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Impaired deformability of erythrocytes and neutrophils in children with newly diagnosed insulin-dependent diabetes mellitus

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Abstract

Aims/hypothesis. Abnormal rheological properties of erythrocytes, leucocytes and plasma may have a role in the development of diabetic microangiopathy. We hypothesized that changed haemorrheological variables may already be found in children with onset diabetes.
Methods. Erythrocyte deformation (rheoscope), neutrophil deformation (micropipette), erythrocyte aggregation, blood and plasma viscosity were measured in 15 children with insulin-dependent diabetes mellitus before initiation of insulin treatment and 4 to 6 weeks later, 15 diabetic children treated with insulin for 5 to 8 years, 15 healthy children and 15 healthy adults.
Results. At a low shear stress of 0.6 Pa, erythrocyte deformation was decreased in the diabetic children before (–28 %), after 4 to 6 weeks (–22 %) and after 5 to 8 years (–17 %) of insulin treatment compared with healthy children. More active neutrophils were counted in the untreated diabetic children (9 ± 6 %) than in healthy children (3 ± 2 %). Deformability of passive neutrophils was greatly decreased in the children with onset diabetes and moderately reduced in the diabetic children who were treated with insulin. Neutrophil deformation ($r = –0.52$) and erythrocyte deformation at 0.6 Pa ($r = –0.62$) were inversely related to haemoglobin A1 c. Haematocrit and blood viscosity were increased in the untreated children and in the children treated with insulin for 5 to 8 years. Plasma viscosity and erythrocyte aggregation were similar in the three groups of children.
Conclusion/interpretation. Decreased erythrocyte deformation at low shear force, increased count of active neutrophils and impaired deformability of passive neutrophils may increase the risk for acute cerebro-vascular complications in children with uncontrolled insulin-dependent diabetes mellitus. [Diabetologia (1999) 42: 865–869]

Keywords Blood viscosity, diabetes mellitus, erythrocyte aggregation, erythrocyte deformability, haemorrheology, neutrophils.

Patients with juvenile onset of Type I (insulin-dependent) diabetes mellitus are at high risk of diabetic microangiopathy and vascular disease. In children and adolescents with Type I diabetes, ischaemic disease of the heart [1], retina [2] and intestine [3] have been observed. These angiopathic complications usually develop after several years of Type I diabetes. Functional impairments of the macrocirculation and microcirculation have, however, been observed at early stages of juvenile Type I diabetes [4, 5].

The development of diabetic angiopathy has been related to abnormal haemorrheological properties as increased blood viscosity, haematocrit, plasma viscosity and erythrocyte aggregation [6, 7], and decreased erythrocyte [6, 8, 9] and leucocyte deformability [9–13]. High values of HbA_{1c} correlated with decreased deformability of erythrocyte [6, 14] and polymorphonuclear neutrophils (PMN) [13] and in-

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Abbreviations: PMN, Polymorphonuclear neutrophils.

Table 1. Erythrocyte indices and haemorrheological variables in children with Type I diabetes

