*DBP (mm Hg)	100.66	92.66	p<0.001
	vWF Ag (mg/dl)	90.53	46.6	p<0.05
GROUP IV	FBG (mg/dl)	296.35	163.29	p<0.001
	HbA _{1c} (%)	11.84	7.78	p<0.001
	SBP (mm Hg)	194.41	157.05	p<0.01
	DBP (mm Hg)	106.76	93.82	p<0.01
	vWF Ag (mg/dl)	149.35	87.47	p<0.05
	Uric acid (mg/dl)	10.9	7.1	p<0.5
GROUP V	vWF Ag (mg/dl)	106.62	81.87	p>0.5

* BT: Before therapy; AT: After therapy; FBG: Fasting blood glucose; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Normal values; FBG: 70-110 mg/dl, Cholesterol: 130-200 mg/dl, Triglyceride: 40-170 mg/dl, Uric acid: 2.5-7.5 mg/dl, SBP: <160 mm Hg, DBP: <95 mm Hg.

Discussion

It is well established that endothelial damage is the primary triggering pathology of the micro and macrovascular complications of diabetes mellitus. However it is not known precisely which of the risk factors among hypertension, hyperlipidemia and hyperglycemia is more important for endothelial damage resulting in angiopathy. There are many different views about the relationship between hyperglycemia and diabetic complications. Diabetologists believe that with a good control of hyperglycemia, major complications of diabetes can be prevented. Fasting hyperglycemia persisting over ten years in any diabetes type resulting in typical complications (17-21); the degree of hyperglycemia correlating with the severity of micro-

angiopathy in diabetic dogs and rats and the transplantation of a kidney from a non-diabetic donor to a diabetic recipient resulting in typical glomerulosclerosis among animals and humans (22,23) could be mentioned in support of this thesis. On the other hand some authors suggest that, as in our study group I where hyperglycemia was the only risk factor, hyperglycemia can not be associated with endothelial damage resulting in microangiopathy. For example, in support of this thesis it is shown that microangiopathy can be detected in patients who have just recently been diagnosed as having diabetes mellitus (24); patients with a long history of diabetes have a slowly progressing vascular disease (25) and lowering the blood sugar level does not decrease the incidence of complications (26). While keeping both of the theories in mind, it is generally accepted that hyperglycemia has an untoward effect on diabetic complications (1,27,28). Our results suggest that hyperglycemia by itself does not cause endothelial damage leading to microangiopathy.

Risk factors such as hypercholesterolemia and hypertension are more effective than isolated hyperglycemia and hyperuricemia in producing endothelial damage. Especially the significant decrease in vWf antigen level after the correction of hypertension in groups III and IV was more pronounced than the decrease after the correction of hypercholesterolemia and this finding supports the untoward effect of hypertension. In the literature it is shown that both hypercholesterolemia (29-33) and hypertension (34-36) have a role in endothelial damage. In addition, as in group IV, whenever hypertension and hyperglycemia are present together, the increase in vWf is greater than each one's separate effect (Figure 1). It is concluded that hypertension and hyperglycemia have a synergistic effect on endothelial damage and microangiopathy.

When hypertension and hypercholesterolemia are investigated comparatively, basal vWf antigen level is higher in the hypercholesterolemic group but after the correction of the present problem, the decrease in vWf antigen level is significantly higher in the hypertensive group (Figure 1).

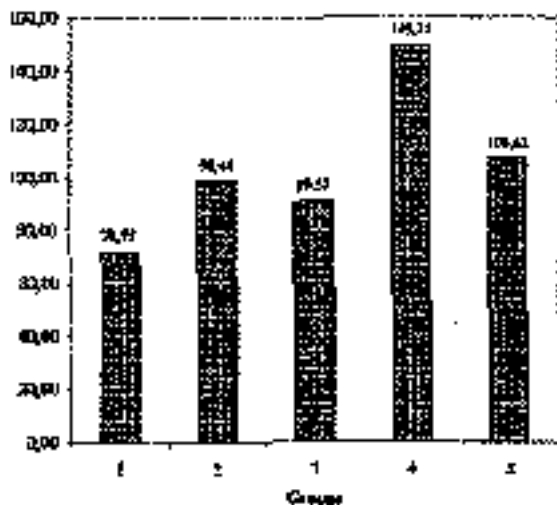


Figure 1. Baseline vWF levels in all groups.

Interestingly, vWf antigen level was high among hyperuricemic patients. However, the decrease in it was not significant after the treatment of hyperuricemia.

As a result, all the risk factors such as hypertension, hyperglycemia, hypercholesterolemia and hyperuricemia, associated with endothelial damage and microangiopathy caused an increase in vWf antigen levels. It is concluded that especially hypertension and hypercholesterolemia are important in the progression of microangiopathy, whereas isolated hyperglycemia does not have such strong negative effects. Therefore, it must once more be emphasized that in the prevention of vascular complications of diabetes mellitus hypertension and hypercholesterolemia must be strictly controlled.

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