

Original

Alterations in Von Willebrand Factor in Diabetic Vascular Disease

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Study was undertaken on 82 patients with noninsulin dependent diabetes to characterise the role of von Willebrand factor (VWF), a glycoprotein synthesized and stored in the vascular endothelium, in vascular complications associated with the disease. An elevated level of this factor was observed only in those patients with macrovascular complications. This is due to endothelial damage in diabetics, related to the duration of the disease. Absence of a raised level of VWF in our diabetics with microvascular disease may suggest the role of other influencing factors such as geographical and or racial differences in the clinical features and pathogenesis of diabetes. Bahrain Med Bull 1995;17:

Accelerated micro- and macro-vascular diseases are well known complications of both insulin dependent and non insulin dependent diabetes mellitus¹⁻³. The pathogenesis of diabetic angiopathy is not well understood. A variety of potentially aggravating factors are involved at different stages of the angiopathic development. Endothelial damage is considered an early event in vascular damage^{4,5}. Von Willebrand Factor (VWF) which circulates in the plasma as part of Factor VIII complex is important for platelet adhesion, and for ristocetin induced platelet aggregation⁶⁻⁷. As it is primarily produced by the endothelium changes in plasma levels may indicate altered endothelial function⁸.

In early studies, elevated plasma levels of VWF in diabetic subjects were found only in the presence of vascular disease⁹⁻¹¹. However several investigators have reported increased levels of VWF in diabetic patients without clinical vascular disease¹²⁻¹⁴. The present study was carried out to establish whether the levels of VWF are*** abnormal in the absence of vascular disease and whether the level correlates with the advancement of vascular disease in diabetics.

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METHODS

Eighty two diabetic patients were randomly selected for this study from the diabetic outpatient clinic at the Nehru Hospital of the Postgraduate Institute of Medical Education & Research, Chandigarh, India, from January to December 1991. All the patients had non-insulin dependent diabetes (NIDDM). Thirty five patients had microangiopathic disease (group 1) and these included mostly patients with non-proliferative retinopathy and clinical nephropathy. Ten patients had coronary artery (macroangiopathic) disease (group 2) and 37 patients were without any angiopathic complications (group 3). The study also includes 30 healthy persons to be considered as "Control Group".

Blood samples for coagulation assays were collected from all above groups with minimum venous stasis in 3.8% (W/V) sodium citrate (9:11 dilution) and EDTA and immediately taken to the coagulation laboratory. The assay for VWF was done by

the Laurell's electroimmunoassay method¹⁵. The results are referred to as factor VIII related antigen (VIII R:Ag) and since VWF is mostly responsible for the immunologic activity of the complex⁸, they are taken as indicative of VWF levels.

RESULTS

Table 1 shows the results of VIII R: Ag in the 3 different groups of diabetic subjects. No significant difference was observed in Factor VIII R:Ag levels between the control and the diabetics without any vascular complications (group 3) and the diabetics with microvascular complications (group 1). Factor VIII R:Ag levels were found significantly raised in the presence of macrovascular complications (group 2). The increase was significant when compared with the control group ($P < 0.01$), with diabetics without any vascular complications ($P < 0.01$), and diabetics with microvascular complications ($P < 0.05$).

Table 1

Factor VIII R:Ag in diabetics with and without vascular disease				
	Group 1	Group 2	Group 3	Controls
No. of patients	35	10	37	30
Factor VIII R:Ag %	106.5±57.2	168.8±74.5	93.1±46.3	102.2±11.7
Range	(44.6-246.4)	(66.2-284.7)	(40.1-244.3)	(50.5-200.4)
P value	Groups 1 vs 2 0.05, 3 vs 2 0.01, Controls vs 2 0.01			

DISCUSSION

Early reports of high levels of plasma coagulation factors in some diabetic patients date back to the early fifties¹⁶. Later on in 1964, Odegaard et al showed that plasma from diabetic patients was more effective than plasma from normal donors in normalising prolonged bleeding time of patients with VW disease who are deficient in VWF¹⁷. Further studies of plasma Factor VIII-complex in diabetes yielded conflicting reports, increased in some studies but normal in others^{9,13,18,19}. Plasma VIII R:Ag was however unanimously found to be elevated in diabetics although some discordance exists as to whether this is the case only in the presence of vascular complications or even in their absence^{10,11,13,19,20}.

