The Effect of Improvement in Diabetic Control on Plasma and Whole Blood Viscosity

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Summary. Rheological studies were made on the blood of 12 diabetic patients after a period of poor diabetic control (HbA₁ $12.6 \pm 0.7\%$ (mean $\pm$ SD); mean home capillary blood glucose level 11.7 ± 1.2 mmol/l), and after at least three months of improved control (HbA₁ $9.1 \pm 0.4\%$, $p < 0.01$; mean home capillary blood glucose level 9.2 ± 0.6 mmol/l). There were significant decreases in plasma fibrinogen levels (4.1 ± 0.6 to 3.7 ± 0.6 g/l, $p < 0.01$), plasma viscosity (1.31 ± 0.1 to 1.25 ± 0.04 , $p < 0.001$), and whole blood viscosity at low (22.8 ± 2.7 to 20.2 ± 2.9 , $p < 0.01$) and high shear rates (3.4 ± 0.2 to 3.1 ± 0.2 , $p < 0.01$). Ten diabetics with clinically evident complications were matched with diabetics of similar age, sex, duration and current control of diabetes. There were no significant differences in plasma or whole blood viscosities between the two groups. Hyperviscosity in diabetes seems strongly related to hyperglycaemia and to be influenced by the quality of diabetic control.

Key words: Rheology, plasma fibrinogen level, plasma viscosity, whole blood viscosity, shear rate, Contraves rotational viscometer, glycosylated haemoglobin.

There is evidence that diabetics have higher than normal plasma and whole blood viscosity [1, 2, 3], and it has been reported that diabetics with complications have higher viscosities than those with no complications [4, 5]. There have been suggestions that hyperviscosity might contribute to the development of vascular disease in diabetics, as in the retinopathy of the dysgammaglobulinaemias [6, 7, 8, 9]. The present study was undertaken to see whether improve-

ment in diabetic control affects blood viscosity, and whether patients with diabetic complications have higher viscosities than matched diabetics with no complications, but a similar degree of recent hyperglycaemia.

Patients and Methods

Patients

Twelve diabetics were studied for 8–12 weeks and all gave informed consent to the study. Their characteristics are shown in Table 1.

Persistent poor control of blood glucose was shown by home blood glucose monitoring and measurement of glycosylated haemoglobin (HbA₁). Improvement was achieved by changing four patients from once to twice daily insulin regimes, two from Actrapid and Semitard to Actrapid and Monotard, and just increasing the insulin dose in a further five patients. In one patient (Number 6, Table 1), hyperglycaemia was reduced by increasing his dose of glibenclamide. Rheological measurements were performed after both periods of study.

Ten diabetics with clinically apparent complications (always including retinopathy) were matched for age, sex, treatment, current control and duration of diabetes, with ten diabetics without clinical evidence of complications. Characteristics of all twenty are given in Table 2.

Laboratory Methods

Home capillary blood glucose levels were measured pre and postprandially by a method previously described [10] to give 7–8 samples in 24 h every 2–4 weeks. HbA₁ was measured by Quik-sep column (normal range 6–8%, coefficient of variation (CV) 4.5%). Plasma fibrinogen levels were measured on immuno-diffusion plates (Hoechst), normal range 2.5–4.0 g/l, (CV 10%). Plasma viscosity was measured at 37° C by capillary Viscometer (normal range 1.16–1.35 centipoise, CV 3%). Whole blood viscosity was measured both at high shear rate (1000 sec^{-1}) with the capillary viscometer (normal range 2.5–3.8 centipoise, CV 3.4%) and at low shear rate (1 sec^{-1}) with the Contraves rotational viscometer (normal range 15–23 centipoise if samples initially adjusted to PCV 45%, CV 5%).

Table 1. Characteristics of patients in the study of improved diabetic control and viscosity. Patients were studied before and after changes in insulin treatment or increase in sulphonylurea. All patients were within 10% of ideal body weight