	Onset Type I before insulin	Children with Type I treated with Insulin for		Healthy children	Healthy adults
		4–6 weeks	5–8 years		
Age (years)	10 ± 2	10 ± 2	13 ± 2[b]	10 ± 2	25 ± 3[c]
Blood glucose (mmol/l)	28.2 ± 6.0[c]	8.5 ± 2.3[c]	9.6 ± 2.6[c]	4.1 ± 0.9	4.5 ± 1.1
Haemoglobin A_{1c} (%)	13.6 ± 3.3[c]	9.8 ± 1.8[c]	7.3 ± 1.7[c]	4.6 ± 1.1	4.2 ± 0.8
Haematocrit (%)	44.4 ± 4.8[a]	38.6 ± 3.9	43.1 ± 3.5[a]	39.2 ± 3.6	47.2 ± 5.0[a]
MCV (fl)	88.9 ± 3.2	92.4 ± 3.5	89.5 ± 2.5	90.6 ± 3.3	90.7 ± 4.8
MCH (pg)	29.8 ± 1.9	29.3 ± 1.7	28.9 ± 1.8	28.4 ± 1.6	29.5 ± 1.7
MCHC (g/dl)	33.5 ± 1.2	32.1 ± 1.5	31.9 ± 1.4	32.0 ± 1.2	32.9 ± 1.0
Reticulocyte count (10^3/μl)	49 ± 23	53 ± 28	78 ± 32[a]	50 ± 26	52 ± 27
Total plasma protein (g/l)	65 ± 6	68 ± 7	65 ± 6	68 ± 5	73 ± 7
Plasma albumin (g/l)	44 ± 3	42 ± 4	43 ± 3	45 ± 3	48 ± 5
Plasma fibrinogen (g/l)	2.8 ± 0.5	2.8 ± 0.7	3.0 ± 0.6	2.7 ± 0.6	3.4 ± 0.6[a]
Erythrocyte elongation at 0.6 Pa	13 ± 3[b]	14 ± 2[b]	15 ± 2[a]	18 ± 2	17 ± 3
Erythrocyte elongation at 8.5 Pa	41 ± 4	42 ± 5	41 ± 4	44 ± 3	43 ± 6
Erythrocyte aggregation	8.7 ± 2.1	9.5 ± 2.6	9.3 ± 2.3	8.9 ± 1.8	10.3 ± 2.5
Plasma viscosity (mPa · s)	1.2 ± 0.2	1.3 ± 0.2	1.2 ± 0.1	1.2 ± 0.1	1.3 ± 0.1
Blood viscosity (mPa · s)	3.0 ± 0.4[a]	2.6 ± 0.4	3.0 ± 0.5[a]	2.5 ± 0.5	3.4 ± 0.6[a]
Leucocyte count (× 10^9/l)	12.5 ± 3.7[c]	7.3 ± 2.4	6.8 ± 1.8	6.5 ± 1.4	6.1 ± 1.3
Neutrophil count (× 10^9/l)	9.2 ± 3.3[c]	4.5 ± 1.3	3.6 ± 1.0	3.0 ± 0.7	3.2 ± 0.6
Neutrophil volume (fl)	396 ± 61	358 ± 42	369 ± 44	360 ± 46	348 ± 50
Active neutrophils (%)	9 ± 6[b]	6 ± 4[a]	5 ± 3	3 ± 2	4 ± 3
Neutrophil tongue length (μm; at 60 s)	5.8 ± 1.0[c]	6.9 ± 1.2[b]	7.7 ± 1.3[a]	9.5 ± 1.4	9.1 ± 1.5

Diabetic children and healthy adults were compared with healthy children ([a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$)
MCH, mean corpuscular volume; MCHC, mean corpuscular haemoglobin; MCV, mean corpuscular haemoglobin concentration

creased plasma fibrinogen [15], the major determinant of plasma viscosity and erythrocyte aggregation [7].

During the initial presentation, children with Type I diabetes frequently show severe hyperglycaemia and HbA_{1c} values greater than 10% [4, 16, 17]. Brain swelling is a serious complication of new onset Type I diabetes in children [17, 18]. Brain swelling may occur before treatment with fluids and insulin, suggesting that severe hyperglycaemia and ketoacidosis themselves contribute to the development of cerebral oedema [18]. Although animal experiments have shown that acute hyperglycaemia induces considerable cerebral blood flow disturbances and impaired cerebrovascular reactivity [19], it is not clear whether vascular changes are involved in cerebral complications of patients with uncontrolled Type I diabetes.

Moreover, it is not known whether onset Type I diabetes is associated with abnormal haemorrheological properties. In particular, PMN could play a part in the pathogenesis of cerebral complications during onset of Type I diabetes, since PMN have been shown to have an important role in the production of hypoxic-ischaemic brain injury in adult and neonatal animal models [20, 21]. Studies on diabetic rats showed increased counts of PMN at the time of overt onset of diabetes [22] and of active PMN in circulating blood at 2 to 9 months of diabetes [23]. The rise – in active PMN, which are extremely rigid [24] – was associated with capillary occlusions by leucocytes [23].

Our study was designed to determine several haemorrheological variables in children with Type I diabetes and severe ketoacidosis before commencing insulin treatment and during insulin treatment. These variables included blood and plasma viscosity, aggregation and deformability of erythrocytes and deformability of neutrophils. Moreover, activated neutrophils were counted.

