Association among low whole blood viscosity, haematocrit, haemoglobin and diabetic retinopathy in subjects with type 2 diabetes

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Accepted 8 March 2010
Published Online First 8 June 2010

ABSTRACT

Objectives Haemorheological variables influence endothelial function through the release of several factors. Clinical studies have described an association among blood viscosity, haematocrit, haemoglobin and macro-angiopathy. Few data are reported about the association between haemorheological variables and micro-angiopathy. The aim of the present study was to evaluate the association between these variables and retinopathy in subjects with type 2 diabetes.

Methods 111 men, 79 postmenopausal women, and 95 healthy age- and sex-matched controls were recruited. Haematocrit and haemoglobin were measured by standard methods. Blood viscosity was calculated according to the formula (0.12× haematocrit)+(0.17× (plasma proteins−2.07)). Subjects were grouped according to the presence or absence of diabetic retinopathy, while the severity of retinopathy was classified according to the Early Treatment Diabetic Retinopathy Study scale.

Results Haemoglobin, haematocrit and whole blood viscosity were significantly lower in subjects with retinopathy compared to subjects without retinopathy in both sexes. These variables significantly decreased with increasing severity of retinopathy. A multiple logistic regression analysis confirmed the independent inverse association among viscosity, haematocrit, haemoglobin and retinopathy ($p<0.01$).

Conclusion Results demonstrate the association among low viscosity, haemoglobin, haematocrit and diabetic retinopathy. The mechanisms responsible for this association can be hypothesised. Reduced haemoglobin might cause direct organ damage. Low blood viscosity, through the reduction of shear stress, might inhibit the anti-atherogenic functions of endothelial cells.

Blood flow velocity and pattern influence vessel tone, structure and function through interaction of blood with the endothelial surface. The characteristics of the blood, that is viscosity, haemoglobin concentration and haematocrit, strongly influence blood velocity and pattern and, as a consequence, the function and structure of the vessels.[1]

In vitro experimental models and in vivo studies have demonstrated the association between whole blood viscosity (WBV) and atherosclerosis in some arterial districts.[2 3] Chronic angina and acute myocardial infarction are significantly influenced by haematocrit, and anaemia has been associated with an increased mortality for cardiovascular disease.[4 5] While high WBV seems to be involved in the development of atherosclerosis and acute cardiovascular events, few data have been reported on the association between WBV and small-vessel disease.

It is well known that diabetic subjects can experience macro- and micro-angiopathy, the latter leading to clinical complications like retinopathy, nephropathy and neuropathy. Actually, diabetic retinopathy (DR) is considered the most important risk factor for blindness in adults, and the prevalence of DR increases with age and with diabetes duration. It is estimated that after 20 years of disease >60% of type 2 diabetic subjects have some degree of DR.[6] Large prospective intervention studies have demonstrated that optimal glycaemic control reduces the incidence of DR as well as the progression of the disease.[7 8] In spite of this evidence, the mechanisms involved in the pathogenesis of DR are still unknown.

Apart from classical risk factors for DR, haemorheological parameters have also been considered in the pathogenesis of this complication, with conflicting results. The aim of the present study was to verify if blood viscosity, haematocrit and haemoglobin associate with DR in subjects with type 2 diabetes.

SUBJECTS AND METHODS

Participants and measurements

For our aim, we selected subjects with type 2 diabetes among outpatients regularly attending our metabolic unit and with a complete laboratory examination and full visit in the last 2 months. One hundred and ninety diabetic subjects consented to participate in the study. Men and post-menopause women were included. Menopause was defined as absence of menses for 12 consecutive months. Pre-menopausal women, as well as individuals with elevated urine albumin excretion measured in 12-h nocturnal urine, were excluded because of the possible influence of menstruation and impaired renal function on haemorheological parameters. A control group of 95 age- and sex-matched, non-diabetic subjects were recruited. They were clinically healthy and had no identified cardiovascular risk factors. The local Ethical Committee (Azienda Ospedaliera Mater Domini) approved the study protocol, and the investigations were carried out in accordance with the principles of the Declaration of Helsinki. The protocol included physical examination, blood withdrawal for serum analysis and complete ophthalmologic examination. Physical examination included height and weight measurement, calculation of the body mass index (BMI) and measurement of blood pressure.

