DIABETES

BLOOD RHEOLOGY IN DIABETES MELLITUS

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INTRODUCTION

Diabetes is one of the commonest chronic diseases in Western Europe, probably affecting nearly 2 % of the population. Although insulin, oral hypoglycaemic agents and improved dietary therapy have strikingly prolonged the life of literally millions of diabetics, many of these individuals now live on to develop the long term circulatory complications associated with their condition.

Diabetics suffer from both large and small blood vessel disease. Histologically large vessel disease in diabetes is indistinguishable from that of non-diabetics. The clinical manifestations of this include an increased prevalence of cerebral, cardiac and lower limb ischaemia. The microcirculatory disturbance of diabetes is specific to the disease itself and will be discussed in more detail later. The clinical consequences of small vessel pathology reveal themselves most obviously in the eye and the kidney. Indeed is the commonest cause of blindness in middle age in Great Britain and one of the leading causes of renal failure.

Blood pressure, vascular morphology and blood viscosity are the three primary determinants of blood flow in man. Thus, abnormalities of any of these could influence the circulation in diabetics and either lead or contribute to the tissue ischaemia so frequently observed by clinicians. Vascular morphology (quantitatively the most powerful determinant) has been very intensively studied in diabetes and is well reviewed elsewhere. Although abnormally low blood pressure is occasionally found in diabetics with autonomic neuropathy, the few studies that have been carried out indicate an increased prevalence of hypertension (particularly systolic) in diabetes. The possibility that abnormalities of blood viscosity (the third primary flow determinant) might occur in diabetes and be a factor in circulatory and microcirculatory complications, is an intriguing one.

The purpose of this paper is to describe studies of haemorheology in diabetes and to comment on the relevance of this group of variables to diabetic complications.

WHOLE BLOOD VISCOSITY

As long ago as 1953 Reubi [1] made calculations of blood viscosity in diabetes using Lamport's formulae and found levels to be twice as high during ketoacidosis compared with post treatment values. In 1961 Cogan et al [2] using a capillary viscometer described an increase in serum viscosity in diabetics compared with non-diabetic control subjects but they found no difference in viscosity between diabetics with and without retinopathy. Subsequently in 1966 Skovborg and colleagues [3] found whole blood viscosity to be higher in diabetics when measurements were made with the Wells Brookfield viscometer. Since that time a large number of laboratories have recorded whole blood, plasma and serum viscosity in patients with diabetes; these papers have been reviewed in detail elsewhere [4] and will not be dealt with here. Measurements of whole blood viscosity with and without correction for packed cell volume (PCV) in a group of 64 long-standing diabetics are shown in Table 1. Viscosity was recorded at high shear rates with a Wells Brookfield viscometer and at low shear rates with a Contraves Low Shear 100 viscometer. It can be seen that whole blood viscosity was highest when corrected for PCV (with a regression line of PCV/blood viscosity) and when measured at low shear rates. This shear dependence of blood viscosity suggested that factors promoting red cell aggregation might account for some of the difference between diabetics and non diabetics. Plasma fibrinogen, the most powerful factor in this context was in fact higher in the diabetic patients than in the controls and correlated significantly with PCV corrected whole blood viscosity. Patients with more extensive complications were found to have higher levels of blood viscosity than those with minimal or no complications.

Several groups of workers have found a relationship between impaired blood viscosity and poor metabolic control.[4] Levels of increased whole blood viscosity before and after therapy are shown in ketoacidotic type 1 diabetics and type 2 diabetics over the first few weeks of diet treatment (Fig. 1). In both groups whole blood viscosity fell significantly. This fall was mainly due to the improved hydration of the patients leading to low levels of PCV but some contribution was probably made by the fall in circulating proteins, especially fibrinogen. It is possible that an improvement in red cell deformability may also have contributed to the fall in high shear blood viscosity during treatment.

It is quite likely that larger variations in haematocrit occur in diabetics than in the normal population causing transient but subs-

TABLE 1 **Measured blood viscosity (Mean ± SEM) and viscosity corrected to a standard PCV of 45 % in 64 long-standing diabetics and 61 control subjects of similar age, sex and weigh.**

	Shear Rate 0.77 sec^{-1}		Shear Rate 2.62 sec^{-1}		Shear Rate 23 sec^{-1}		Shear Rate 230 sec^{-1}	
	M	C	M	C	M	C	M	C
Diabetics	35.64 ±1.12	36.38 ±0.97	17.33 ±0.49	17.43 ±0.38	6.68 ±0.12	6.73 ±0.09	4.54 ±0.07	4.57 ±0.05
Controls	31.26 ±1.02	31.30 ±0.52	15.75 ±0.44	15.76 ±0.23	6.56 ±0.11	6.56 ±0.08	4.50 ±0.06	4.48 ±0.04
Significance of difference	P<0.02	P<0.001	P<0.05	P<0.001	NS	NS	NS	NS