In the present study Factor VIII R:Ag was found significantly higher in NIDDM subjects with macrovascular disease than in non diabetic controls. Rise in Factor VIII R:Ag was not significant in patients with retinopathy and nephropathy. Our observations are thus in agreement with investigators who have reported increased levels in the presence of macrovascular disease and differs from those who have reported increased levels in the presence of microvascular disease and without clinical vascular disease⁹⁻¹¹. Geographical and or racial differences in the clinical features and pathogenesis of diabetes have been observed²¹. There is also the extent of the vascular complication to be considered. Further more, these racial differences in the haemostatic variables are also established in health and disease²².

The increase in VWF in diabetics is possibly explained on the basis of the following. Increase in VWF has been reported in diabetic patients with vascular disease following venous stasis of forearm and infusion of 1-deamino-8-D-arginine vasopressin (DDAVP) suggesting its release from endothelium stores and possibly stimulated synthesis of VWF^{23,24}. Further as VWF is an acute phase

reactant, its plasma levels increase in the presence of infections, shock and other conditions of acute stress including ketoacidotic coma²⁵. One therefore might envisage diabetes as a condition where minor albeit repeated stress applied to the endothelium, results in the increased release of VWF. This may be a part of a response finalised to as yet unidentified repair mechanisms, or a reflection of widespread degenerative changes occurring in the endothelial surface of blood vessels²⁶. In the relatively few years since the introduction of techniques to culture human vascular endothelial cells in the laboratory an explosion of knowledge, concerning the crucial role of these cells in modulating both pro and anticoagulant aspects of haemostasis has ensued. A general concept has emerged of the endothelium as a strategically placed barrier at the interface between blood and vessel wall where in the normal unperturbed state, anticoagulant functions dominate and fibrin generation and platelet deposition are resisted²⁷. However a body of data indicates that the perturbation of endothelial cells by various means may lead to loss of this normal state of thromboresistance because of down regulation of active anticoagulant properties as well as the expression of latent procoagulant pathways²⁸. The increase in VWF in diabetics supports this.

CONCLUSION

The increase in Factor VIII R:Ag in non-insulin dependent Indian diabetics with macrovascular complications suggests endothelial damage as part of the disease process and is related to the duration of the disease. Further studies from different countries are required to compare these findings.

REFERENCES

1. Barrett-Conner E, Orchard T. Diabetes and heart disease. In: Harris MI, Hamman RF, eds. Diabetes in America. Vol. XVI. National Diabetes group: US Department of Health and Human Services, 1985;16:1-41. [NIH pub No.85-1468].
2. Kuller LH, Dorman JS, Wolf PA. Cerebrovascular disease and diabetes. In: Harris MI, Hamman RF, eds. Diabetes in America. Vol. XVIII. National Diabetes group: US Department of Health and Human Services, 1985;18:1-18. [NIH pub No. 85-1468].
3. Palumbo PJ, Melton LJ. Peripheral vascular disease and diabetes. In: Harris MI, Hamman RF, eds. Diabetes in America. Vol. XV. National Diabetes group: US Department of Health and Human Services, 1985;15:1-21. [NIH pub No. 85-1468].
4. Ross R, Glomset JA. The pathogenesis of atherosclerosis. N Engl J Med 1976;295: 369-77.
5. Ross RF. The pathogenesis of atherosclerosis. An update N Engl J Med 1986;314:488-500.
6. Bloom AL. The biosynthesis of factor VIII. Clin Haematol 1979;8:53-77.
7. Tschopp BT, Weiss HJ, Baumgartner HR. Decreased adhesion of platelets to subendothelium in von Willebrand disease. J Lab Clin Med 1974;83:296-300.
8. Wagner DD, Olmsted JB, Marder VJ. Immunolocalization of von Willebrand protein in Weibel-Palade bodies of human endothelial cells. J Cell Biol 1982;95:355-60.
9. Pandoliti M, Almer LO, Holmberg L. Increased von Willebrand-antihemophilic factor A in diabetic retinopathy. Acta ophthalmol 1974;52:823-8.