Biochemical analysis

A venous blood sample was withdrawn after 12 h fasting. Serum glucose was assessed by a modified hexokinase/gluose-6-phosphate dehydrogenase procedure. Cholesterol and triglycerides were measured by enzymatic methods; high-density lipoprotein (HDL)-cholesterol was measured after dextran-magnesium precipitation, and low-density lipoprotein (LDL) was calculated according to Friedewald formula. Fibrinogen measurement was performed by radial immunodiffusion (NOR-Partigen, Behring, Marburg, Germany). The haematocrit (Hct) level was calculated from the measurement of red blood cells, haemoglobin (Hb) by high-pressure liquid chromatography (HPLC) and plasma proteins by the biuret method. Glycated haemoglobin (HbA_{1c}) was estimated by HPLC. Renal function was evaluated by the estimation of glomerular filtration rate (GFR) using the modified Cockroft and Gault formula.[9] WBV was estimated according to a validated formula that takes into account haematocrit and plasma protein[10];[1]

$$WBV = [0.12 \times \text{haematocrit}] + [0.17 \times (\text{plasma proteins} - 2.07)]$$

where haematocrit is in % and plasma protein in g/l. The unit for viscosity is the centipoises (cP) corresponding to the ratio of the shear rate of blood to the shear rate of water. The formula has been validated with direct viscosity measurement through a wide range of haematocrit (32–53%) and plasma protein (5.4–9.5 g/dl).[11]

Cardiovascular risk factors, that is hypertension, hyperlipidaemia and obesity were defined as follows: hypertension as systolic blood pressure and/or diastolic blood pressure ≥130/85 mmHg or use of antihypertensive agents; hyperlipidaemia as total cholesterol and/or triglycerides >5.1 and/or >2.2 mmol/l, respectively, or use of hypolipidaemic drugs. Smokers included subjects that smoked cigarettes or cigars daily. Subjects were defined as having cardiovascular disease (myocardial infarction, stroke, peripheral arterial disease) only if they had a medical record describing the event.

Ophthalmologic examination

During the same day of physical examination and blood withdrawal, all subjects underwent a complete bilateral retinal examination, including fundus photography after mydriasis. Subjects were grouped according to the presence or absence of DR (With DR; Without DR). Retinopathy was graded on the presence of microaneurysms, haemorrhages, hard exudates, area of revascularisation, fibrous proliferation and and/or laser scars in the more severely affected eye. The Early Treatment Diabetic Retinopathy Study (ETDRS) scale was used to define the severity of DR: 1, absence of retinopathy (level 10); 2, minimal non-proliferative diabetic retinopathy (NPDR) (level 20, 35, 43); 3, moderate to severe NPDR and proliferative DR (level≥47).[12]

Statistical analysis

Values are shown as mean (SD). Comparisons were performed using Stat View 5.0 for McIntosh. Differences in clinical and biochemical variables between control and diabetic subjects and between subjects with and without DR were evaluated using two-tailed t test for unpaired data. The groups classified according to the severity of DR were compared using analysis of variance test with Bonferroni/Dunn as post hoc test. Triglycerides and disease duration were not normally distributed; therefore, they were log-transformed before applying the parametric tests. The independent association between DR and WBV, Hb and Hct after adjustment for age, sex, HbA_{1c}, fibrinogen, disease duration, GFR, cardiovascular risk factors, different antidiabetic treatment and previous cardiovascular events was evaluated using a logistic regression analysis model.

RESULTS

Characteristics of studied subjects

The age range of the 190 diabetic subjects was 40–75 years (mean (SD) 59.9 (9.0)). Among these, 111 were men (58%) and 79 women (42%), and the mean disease duration was 11.5 years. One hundred and forty were being treated with oral antidiabetic drugs (sulfonylureas and/or insulin sensitiser), 32 were treated with insulin therapy, and 18 were using both. Women had higher BMI (32.1 (4.3) vs 30.2 (4.4) kg/m^2, $p<0.01$), total cholesterol (5.1 (0.9) vs 4.7 (1.1) mmol/l, $p<0.01$), HDL-cholesterol (1.4 (0.4) vs 1.2 (0.3) mmol/l, $p<0.01$) and longer disease duration (13.4 (9.5) vs 10.1 (8.0) years) compared to men. As far as cardiovascular risk factors are concerned, the prevalence of hypertension and hyperlipidaemia was, respectively, 55% and 66% in all diabetic subjects, without any significant difference between men and women. No diabetic subjects were currently smokers. Twenty-eight subjects (15%) had a previous acute ischaemic event, and the prevalence was not significantly different between diabetic men and women.