Subjects and methods

Patients. The studies were undertaken in accordance with the ethical standards laid down in the Declaration of Helsinki. Informed consent of the blood donors or their parents was given and the approval of the ethics committee of the Department of Paediatrics was obtained. We studied 4 groups (Table 1) each of which comprised 15 subjects: (1) children with Type I diabetes (aged 7 to 12 years) studied before and 4 to 6 weeks after initiation of insulin treatment; (2) children with Type I diabetes (10 to 15 years old) who had been treated with insulin for 5 to 8 years; (3) healthy children (7 to 12 years old); and (4) healthy non-obese men (21 to 29 years old). Children and adults with a family history or manifestation of hypertension or hyperlipoproteinaemia and those who reported active or passive smoking, alcohol or drug consumption were excluded. The healthy children were patients of the Department of Paediatric Surgery who had had minor selective operations (e.g. inguinal hernia, phimosis). In the children with onset Type I diabetes, blood sugar was 21 to 36 mmol/l, HbA_{1c} 10 to 19%, plasma osmolality 302 to 356 mosmol/kg, arterial pH 7.05 to 7.22, bicarbonate 7 to 16 mmol/l, base excess –25 to –13 mmol/l and pCO_2 21 to 41 mmHg at admission. All infants with newly diagnosed Type I diabetes had subtle central nervous system signs such as dizziness, headaches or sleepiness but none developed obvious symptoms of severe brain swelling such as severe deterioration in neurological or vital status. In

group 1, blood was taken immediately prior to treatment with insulin and again 4 to 6 weeks later when blood gases were normal and blood sugar was less than 10 mmol/l. In the patients of group 2, blood gases and osmolality were normal, blood sugar was less than 10 mmol/l and HbA_{1c} less than 10%. None of the patients had retinopathy or other manifestastions of diabetic microangiopathy.

Methods. Blood samples were obtained by venipuncture into EDTA (1 mg/ml). Haematocrit (microcentrifuge), mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, total leucocyte count (Coulter Counter, Harpenden, Herts, UK), reticulocyte count (brilliant cresyl blue), total plasma protein (Biuret method; Boeringer, Mannheim, Germany), fibrinogen and albumin concentrations (radial-immunodiffusion; Behring, Marburg, Germany) were measured as described previously [25]. Serum glucose was measured by the glucose oxydase method and HbA_{1c} by the Bio-Rad Column test (Biorad, Richmond, Calif., USA).

All haemorrheological methods have been described previously [24–27]. The measurements were made within 4 h after blood collection. Blood and plasma viscosities were determined by means of a tube viscometer (diameter 100 μm) [25]. Aggregation of erythrocytes suspended in autologous plasma at a haematocrit of 40% was assessed at 22 °C using a Myrenne Aggregometer MA2 (Myrenne Roetgen, Germany) [25]. The deformation (elongation, E) of single erythrocytes was studied at 22 °C using a rheoscope at six different shear stresses [26]; E = 100 (L-W)/(L + W), where L is the length and W the width of the deformed cell, E is zero in the absence of deformation and 100 with maximum deformation.

Deformation of neutrophils (PMN) was studied by means of a micropipette system. Details of the leucocyte preparation, the micropipette system, the identification of passive and active PMN, the procedure of PMN deformation and volume studies have been described elsewhere [24, 27]. Pipettes with internal diameters of 2.5 μm were used to aspirate membrane-cytoplasm tongues of PMN at an aspiration pressures of 2 cm H_2O. The length of the aspirated tongue was measured from video recording after 5, 10, 20, 30, 40, 50 and 60 s. We studied 20 passive mature neutrophils in each sample. Activation of neutrophils was assumed if pseudopod projections greater than 0.5 μm were visible, tongue growth in the pipette abruptly slowed or stopped, or tongues partially retracted from the pipette during aspiration [24]. Since activated PMN are extremely rigid [24], they were not included in the deformation analysis but their number was counted in each sample.

Statistics. Analysis of variance for paired observations was used to test for changes in the measured variables during the first 4 to 6 weeks of insulin treatment. The four groups were compared using analysis of variance for unpaired observations.