NS=not significant; M=measured viscosity; C=viscosity corrected for PCV

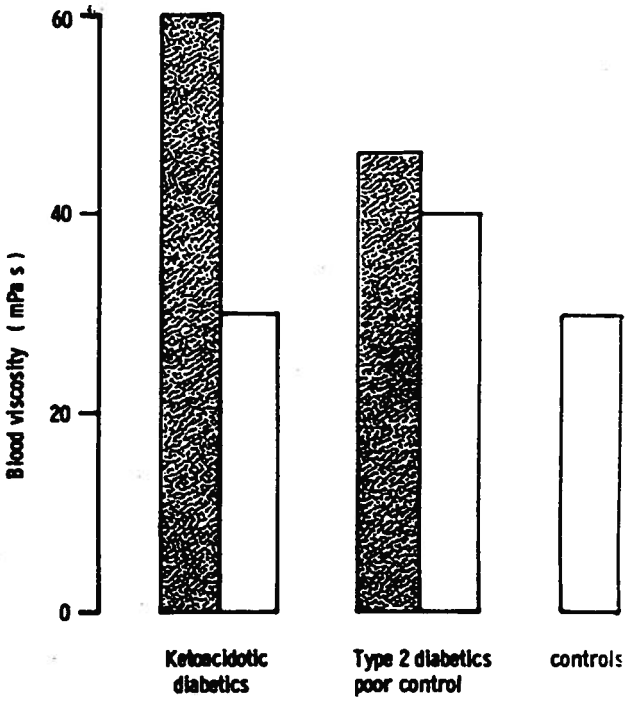

Figure 1: Blood viscosity (0.77 s^{-1}) before and after improved metabolic control

tantial elevations of viscosity. This is supported by the fact that PCV rose extensively in response to exercise, probably due to increased vascular permeability; furthermore glycosuria readily leads to dehydration and haemoconcentration. Thus, apart from being higher in diabetics than non diabetics, whole blood viscosity values may well show much larger swings. In renal failure where normocytic normochronic anaemia is a feature, blood viscosity may, in consequence, fall towards, or even below, normal levels.

The hyperfibrinogenaemia of diabetes is of uncertain aetiology. An increase in plasma clearance of this glycoprotein has been found in complication free diabetics and in the presence of raised circulating levels of fibrinogen, suggests enhanced hepatic synthesis.[5] Plasma fibrinogen has been found to correlate with haemoglobin AIC[6] and the shortened fibrinogen survival of hyperglycaemia was corrected by restoration of normal blood glucose levels.[7] A number of factors are known to stimulate hepatic fibrinogen synthesis including non esterified fatty acids (NEFA), growth hormone (HGH), insulin, cortisol, prostaglandins and interleukin-1.[8] Of these NEFA and HGH are raised in diabetes and revert towards normal with improved metabolic control. Whether these are responsible for the hyperfibrinogenaemia of diabetes, remains to be established.

ERYTHROCYTE DEFORMABILITY AND PLASMA VISCOSITY

Whole blood viscosity has been shown to influence blood flow in large and medium sized vessels but in the microcirculation erythrocyte deformability and plasma viscosity are believed to assume greater importance. Plasma viscosity has been found to be raised in diabetes by some workers but similar to that of non diabetics by others. The increases, when reported, were largely related to higher concentrations of plasma proteins in the diabetics, particularly fibrinogen.

Erythrocyte deformability has been measured in diabetics by many laboratories, using a wide spectrum of methodology. This is dealt with in this publication in the chapter by Dr. Irene Juhan. Suffice it to say that blood filtration has been found to be impaired in diabetes by most workers but the measurement of erythrocyte deformability by other methods has yielded conflicting results.

DISCUSSION

Clearly many of the flow properties of blood are abnormal in diabetes, indeed some diabetics show substantial irregularities. How important are these findings in the patients' circulatory and microcirculatory pathology? Unfortunately, almost all the investigations of rheological variables in diabetics so far carried out have been cross sectional in design. Thus, although significant correlations between abnormalities of these variables and the extent of diabetic complications have been reported, the question of cause and effect remains unresolved. In other words, do abnormalities in blood rheology actually cause or accelerate diabetic complications or are complications a component of some more generalised pathological process of which hyperviscosity is merely a secondary and clinically insignificant manifestation?

Further information pertinent to these questions might be obtained by prospective longitudinal studies where abnormalities of viscosity can be examined in temporal relation to the evoluton of different diabetic complications. Such investigations are in progress in our laboratory and should be completed by Autumn 1985. Further prospective studies of lowering blood viscosity in patients with very high levels of these variables would also yield valuable information.