Hypertensive subjects were on treatment with renin–angiotensin system blockers, and among these, 35% were on treatment combined with calcium channel blockers. Subjects with a previous acute ischaemic event were on treatment with antiplatelet agents. Eighty-eight per cent of all diabetic subjects were being treated with statins.

The 95 control subjects had lower fasting glycaemia, lipids, blood pressure and BMI. Mean age of the control subjects was 57.5 (9.1) years, and male sex prevalence was 58% (p=NS compared to diabetic subjects). Table 1 shows fibrinogen, Hb, Hct and WBV in control and diabetic subjects, according to sex. In both women and men, fibrinogen was significantly higher in diabetic subjects compared to controls. Male diabetic subjects had Hb, Hct and WBV comparable to those of control subjects. In contrast, diabetic women had significantly lower

Table 1 Haemorheological variables in controls and subjects with diabetes

Haemorheological variables	Control subjects			Subjects with diabetes		
	All	Men	Women	All	Men	Women
Number	95	55	40	190	111	79
Fibrinogen (mg/dl)	234.7 (58.8)	233.1 (61.1)	236.1 (55.2)	352.3 (72.6)*	345.7 (75.5)*	361.5 (67.7)*
Hb (g/l)	144 (10)	147 (10)	140 (10)	141 (13)	147 (11)	132 (10)† ‡
Hct (%)	41.6 (2.6)	42.1 (2.3)	41.0 (2.9)	41.1 (3.3)	42.6 (2.8)	39.0 (2.7)† ‡
WBV (cP)	4.7 (0.3)	4.8 (0.3)	4.7 (0.3)	4.7 (0.4)	4.9 (0.3)	4.5 (0.3)† ‡

*$p<0.001$ versus control.
†$p<0.005$ versus control women.
‡$p<0.0001$ versus men with diabetes.

Table 2 Characteristics of subjects with diabetes divided according to sex and presence or absence of diabetic retinopathy (DR)

	Women		Men	
Variables	**With DR**	**Without DR**	**With DR**	**Without DR**
Number	41	38	33	78
Age (years)	60.5 (9.3)	59.9 (8.1)	62.6 (8.6)	58.6 (9.4)
BMI (kg/m^2)	31.3 (3.4)	33.1 (5.0)	29.6 (4.4)	30.5 (4.5)
Disease duration (years)	18.5 (9.2)**	7.7 (6.0)	12.3 (8.8)	9.2 (7.6)
Fasting glucose (mmol/l)	10.6 (2.9)**	7.6 (1.9)	10.3 (3.1)**	8.7 (2.7)
HbA_{1c} (%)	8.1 (1.6)**	6.5 (1.2)	7.7 (1.4)***	6.9 (1.7)
Total cholesterol (mmol/l)	5.0 (0.9)	5.2 (1.0)	4.5 (1.2)	4.8 (1.0)
HDL cholesterol (mmol/l)	1.4 (0.3)	1.5 (0.4)	1.1 (0.2)	1.2 (0.3)
Triglycerides (mmol/l)	1.8 (1.0)	1.8 (1.0)	1.8 (1.3)	1.6 (0.8)
LDL-cholesterol (mmol/l)	2.9 (1.0)	3.0 (0.9)	2.5 (1.1)*	2.9 (1.0)
GFR (ml/min)	99.7 (22.3)	106.5 (30.8)	105.7 (31.4)	106.4 (46.5)
Haemorheological variables				
Fibrinogen (mg/dl)	366.0 (77.8)	356.8 (56.3)	361.7 (84.4)	339.2 (62.3)
Haemoglobin (g/l)	130 (10)*	135 (10)	139 (10)**	149 (11)
Haematocrit (%)	38.2 (2.4)**	40.0 (2.8)	40.9 (2.6)**	43.3 (2.6)
Wall blood viscosity (cP)	4.4 (0.3)***	4.6 (0.3)	4.7 (0.3)**	5.0 (0.3)

*p<0.05; **p<0.01; ***p=0.02.

haemorheological values compared to both control female and diabetic male subjects.