Results

Blood glucose concentrations and HbA_{1c} in the children with Type I diabetes were high before insulin treatment and decreased during insulin treatment but were still increased in the children treated for 5 to 8 years (Table 1).

The haematocrit was higher ($p < 0.05$) in the untreated children with Type I diabetes and in the children treated for 5 to 8 years. Reticulocyte counts were normal in the untreated diabetic children but higher in the children with Type I diabetes treated for 5 to 8 years, compared with the control subjects (Table 1). The plasma concentrations of total protein, albumin and fibrinogen and the rheological variables depending on plasma proteins (i.e. plasma viscosity and erythrocyte aggregation) were similar in all groups of children.

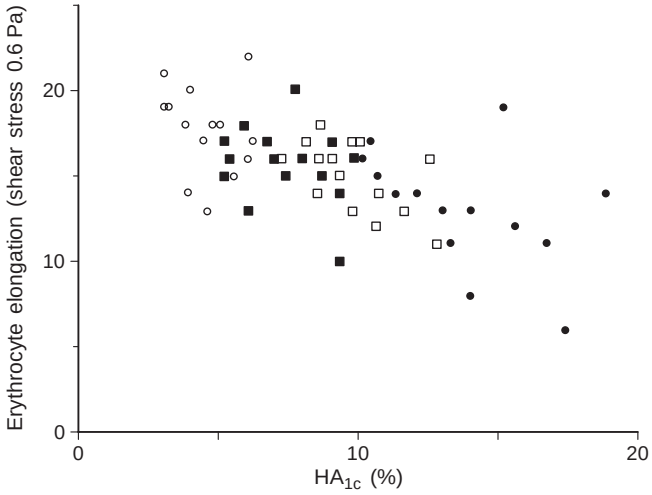

Fig. 1. Relation between HbA_{1c} and erythrocyte elongation (E) in the rheoscope at a shear stress of 0.6 Pa. $E = 19.8–0.49 \times HbA_{1c}$ ($r = –0.62$). ○ Healthy children, □ Type I 5–8 years, ■ Type I 4–6 weeks, ● Type I no insulin

Erythrocyte elongation in the rheoscope at a shear stress of 0.6 Pa was decreased in the untreated and treated children with Type I diabetes compared with the control children and adults, whereas no differences were observed at higher shear stresses. There was an overall relation ($p < 0.001$) between HbA_{1c} and erythrocyte elongation at a shear stress of 0.6 Pa (Fig. 1). Whole blood viscosity was increased ($p < 0.05$) in the untreated children with Type I diabetes, the children treated for 5 to 8 years and the adults compared with the control children. Increased blood viscosity was related to increased haematocrit.

Total leucocyte and PMN counts were increased in the children with Type I diabetes before insulin treatment but normal during insulin treatment. The volume of PMN was not affected by Type I diabetes. The lengths of PMN membrane-cytoplasm tongues formed during aspiration in a micropipette were greatly reduced before insulin treatment and moderately decreased during insulin treatment, compared with the control children (Fig. 2). There was an inverse overall relation between HbA_{1c} and the PMN membrane-cytoplasm tongue length at 60 s of aspiration ($r = –0.52$; $p < 0.001$). The percentage of active neutrophils was higher in the children with Type I diabetes before insulin treatment (9%) than in the healthy children (3%).