10. Bensonssan D, Levy-Toledano, Passa P, et al. Platelet hyperaggregation and increased levels of von Willebrand factor in diabetics with retinopathy. *Diabetologia* 1975;11:307-12.
11. Collier BS, Frank RN, Milton RC, et al. Plasma co-factor of platelet function: Correlation with diabetic retinopathy and hemoglobins Ala-c. Studies in diabetic patients and normal persons. *Ann Int Med* 1978;88:311-6.
12. Colwett JS, Nair RMG, Halushka PV, et al. Platelet adhesion and aggregation in diabetes mellitus. *Metabolism* 1979;28:394-400.
13. Gensini GF, Abbate R, Farilla S, et al. Changes of platelet function and blood clotting in diabetes mellitus. *Thromb Haemost* 1979;42:983-93.
14. Giustolisi R, Lombardo T, Musso R, Cacciola E. Factor VIII antigen plasma levels in diabetes mellitus. Enhanced endothelial release and storage. *Thromb Haemost* 1980;44:46.
15. Laurell CB. Electroimmunoassay. *Scand J Clin Lab Invest* 1972;29:21-37.
16. Introzzi P, De Nicola P: Thrombophilia in Diabetes: thromboelastographic investigations. *Diabetes* 1957;6:433-5.
17. Odegaard AE, Skaihegg BA, Hellen AJ. Increased activity of "anti-Willebrand factor" in diabetic plasma. *Thromb Diath Haemorrh* 1964;11:27-37.
18. Mekki MO, Jaykumar RV, Galil A, et al. Hemostatic variables in Arab diabetics. *Ann Saudi Med* 1992;12:345-51.
19. Fuller JH, Keen TT, Jarret RJ, et al. Haemostatic variables associated with diabetes and its complications. *Br Med J* 1979;2:964-6.
20. Lufkin EG, Fass DN, O'Fallow WM, et al. Increased von Willebrand factor in diabetes mellitus. *Metabolism* 1979;28:63-6.
21. Falhi HH, Mira SA, El-Zubier AG. The pattern of complications in Saudi Arabian diabetics. *Ann Saudi Med* 1989;9:44-7.
22. Ogston D. Ethnic and blood group variations in the Hemostatic mechanism. In: Helm C, ed. *The Physiology of Hemostasis*. London:Canberra, 1983:266-75.
23. Porta M, Ricchetti I, La Selva M, et al. Quantitative and qualitative assessment of plasma von Willebrand factor variations, as induced by forearm venous stasis in patients with diabetic microangiopathy. *Diabetes Res* 1984;1:219-21.
24. Porta M. Availability of endothelial von Willebrand factor and platelet function in diabetic patients infused with a vasopressin analogue. *Diabetologia* 1982;23:452-5.
25. Paton RC. Haemostatic changes in diabetic coma. *Diabetologia* 1981;21:172-7.
26. Benga JD, Sixma JJ. Diabetes mellitus, vascular disease and thrombosis. In: *Thrombosis and vessel wall*. Clin Haematol 1986;15:465-92.
27. Rodgers GM. Hemostatic properties of normal and perturbed vascular cells. *Faseb J* 1988;2:116-23.
28. Key NS. Scratching the surface: Endothelium as a regulator of thrombosis, fibrinolysis and inflammation. *Lab Clin Med* 1992;120:184-6.