Associations among DR, sex and haematological values

In all diabetic subjects, the prevalence of any degree of DR was 39%, and the prevalence was higher in women compared with men (52 vs 30%, p<0.05). Women and men with DR both had a significantly higher fasting glucose and HbA_{1c}, compared with women and men without DR. Disease duration was longer only in women with DR. In both sexes, Hb, Hct and WBV were significantly lower in subjects with DR compared to subjects without DR (table 2).

Associations among severity of DR, sex and haematological values

Haematological values were compared among the three DR severity groups for each sex. In both sexes, Hb, Hct and WBV significantly decreased with increasing severity of DR. Fibrinogen increased only in women, while it was comparable in the three male groups (table 3). Clinical and biochemical variables were not different among men, while among women fasting glycaemia (7.7 (2.3), 10.3 (2.9), 11.8 (2.5) mmol/l; p<0.01), HbA_{1c} (6.5 (1.2), 7.9 (1.5), 8.3 (1.5)%; p<0.01) and disease duration (7.6 (6.0), 17.5 (9.1), 18.9 (2.9) years; p<0.01) progressively increased with increasing DR severity.

Table 3 Haemorheological variables of subjects with diabetic retinopathy DR divided according to sex and severity of DR

Haemorheological variables	Group 1	Group 2	Group 3
Men	n=78	n=18	n=15
Fibrinogen (mg/dl)	339.2 (62.4)	344.1 (82.6)	381.8 (97.6)
Haemoglobin (g/l)	149 (11)**	141 (10)	137 (08)
Haematocrit (%)	43.3 (2.6)**	41.3 (2.5)	40.4 (2.4)
Wall blood viscosity (cP)	5.0 (0.3)**	4.7 (0.3)	4.6 (0.1)
Women	n=38	n=30	n=11
Fibrinogen (mg/dl)	356.8 (56.2)*	349.9 (78.6)*	417.9 (49.0)
Haemoglobin (g/l)	134 (10)**	130 (10)	129 (10)
Haematocrit (%)	39.9 (2.8)*	38.5 (2.5)	37.4 (1.9)
Wall blood viscosity (cP)	4.6 (0.3)***	4.4 (0.3)	4.3 (0.2)

Post hoc test:
*p<0.05 versus 3;
**p<0.001 versus 2, 3;
***p<0.01 versus 3.

Association between DR and haemorheological variables

To evaluate the independent association among Hb–DR, Hct–DR and WBV–DR, the multiple logistic regression analysis was performed for each variable. In each model, the association was assessed after adjustment for age, sex, fasting glycaemia, HbA_{1c}, fibrinogen, disease duration, GFR, cardiovascular risk factors, different antidiabetic treatment and previous cardiovascular events. As shown in table 4, all three variables were significantly and independently associated with DR. The mean odds ratios and the confidence intervals were all negative, indicating that higher WBV, Hct and Hb values associated with a lower risk of DR. The other variables associated with DR were HbA1c, disease duration and previous cardiovascular events (data not shown).

DISCUSSION

The main finding of the present study is that WBV, Hct and Hb are lower in diabetic subjects with retinopathy compared to subjects without retinopathy. Furthermore, levels of these haemorheological variables decrease with increasing degree of retinopathy.

The relationship between WBV and DR is quite controversial, and the number of reports on this topic is limited. Some studies have reported a positive correlation, suggesting a possible role of increased WBV in the pathogenesis of DR. However, this finding has not been confirmed in other studies.[13–16] In large-artery districts, increasing blood viscosity is generally considered

Table 4 Logistic regression analysis between diabetic retinopathy (DR: 0=absence; 1=presence) and haemoglobin, wall blood viscosity, and haematocrit, evaluated separately after adjustment for age, sex, HbA_{1c}, fibrinogen, disease duration, GFR, cardiovascular risk factors, different antidiabetic treatment and previous cardiovascular events

Independent variable	OR	95% CI lower	95% CI upper	p Value
Wall blood viscosity	0.13	0.04	0.46	0.002
Haematocrit	0.78	0.67	0.91	0.002
Haemoglobin	0.64	0.44	0.94	0.02

potentially dangerous since it affects peripheral vascular tone, increases blood pressure and causes disturbance of coagulation.[17] However, there is also evidence that low haematocrit influences negatively the prognosis of subjects with cardiovascular disease.[18] A recent published paper of Salazar-Vasquez[19] might explain these conflicting results. He found a U-shaped relationship between Hct and blood pressure, suggesting that both lower and higher Hct values associate with higher mean arterial pressure.