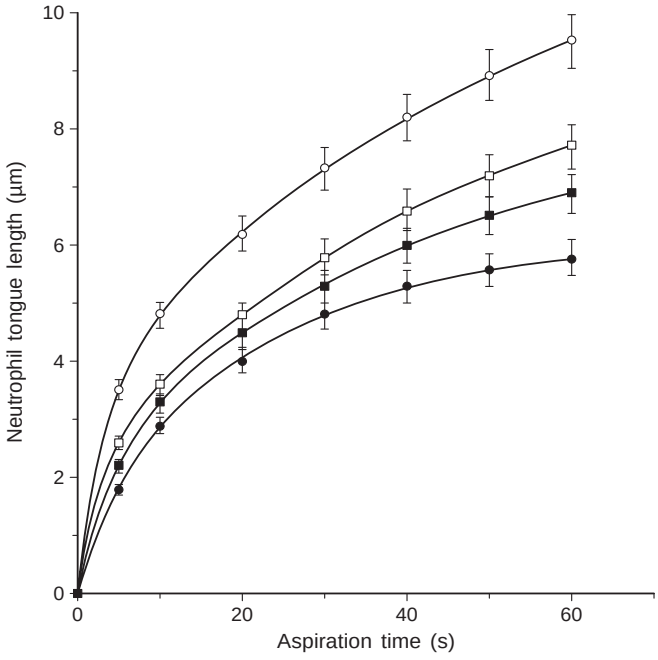

Fig. 2. Tongue length of passive mature neutrophils plotted against aspiration time. Membrane-cytoplasm tongues were formed due to aspiration into micropipettes with diameters of 2.5 µm at a suction pressure of 2 cm H_2O. Children with Type I diabetes were studied before insulin treatment, at 4–6 weeks or 5–8 years of insulin treatment. Values represent means ± 1 SEM. ○ Healthy children, □ Type I 5–8 years, ■ Type I 4–6 weeks, ● Type I no insulin

Discussion

From this data, we have drawn three major conclusions regarding children with onset Type I diabetes before insulin treatment: (1) they show decreased erythrocyte deformation at low shear stress; (2) the counts of total and active PMN are increased and the deformability of passive PMN considerably decreased; and (3) plasma vicosity and erythrocyte aggregation are normal compared with healthy children (Table 1). Both erythrocyte aggregation and plasma viscosity are related to plasma fibrinogen [7] which was also normal in the children with Type I diabetes (Table 1). This confirms the assumption that plasma fibrinogen is not directly affected by the control of diabetes [15]. In adults with long-term diabetes, both plasma viscosity and erythrocyte aggregation may be increased due to increased plasma fibrinogen [6, 7]. Thus, it seems to take more than 5 to 8 years of youth-onset Type I diabetes for a meaningful rise of plasma fibrinogen to occur [16, 28].

Previous studies on erythrocyte deformability in diabetics used filtration techniques or rotating chambers with defined shear stresses (i.e. rheoscope and ektacytometer). Several studies showed decreased erythrocyte filtration rates, particularly in poorly controlled diabetic patients [6, 8, 14]. In adult diabetic patients normal erythrocyte deformation has been observed using a rheoscope [29] or an ektacytometer [30] at shear stresses of 1 Pa and higher. We observed decreased erythrocyte deformation in children with Type I diabetes only at a shear stress of 0.6 Pa. Thus, previous studies could have missed abnormal erythrocyte deformation at low shear stresses. At low shear stress, erythrocyte deformation is primarily influenced by membrane properties [31]. Abnormal erythrocyte membrane properties in diabetic children include increases in glycated proteins [32], microviscosity [32], lipid peroxidation [33] and membrane-bound haemoglobin [14].

A micropipette system resembling our device has been used for PMN deformation studies in adults with Type II (non-insulin-dependent) diabetes mellitus [12]. Aspirated PMN tongue lengths were 20% shorter after 60 s of aspiration than in healthy control subjects. This corresponds to our findings in insulin-treated children with Type I diabetes, whereas untreated children had much shorter tongue lengths (Fig. 2). Both decreased deformability and impaired phagocytosis of PMN could be due to increased intracellular calcium concentration [34].

A high percentage of active PMN (9%) was found in untreated diabetic children (Table 1). Active PMN are extremely rigid [24] and activation may cause expression of adhaesion molecules [35]. Active PMN have been shown to obstruct retinal [23] and muscle [36] capillaries of diabetic rats. Impaired erythrocyte deformability at low shear stress may further diminish microvascular flow at low perfusion pressure.

We conclude that untreated children with onset Type I diabetes show more pronounced alterations of erythrocyte and PMN deformability than insulin-treated children with Type I diabetes. High counts of rigid active PMN, impaired deformability of resting PMN and decreased flexibility of erythrocytes at low flow may contribute to the high risk children with onset Type I diabetes have of acute vascular complications (e.g. cerebral oedema). Note that treatment with C peptide improves mircrocirculation of the skin and other tissues in adult patients with Type I diabetes, thereby improving tissue oxygen supply and nutrition [37, 38]. It is not clear whether C peptide infusion could also prevent or ameliorate severe vascular complications in children with onset Type I diabetes.

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