Patient	Age	Sex	Initial body weight (kg)	Duration (years)	Poor control					Improved control				
					Mean blood glucose (mmol/l)	HbA _{1c} %	T.G. (mmol/l)	Cholesterol (mmol/l)	HCT %	Mean blood glucose (mmol/l)	HbA _{1c} %	T.G. (mmol/l)	Cholesterol (mmol/l)	HCT %
1	35	M	69.0	29	18.0	18.8	—	—	42	10.9	7.8	—	—	44
2	22	F	58.5	16	15.9	15.4	2.0	7.9	48	12.0	11.2	1.8	4.9	43
3	42	M	71.3	4	9.6	11.0	1.1	4.2	45	6.5	6.3	0.9	4.6	45
4	24	F	59.6	5	9.6	11.6	1.3	5.8	47	7.7	8.7	1.2	5.6	45
5	23	M	71.4	5	8.2	9.7	1.1	3.9	50	6.0	8.0	1.1	3.2	49
6	40	M	68.1	5	11.5	12.9	—	—	50	9.8	10.3	—	—	50
7	40	M	71.9	2	10.3	11.5	0.7	4.3	47	8.3	8.9	0.6	4.4	42
8	56	F	59.8	10	9.6	9.4	0.7	6.7	45	7.6	7.4	0.6	7.2	46
9	29	M	68.5	7	12.8	14.0	1.1	5.4	49	11.0	10.4	1.0	5.3	49
10	18	F	50.0	2	13.3	12.7	—	—	43	12.5	11.2	—	—	42
11	36	M	70.1	2	10.0	11.4	1.0	5.3	47	8.4	9.4	0.9	5.0	47
12	54	F	61.5	8	11.0	11.8	—	—	40	9.5	10.0	—	—	42
Mean	35.0			7.9	11.7 ^a	12.6 ^b	1.10	5.4	46.1	9.2 ^a	9.1 ^b	1.0	5.0	45.5
± SEM	± 3.6			± 2.2	± 1.19	± 0.7	± 0.1	± 0.5	± 0.9	± 0.6	± 0.4	± 0.1	± 0.4	± 0.81

^a Difference significant at 5% level^b T.G., serum triglyceride; HCT, haematocrit

Difference significant at 1% level – paired t test

Table 2. Characteristics of matched patients with and without complications of diabetes

Patients with complications							Matched patients free from complications						
Patient	Age	Sex	Duration (years)	Treatment	Mean blood glucose (mmol/l)	HbA _{1c} %	Patient	Age	Sex	Duration (years)	Treatment	Mean blood glucose (mmol/l)	HbA _{1c} %
13	63	F	10	Glipizide	12.3	13.9	23	68	F	6	Glipizide	12.9	12.1
14	64	M	2	Gliben.	8.7	9.6	24	63	M	6	Gliben.	9.0	10.7
15	58	F	15	Insulin	6.4	6.3	25	56	F	10	Insulin	7.3	7.6
16	51	M	10	Glipizide	6.0	6.5	26	55	M	10	Glipizide	6.4	7.6
17	22	F	16	Insulin	12.0	14.0	27	25	F	12	Insulin	12.0	13.5
18	34	M	29	Insulin	8.0	7.8	28	30	M	21	Insulin	11.0	10.6
19	50	F	23	Insulin	12.0	11.8	29	54	F	21	Insulin	11.5	11.8
20	48	F	17	Insulin	11.4	11.9	30	46	F	15	Insulin	10.0	10.4
21	50	M	8	Insulin	9.0	8.9	31	57	M	10	Insulin	9.5	10.1
22	62	F	6	Insulin	5.5	6.4	32	50	F	8	Insulin	6.0	7.8
Mean	51.2		13.6		9.1	9.7		50.4		11.7		9.6	10.2
± Sem	± 4.3		± 2.4		± 0.8	± 1.0		± 4.1		± 1.5		± 0.8	± 0.6

All patients were within 10% of ideal body weight

Glipizide – before meals

Gliben. – Glibenclamide twice daily

Collection and Transport of Samples

All samples were taken between 0930 and 1100 h. Sequestrene (EDTA) samples were gently inverted 15 times then placed immediately on ice, and kept at 4° C during transport from Bristol to Taunton where viscosity measurements were performed

22–24 h afterwards at 37° C. To establish the validity of measurements after this procedure ten blood samples were tested for whole blood viscosity both before and after 24 h storage at 4° C. Results were as follows:– whole blood viscosity at high shear rate 3.31 ± 0.4 centipoise when measured immediately, 3.31 ± 0.4 centipoise after 24 h at 4° C; whole blood viscosity at 1 sec^{-1} 20.7 ± 4.3

Fig. 1. Changes in plasma fibrinogen, plasma viscosity and whole blood viscosity at low and high shear rates after reduction of hyperglycaemia. Each pair of points represents one patient before and after improvement in glucose control. The scale has been expanded to emphasise these changes, but it is notable that all patients showed a fall in viscosity measurements, not only when made on blood corrected for PCV of 45% but also when tested before this correction

centipoise when measured immediately, 21.0 ± 4.2 centipoise after 24 hours at 4°C . We have found whole blood viscosity to increase after storage of blood at room temperature as previously reported [11], but changes in red cells causing this increase are prevented for up to 24 h by storage at 4°C .