Blood viscosity and haematocrit strongly influence shear stress, that is the frictional force exerted by the flowing blood on the endothelial surface. Shear stress, in physiological range, is known to be crucial for normal vascular functioning, which includes the regulation of vascular tone and the synthesis of anti-atherogenic substances. Low shear stress, as well as high shear stress, reduces the protective action mediated by endothelium and influences plaque formation (see Cunningham and Gotlieb[1]). In small-vessel districts, shear stress is as well important regulating the synthesis of nitric oxide and controlling vessel tone and angiogenesis in order to adapt the structure to the function.[20 21] It is likely that shear stress also influences the function and the activity of retinal microvessels, acting on endothelial cells and pericytes, which are important regulators of vascular remodelling and tone. The dysfunction and the loss of these cells can promote the development or worsening of DR.[22] Our findings are consistent with the hypothesis that low haematocrit and WBV, through a reduction in shear stress, foster the development of DR.

These results are in line with those reported in a large prospective study, the ETDRS, aimed to identify the factors responsible for the progression of DR to high-risk proliferative retinopathy. The authors have found decreased Hct and Hb levels associated with increased risk of retinopathy progression. Interestingly, this study has shown an increased risk of disease progression already for Hct values <45 in men and <40 in women.[23]

Little attention has been given to anaemia as risk factor for the development or worsening of DR. Small studies have previously demonstrated that the development of severe anaemia causes the progression of retinopathy to florid proliferative stage, and the treatment of anaemia with erythropoietin improves visual acuity and non-proliferative retinopathy.[24 25] In a more recent cross-sectional study of subjects attending a diabetic clinic, DR was found to be twice the level among patients with mild anaemia (Hb<12 g/dl) with a prevalence of severe retinopathy significantly higher compared to subjects with DR and Hb>12 g/dl.[26] These results suggest that low Hb levels, even within normal range, might contribute to the development and progression of DR. There is no clear evidence that anaemia per se causes a direct vascular injury; however, there is some evidence supporting that anaemia may modulate the activity of pathways that lead to progressive organ damage. For instance, hypoxia influences a wide range of mitogenic and fibrogenic effects and modifies the expression of genes involved in angiogenesis and capillary permeability, vasomotor response, glycolysis, matrix metabolism and cell survival. The activity of these pathways can lead to specific diabetic complications.

Possible mechanisms contributing to the onset of anaemia in type 2 diabetes include reduced red cell survival and inhibitory effect of cytokines on erythrocyte stem cells.[27 28] The role of some inflammatory molecules, like fibrinogen and C reactive protein, on development of DR has been clearly reported in several papers, and our data about fibrinogen are confirmatory of this association.[29 30]

The present study has some limitations. First, WBV has not been directly measured but has been calculated. However, others have previously demonstrated a very high correlation between measured and calculated viscosity.[11] Second, the present is an observational study that cannot be used to define a cause–effect relationship but can anyway give important information on the association between DR and clinical and biochemical profile of diabetic subjects. Third, the majority of the diabetic subjects investigated had hypertension and hyperlipidaemia, whereas none of the controls did. Therefore, differences between diabetic and control group might be due to the presence of these vascular risk factors. However, this difference is unlikely to lead to bias in the comparison of the three levels of retinopathy. Finally, based on the findings of our study, an important clinical question arises: should we therapeutically raise the oxygen-carrying capacity of blood by treating diabetic patients with anaemia and low haematocrit in order to prevent possible ocular complications? Unfortunately, it is currently not possible to give an answer to this question, and probably, double-blind randomised clinical trials are needed to clarify this point.

In conclusion, the present study demonstrates a clear inverse association among WBV, Hb, Hct and DR, both proliferative and non-proliferative, in subjects with type 2 diabetes and without overt nephropathy, supporting the hypothesis that haemorheological variables play an important role in the development of DR. While further studies are needed to clarify through which mechanisms WBV influences DR, the finding that WBV, Hb and Hct are reduced in subjects with DR should drive the accomplishment of intervention studies to verify whether the correction of these alterations can represent a valid therapeutic approach to prevent DR beyond the strict control of glycaemia.

Competing interests None.

Ethics approval This study was conducted with the approval of the Local Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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Br J Ophthalmol 2011 95: 94-98 originally published online June 8, 2010
doi: 10.1136/bjo.2009.172601