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A Study on Factor VIII: Coagulant and Von Willebrand Activities in Diabetic Retinopathy

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Abstract

The relation between factor VIII coagulant activity (F VIII:C), Von Willebrand Factor (vWF) and diabetic retinopathy was studied in this work. The study was conducted upon 38 insulin dependant diabetics, 14 without retinopathy, 13 with background retinopathy and 11 with proliferative retinopathy. They were matched to 10 non diabetic controls. The study revealed the vWF activity increases significantly in diabetics in general. This increase tends to go in parallel with the increase in the severity of retinopathy. However, no significant difference in vWF activity was found between diabetics with and without retinopathy. This means that vWF has no role in the pathogenesis of retinopathy. On the other hand, F VIII:C showed marked increase in the diabetics in general. This increase was more prominent with proliferative retinopathy than background retinopathy. However, no difference was found between existence or absence of retinopathy. In conclusion both F VIII:C and vWF levels are increased in diabetics, but their relation to the process of vascular endothelium damage are merely a sequence of vascular damage in case of vWF, while F VIII:C increase represents activation of the haemostatic system in diabetic patients.

Introduction

PATIENTS with diabetes mellitus have significantly increased morbidity and mortality as a consequence of specific microvascular disease which results in diversity of conditions such as retinopathy and nephropathy. Although the precise cause of these vascular complications remains uncertain, evidence is accumulating that an imbalance of the different haemostatic mechanisms may be entailed in their initiation or propagation.

Diabetic patients show a hypercoagulability state and thrombophilia. These are due to many factors including increased platelets adhesiveness, hypersensitivity to platelet aggregating agents [1,2,3] an increase of plasma thromboglobulin, changes in prostaglandin synthesis [4] and abnormalities in factor VIII complex [5].

In addition, several studies have reported elevation of some coagulation factors in diabetics plasma, F,V,IX,F XII [6], factor VIII [5], factor VII [7] and fibrinogen [8].

Also, contact phase activation have been observed including F XI, F, XII, prekallikerin and high molecular weight kininogen [9].

Proliferative retinopathy is one of the most common and serious vascular complications of diabetes leading to blindness of 50% of patients within 5 years [10]. The major pathological finding in the eye is neovascularization [11]. The exact factors controlling this process are unknown, however, growth hormone is suggested to play a role [12].

The aim of the present work was to assess the activities of F VIII:C and vWF in the plasma of a group of insulin dependant diabetic patients (IDDM) with and without retinopathy and to compare them with a matched group of non diabetic control for age and weight in a trial to provide additional information about haemostatic changes in diabetics and to declare any possible relationship between F VIII:C and vWf and pathogenesis of diabetic retinopathy.

Material and Methods

The study was conducted upon 38 IDDM patients: 14 without retinopathy, 13 patients with background retinopathy and 11 patients with proliferative retinopathy.

They were matched for the duration of disease, fasting blood glucose level and insulin dose and were compared to a group of 10 non-diabetic control subjects.

All subjects were submitted to:

- Complete history taking.
- Fundal examination.
- Laboratory determination of:
  1- Fasting blood glucose level.
  2- F VIII: coagulant activity (F VIII: C) by determining its clotting activity by means of F VIII:C deficient plasmas [13] (Behringwerke Kit).
  3-Functional Von Willebrand factor (vWF); by ristocetin-induced macroscopic clumping assay with formalinized platelets [14] (Behringwerke Kit).

Results

Our results were summarized in tables 1,2,3.

Discussion

Diabetic retinopathy is one of the commonest complications of diabetes mellitus. Factor VIII complex with both of its activities i.e. F VIII: coagulant and Von Willebrand (F VIII:C and vWF), has a close relationship to the vascular endothelium [10,11]. In this work we aimed to spot some light on the changes of the activities of F VIII C and vWF in diabetic patients. In addition we tried to clarify any interrelationship between diabetic retinopathy of different types and F VIII complex activity in insulin dependant diabetics.

In the present study vWF activity was significantly elevated in the diabetic group as a whole compared to normal subjects (138.52±66.05 versus 58.8±38.36, p 0.01). This is in agreement with the previous reports [5,15,16,1]. However, other authors have reported normal activity of vWF in diabetic patients [17,18].

Also a statistically significant increase in vWF activity was observed between, each of the diabetic groups and the control ($p < 0.01$).

However, the differences of these increases between the various diabetic groups with without retinopathy were not statistically significant $p > 0.05$ and these findings agree with the findings of Lam-

Table (1): Clinical and Laboratory Data of the Different Groups.