What are the haemodynamic consequences of the abnormal rheological variables found in diabetes and by what mechanism may hyperviscosity contribute to the aetiology or progression of diabetic complications? Changes in whole blood viscosity would be expected to influence flow in large and medium sized vessels and also be linked to microcirculatory flow via a plasma viscosity effect. Three organs in diabetes where abnormal blood viscosity may be of clinical importance are the brain, the heart and the lower limb.

Although there is known to be an increased frequency of cerebral circulatory disease in diabetics, resting cerebral blood flow has been found to be similar in diabetics and non diabetics, in both groups declining with increasing age.[9] Unlike normal subjects, however, many diabetics appear to be unable to increase their cerebral blood flow in response to hypercapnia suggesting that these individuals may have a diminished circulatory reserve which in certain situations might result in cerebral hypoxia.[9] In non diabetic subjects cerebral blood flow has been found to be reduced in both absolute and relative polycythaemia and reverted back to normal after venesection.[10] In quantitative terms lowering blood viscosity by 30 % at 0.7s-1 and by 20% at 91s-1 led to a rise in overal cerebral blood flow of 84 %. The question is whether such increases in flow were the direct result of lowering blood viscosity or whether they represented autoregulatory adaptation (by adjustment of vessel diameter) to the reduced oxygen transport capacity of the blood following removal of haemoglobin and were, in fact, mediated by hypoxia. The study of Brown and Marshall [11] amongst others, sheds further light on this problem. When blood viscosity was reduced (by 40 % at low shear rates and 15 % at high shear rates) by plasma exchange (PCV kept constant) it was observed that there were no significant changes in blood flow. The cerebral circulation is known to have considerable powers of autoregulation with which it protects the metabolic environment of the brain from changes in systemic blood pressure, oxygen availability and also blood viscosity. Therefore, in normal individuals whilst alterations in blood viscosity may play a compensatory role in maintaining cerebral oxygenation following a fall or rise in haematocrit, under most circumstances viscosity changes can be over-ridden if necessary by local alterations in vessel diameter. In diabetics as has been discussed, cerebral autoregulatory mechanisms may be impaired and therefore the haemodynamic influence of viscosity may be much greater than in normal subjects. Abnormalities in blood viscosity may also affect blood flow in the collateral supply to an area of infarction after a stroke if there is maximum vasodilatation or vasoparalysis maintained by ischaemia.[12] Clinical studies support an aetiological role for raised blood viscosity as a factor in cerebrovascular morbidity and mortality in diabetes. Firstly, a raised haematocrit has been found to be a risk factor in a variety of cerebrovascular disorders.[13, 14] Secondly, in diabetic ketoacidosis where very high levels of blood viscosity and other haemostatic factors occur, cerebral (and visceral) thromboses are a well-recognised complication.[15, 16]

Cardiac mortality and morbidity are increased in diabetes, partly because of a greater prevalence of coronary artery disease and partly because myocardial function itself is impaired in many patients due to either metabolic factors or microangiopathy. Resting cardiac output is raised in diabetic individuals and this is likely to represent a compensatory response to an increase in the basal metabolic rate (BMR).[17] With improved metabolic control both BMR and cardiac output fall towards normal values. In view of the near maximal oxygen extraction in the coronary circulation the relationship between blood viscosity and coronary haemodynamics and myocardial metabolism is of special interest. In non diabetic individuals coronary blood flow increases after haemodilution [18] so that haemoglobin delivery is maintained; in experimental animals the range of optimum haematocrit for maximum oxygen transport was found to be wide, varying from 0.2 to 0.6, coronary vasodilatation occurring outside this range.[19] In hypotensive animals, at a systolic blood pressure of 50 mm Hg PCV was much more important; here maximal oxygen consumption occurred at a haematocrit of 0.25 which fell when PCV was moved either side of this value.[20] To summarise, when blood pressure is normal and there is no significant degree of coronary artery-narrowing, changes in blood viscosity within the range found in diabetes probably have little influence on myocardial metabolism. However, when perfusion pressure falls, eg. after myocardial infarction, pulmonary embolus or septicaemia, or when narrowing of the coronary arteries occur, alterations in rheological variables may assume a much greater degree of significance. No specific studies of the importance of hyperviscosity on angina, on the incidence and extent of myocardial infarction or on myocardial performance after infarction have yet been published in diabetic patients.