Statistical analysis was performed using paired and unpaired t tests. All results are given as mean $\pm$ SD unless otherwise state.

Results

There was no consistent change in haematocrit or serum cholesterol after reduction in hyperglycaemia, though fasting triglyceride levels fell in all of the eight patients in whom this was measured. Figures 1a–d

show the corresponding reductions in plasma fibrinogen (4.1 ± 0.6 to 3.7 ± 0.6 g/l, $p < 0.01$), plasma viscosity (1.31 ± 0.1 to 1.25 ± 0.04 centipoise, $p < 0.001$), whole blood viscosity at low shear rate (22.8 ± 2.7 to 20.2 ± 2.8 centipoise, $p < 0.01$), and whole blood viscosity at high shear rate (3.4 ± 0.2 to 3.1 ± 0.2 , $p < 0.001$).

In contrast, the plasma fibrinogen levels and mean viscosities in 10 diabetics with complications were not significantly different from measurements in diabetics matched for age, sex, treatment, current control, and duration of diabetes. Results were as follows, fibrinogen levels 4.3 ± 0.9 and 4.1 ± 0.8 g/l; plasma viscosities 1.4 ± 0.1 and 1.4 ± 0.1 centipoise; capillary whole blood viscosity at high shear rate 3.5 ± 0.5 and 3.6 ± 0.4 centipoise; and whole blood viscosity at low shear rate 22.9 ± 6.9 and 23.4 ± 3.1 centipoise.

Discussion

In this study there was no consistent change in haematocrit after reduction of hyperglycaemia, though in a larger study, with greater changes in blood glucose levels, a fall in haematocrit might be expected. There is a relationship between haematocrit, plasma viscosity and whole blood viscosity [12, 13, 14] and any such fall in haematocrit would accentuate the changes which we have found in whole blood viscosity. In our study it is most likely that improvement in diabetic glycaemic control has resulted in decreased whole blood viscosity as a consequence of decreased plasma viscosity, and that this has in turn resulted from the decrease in plasma fibrinogen. Changes in globulins may also have played a part but the small changes in fasting triglyceride levels found in eight patients seem unlikely to be relevant to blood viscosity changes. The high plasma fibrinogen levels when patients were more hyperglycaemic could have resulted from dehydration (reduction of plasma volume) an increase in hepatic synthesis of fibrinogen, or from a combination of the two. Serum globulins might be similarly raised, or their pattern disturbed [4, 15] by the effect of hyperglycaemia on hepatic synthesis. In addition, post translational glycosylation of many serum glycoproteins may occur in proportion to prevailing blood glucose levels [16] (analogous to the glycosylation of HbA), and glycosylation of globulins could produce conformational molecular changes resulting in increased plasma viscosity.

Changes in red cell deformability were not measured in our study, though some changes have been described in diabetes [17, 18], and if hyperglycaemia

decreased red cell deformability then this would have contributed to increased whole blood viscosity.

Whether changes in blood viscosity of the order seen in our patients could affect tissue perfusion, particularly in the retina, is not known, though experimental increases in blood viscosity have been shown to reduce retinal blood flow [19]. However, in our second group of patients there was no difference in rheological variables between those with extensive complications of diabetes and the matched patients without clinically apparent complications. Six of these patients had advancing retinopathy under current photocoagulation treatment and four of these (Numbers 16, 18, 21 and 22) had plasma and whole blood viscosities within the normal range. This suggests that hyperviscosity is at least not necessary for the continued worsening of retinopathy in some patients. If larger numbers had been studied, a significant increase in blood viscosity might have emerged in those patients with complications. However, all the patients in these matched groups had suffered from diabetes for at least six years and widespread vascular changes could well be present in the patients free from obvious clinical complications. This might affect blood viscosity resulting in overall increases in both patients with and without obvious retinopathy alike, because of the presence of large vessel disease [5, 18]. There is some evidence that the threshold of hyperglycaemia associated with the development of macroangiopathy is lower than that for microvascular disease [20].

Lastly, the patients with complications and their matched controls had a mean duration of diabetes of 12.6 years, and a mean age of 51 years compared with 7.9 and 35 years respectively for patients in the study of diabetic control. These differences might well be associated with more widespread macroangiopathy in the patients with complications and their matched controls and this could have produced the higher blood viscosity levels found in these patients. These factors might also partly explain the increased whole blood viscosity in diabetics with retinopathy, compared with those with no retinopathy in a recent study [21], though these patients were not accurately matched for current glycaemic control of diabetes.

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