Group		Age (years)	Duration (years)	Insuline dose ml/day	Blood glucose mg/dl	F VIII:C %	vWF %
Control (n=10)	Minimum	27			70	68	28
	Maximum	63			110	112	112
	Mean	50.4			92.5	89	58.8
	S.D.±	12.72			12.07	17.14	38.36
	Minimum	42	3	0.5	120	95	56
Group I	Maximum	64	19	2	350	300	224
	Mean	53.85	10.28	1.2	232.85	169.6	128
	S.D.±	6.97	5.37	4.41	61.63	48.96	67.44
Group II	Minimum	28	1	1	120	95	56
	Maximum	67	20	2.5	370	174	224
	Mean	50.07	12.69	1.6	224.23	129.76	120.6
	S.D.±	10.01	5.64	1.15	60.71	22.61	64.03
Group III	Minimum	38	11	1	195	110	112
	Maximum	65	25	2	350	290	224
	Mean	53.72	16	1.5	273.63	182	173.1
	S.D.±	8.3	5.13	0.43	56.03	56.94	58.49

N = Number of cases.
Group I = IDDM without retinopathy.
Group II = IDDM with background retinopathy.
Group III = IDDM with proliferative retinopathy.

Table (2): Comparison of F VIII: C Activities between Different Diabetic Groups and Control Group.

	Control	All diabetics	Group I	Group II	Group III
No. of cases	10	38	14	13	11
Mean	89%	185.89%	169.6%	129.76%	182%
S.D.±	17.14	166.74	48.96	22.61	56.94
t		F: 94.636	4.78	4.53	4.72
p		< 0.001	< 0.001	< 0.01	< 0.01
t				2.728	0.56
p				< 0.01	N.S.
t					2.908
p					< 0.01

Table (3): Comparison of vWF Activities between Different Diabetic Groups and Control Group.

	Control	All diabetics	Group I	Group II	Group III
No. of cases	10	38	14	13	11
Mean	58.8%	135.52	128%	120.6%	173.1%
S.D.±	38.36	66.05	67.44	64.03	58.49
t		3.581	2.8	2.581	4.983
p		< 0.001	< 0.001	< 0.01	< 0.01
t				0.28	1.69
p				N.S.	N.S.
					1.993
					N.S.

berton et al. [19] and Davis et al. [20]. This non significant difference in the increased vWF activity between diabetics without retinopathy (group I) and the other two groups of diabetic retinopathies suggests that vWF has no role in the pathogenesis of retinopathy and he increase of its activity is a sequence of retinal tissue damage. This view is also supported by the trend towards increasing levels of vWF activities in parallel with increase in the severity of retinopathy. This finding agrees with the results of Lamberton et al. [19] and Davis et al. [20].

In addition, the present study showed that the increase of vWF activity was not correlated with the duration of diabetes, blood glucose level, age, nor the daily insulin dose. These findings go in parallel with the results of many investigators [15,19,20].

Regarding the F VIII:C coagulant activity (F VIII:C) double fold activity was recorded in diabetics as a whole group compared to the control group. Also, similar results were obtained by Christe et al. [21], Mutean et al. [22] and Vukouich et al. [5]. Several mechanisms may be involved in that increase, firstly, the trace amounts of thrombin that may be generated by the alteration of primary haemostatic system changes lead to intravascular activation of F:VIII [22]. Secondly, the increased phospholipids in the serum of poorly controlled diabetics [23]. Thirdly, the high level of catecholamines in the diabetics, may also lead to activation of haemostatic system and hence F VIII:C [24]. No significant differences was found regarding F VIII:C activity in diabetics with and without retinopathy as a whole. This is inconsistent with Pandolfi et al. [15]. This can be reasoned by the fact that the alternation of F VIII:C activity during poor diabetic control, seems not necessarily to be correlated with endothelial damage since F VIII:C moiety is not synthesized in the vascular endothelium [25].

Also, a significant elevation of F VIII:C activity in the 3 diabetic groups compared to non-diabetic group was found.In addition the same relation was between the diabetic with proliferative retinopathy and those with background retinopathy. However, no significant difference was observed between F VIII;C in diabetics with proliferative retinopathy and those without

retinopathy. This finding may be referred to the fact that F VIII:C is not secreted by the vascular endothelium, so it has no relation to the existence nor to the degree of endothelium damage. This suggestion was also supported by many other investigators [25,26].

Furthermore, a positive correlation was found between the severity of diabetes as assayed by the fasting blood glucose level and the degree of diabetic control as assessed by the daily insulin dosage in the group of diabetics with proliferative retinopathy only and not in the other groups. This may be explained by the stimulatory proliferative effect of intensive insulin therapy on retinal vascular endothelium and by the increased vWF which acts as a carrier for F VIII:C [5].

No correlation was observed between F VIII:C and age nor duration of diabetes in any of the groups. This is consistent with most of other studies [15,22].

In conclusion, the increase in vWF in diabetes is not a major causal factor in the genesis of diabetic retinopathy as there was no significant difference between diabetics with and without retinopathy, but this does not exclude the possibility that vWF plays a permissible role. The degree to which plasma vWF is elevated indicated the extent of vascular damage in patients with diabetes mellitus.

Secondly, the high plasma F VIII:vWF levels may contribute to the shift of the balance of the haemostatic system toward plasma hypercoagulability and platelet hyperadhesiveness. Therefore the increase in F VIII:C in diabetes represents activation of the haemostatic system.

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