Circulatory insufficiency of the leg is a common finding in diabetes, indeed a patient with the disorder is forty times more likely to suffer from gangrene of the lower extremity than a non diabetic of similar age, sex and smoking habits.[21] In non diabetics blood viscosity and whole blood filtration have been reported to correlate with the progression of peripheral ischaemia. [22,23] Some groups have found that reducing PCV and blood viscosity by venesection both increases overall haemoglobin delivery at rest and after hyperaemia leading to an increase in walking distance in claudicants.[24] Lowering whole blood and plasma viscosity by reducing fibrinogen with *ancrod* has also been reported to improve symptoms in these patients.[25] Bailey et al [26] have reported that pre-operative haemoglobin values in diabetics prior to amputations in the lower limb were higher in patients whose limbs subsequently showed failure of healing than in patients whose amputations healed well. The results of prospective studies in diabetes to see if reducing haematocrit and blood viscosity in patients prior to surgery will improve clinical outcome are eagerly awaited. The diabetic foot is a complex entity where tissue damage may not only be secondary to proximal large vessel disease but also to neuropathy, arteriovenous shunting, trauma, infection and possibly metabolic and hormonal factors. An tissue damage may produce an acute or subacute phase response which will itself adversely affect viscosity. To date no prospectiv studies of haemorheological variables on the natural history of th diabetic foot have been reported.

It was the similarities between the retina of diabetes and that c patients with hyperviscosity syndromes that originally stimulate interest in blood rheology in diabetics. Microaneurysms, haemorrhages, distended veins and even new blood vessels were observed not only in diabetes but also in conditions associated with abnormalities of blood rheology such as sickle cell disease, myeloma and macroglobulinaemia.[27] Furthermore, many of these retinal abnormalities could be induced in experimental animals by increasing their blood viscosity with high molecular weight dextran.[28] Additional evidence implicating blood viscosity in diabetic retinopathy subsequently came from the study of patients with retinal branch vein occlusion.[29] Individuals going on to develop widespread capillary occlusion were found to have higher blood viscosity levels than patients who showed a hyperpermeability response. Thus raised blood viscosity was put forward as a possible factor in the aetiology of capillary non perfusion in this condition. Capillary non perfusion is not only present in the retina of patients with diabetes but is considered to be the central pathophysiological event in diabetic retinopathy in that it preceeds and most likely initiates neovascularisation which is presumed to be a response to retinal hypoxia. Early in diabetes retinal blood flow is increased.[30] As near maximum oxygen extraction from blood occurs in the retina this probably represents an autoregulatory response to an increase in the BMR. Later on in retinopathy blood flow falls [30] and it is possible that hyperviscosity together with other factors predispose to capillary occlusion at this stage. The initial state of hyperfusion will increase shear stresses on capillary walls in the retina and other organs and it has been suggested that this physical stimulus promotes basement membrane thickening.[31] Increased plasma viscosity and less deformable red cells would further enhance such shear stresses and in this way might accelerate this process. Abnormalities in basement membrane properties together with hyperfusion would facilitate the transudation of intravascular components into the retina, a phenomenon well seen in diabetics following injection of intravenous fluorescein.

A role for abnormal haemorheology as an adverse factor in diabetic nephropathy is less clear cut than for retinopathy. However, Simpson [32] has recently pointed out that in congenital cyanotic heart disease normalisation of raised blood viscosity by phlebotomy reduced proteinuria and restored impaired glomerular filtration rate, two abnormalities associated with nephropathy in some diabetics. Stiffened red cells as reported in diabetes might impede blood flow in the microcirculation and stimulate an autoregulated vasodilatation which increased perfusion pressure enhancing transudation. This in itself appart from contributing to the accumulation of fibrinogen and other material in the mesangial zone of the kidney would lead to local elevations of haematocrit resulting in a further rise in blood viscosity and therefore increases of perfusion pressure. In the absence of vasodilatation stasis could lead to vascular occlusion and localised ischaemic necrosis. In the late stages of diabetic nephropathy blood viscosity may fall because of the anaemia of chronic renal failure. However, abnormalities of plasma viscosity and red cell flow properties will persist or even worsen with no net benefit to the patient.

CONCLUSIONS

Abnormalities of whole blood and plasma viscosity and of erythrocyte deformability represent only one category of factors that have been put forward as candidates in the aetiology of circulatory and microcirculatory disease in diabetes mellitus. Growth hormone, insulin deficiency, lactic acid accumulation, lipids, platelet abnormalities and a host of other variables [34] may also be involved in these processes. Clearly sophisticated and costly prospective long term studies will be required in order to unravel the complexities of the multifactorial nature of the complications of diabetes. Rheological factors tend to form a skew distribution in populations of diabetic individuals with the majority of patients having values just above the mean of normal subjects but with a small group of individuals having very abnormal results. Such individuals would appear to be a very suitable group in which to study the natural history of different circulatory and microcirculatory complications as well as mortality and to compare these with findings from patients with normal levels of blood viscosity. Subsequent investigation of the former group of diabetics in response to blood viscosity lowering regimens might yield very valuable data on the importance of haemorheology in diabetes mellitus.

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