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**Association between low Whole Blood Viscosity, Hematocrit, Hemoglobin and Diabetic Retinopathy in subjects with type 2 diabetes**

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## **Abstract**

**Objectives:** Hemorheological variables influence endothelial function through the release of several factors. Clinical studies have described an association between blood viscosity, hematocrit, hemoglobin and macro-angiopathy. Few data are reported about the association between hemorheological variables and micro-angiopathy. Aim of the present study was to evaluate the association between these variables and retinopathy in subjects with type 2 diabetes.

**Methods:** We recruited 111 males, 79 postmenopausal females, and 95 healthy age and sex-matched controls. Hematocrit and hemoglobin were measured by standard methods. Blood viscosity was calculated according to the formula  $[0.12 \times \text{hematocrit}] + [0.17 \times (\text{plasma proteins} - 2.07)]$ . Subjects were grouped according to the presence or absence of DR, while the severity of retinopathy was classified according to the ETDRS scale.

**Results:** Hemoglobin, hematocrit 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 between viscosity, hematocrit, hemoglobin, and retinopathy ( $p < 0.01$ ).

**Conclusion:** Our results demonstrate the association between low viscosity, hemoglobin, hematocrit, and diabetic retinopathy. The mechanisms responsible for this association can be hypothesized. 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.

**Key words:** Whole blood viscosity; hematocrit; hemoglobin; type 2 diabetes; diabetic retinopathy; endothelial function

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**Competing Interest**

None to declare

## **Introduction**

Blood flow velocity and pattern influence vessel tone, structure and function through interaction of blood with the endothelial surface. The characteristics of the blood, i.e. viscosity, hemoglobin concentration and hematocrit 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 hematocrit, and anemia 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 vessels 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 more than 60% of type 2 diabetic subjects have some degree of DR [6]. Large prospective intervention studies have demonstrated that optimal glycemic 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, hemorheological 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, hematocrit, and hemoglobin 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 two months. One hundred and ninety-nine diabetic subjects, consented to participate to the study. Males and post-menopause females were included. Menopause was defined as absence of menses for 12 consecutive months. Pre-menopausal females, as well as individuals with elevated urine albumin excretion, measured in 12-hour nocturnal urine, were excluded because of the possible influence of menstruation and impaired renal function on hemorheological parameters. A control group of 95 age and gender 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 hours fasting. Serum glucose was assessed by a modified hexokinase/glucose-6-phosphate dehydrogenase procedure. Cholesterol and triglycerides were measured by enzymatic methods, HDL-cholesterol was measured after dextran-magnesium precipitation, and LDL was calculated according to Friedewald formula. Fibrinogen measurement was performed by radial immunodiffusion (NOR-Partigen, Behring, Marburg, Germany). The hematocrit level was calculated from the measurement of red blood cells, hemoglobin (Hb) by high-pressure liquid chromatography (HPLC) and plasma proteins by the biuret method. Glycated hemoglobin (HbA<sub>1c</sub>) was estimated by HPLC. Renal function was evaluated by the estimation of glomerular filtration rate (GFR) using the modified Cockcroft and

Gault formula [9]. WBV was estimated according to a validated formula that takes in account hematocrit and plasma protein [10]:

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

where hematocrit 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 hematocrit (32-53 %) and plasma protein (5.4-9.5 g/dl) [11].

Cardiovascular risk factors, i.e. hypertension, hyperlipidemia and obesity were defined as follows: hypertension as SBP and/or DBP  $\geq 130/85$  mmHg or use of antihypertensive agents; hyperlipidemia as total cholesterol and/or triglycerides  $>5.1$  mmol/L and/or  $>2.2$  mmol/L, respectively or use of hypolipidemic drugs. Smokers included subjects that smoked cigarettes or cigars daily. Subjects were defined as having cardiovascular disease (MI, 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, hemorrhages, hard exudates, area of revascularization, fibrous proliferation and and/or laser scars in the more severely affected eye. The ETDRS (Early Treatment Diabetic Retinopathy Study) 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  $\geq 47$ ) [12].

*Statistical analysis:* Values are shown as mean  $\pm$  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 ANOVA-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<sub>1c</sub>, 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  $\pm$  SD 59.9 $\pm$ 9.0). Among these 111 were males (58%) and 79 females (42%), and the mean disease duration was 11.5 years. One hundred forty were being treated with oral antidiabetic drugs (sulfonylureas and/or insulin sensitizer), 32 were treated with insulin therapy and 18 were using both. Females had higher BMI (32.1 $\pm$ 4.3 vs 30.2 $\pm$ 4.4 kg/m<sup>2</sup>, p<0.01), total cholesterol (5.1 $\pm$ 0.9 vs 4.7 $\pm$ 1.1 mmol/L, p<0.01), HDL-cholesterol (1.4 $\pm$ 0.4 vs 1.2 $\pm$ 0.3 mmol/L, p<0.01) and longer disease duration (13.4 $\pm$ 9.5 vs 10.1 $\pm$ 8.0 years) compared to males. As far as cardiovascular risk factors is concerned, the prevalence of hypertension and hyperlipidemia was respectively 55 and 66 % in all diabetic subjects, without any significant difference between males and females. 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 males and females.

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 ischemic event were on treatment with antiplatelet agents. Eighty-eight % of all diabetic subjects were being treated with statins.

The 95 control subjects had lower fasting glycemia, lipids, blood pressure and BMI (Table 1). Mean age of the control subjects was 57.5 $\pm$ 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 gender. In both females and males 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 females had significantly lower hemorheological values compared to both control female and diabetic male subjects.

*Associations Between DR, Gender and Hematological Values:*

In all diabetic subjects the prevalence of any degree of DR was 39% and the prevalence was higher in females compared with males (52 vs 30 %,  $p < 0.05$ ). Females and males with DR both had a significantly higher fasting glucose and HbA<sub>1c</sub>, compared with females and males without DR. Disease duration was longer only in females with DR. In both sexes Hb, Hct, and WBV were significantly lower in subjects with DR compared to subjects without DR (Table 2).

*Associations Between Severity of DR, Gender, and Hematological Values:*

Hematological values were compared between the three DR severity groups for each gender. In both sexes, Hb, Hct, and WBV significantly decreased with increasing severity of DR. Fibrinogen increased only in females while it was comparable in the three male groups (Tab 3). Clinical and biochemical variables were not different among males, while among females fasting glycemia ( $7.7 \pm 2.3$ ,  $10.3 \pm 2.9$ ,  $11.8 \pm 2.5$  mmol/L;  $p < 0.01$ ), HbA<sub>1c</sub> ( $6.5 \pm 1.2$ ,  $7.9 \pm 1.5$ ,  $8.3 \pm 1.5$  %;  $p < 0.01$ ), and disease duration ( $7.6 \pm 6.0$ ,  $17.5 \pm 9.1$ ,  $18.9 \pm 2.9$  years;  $p < 0.01$ ) progressively increased with increasing DR severity.

*Association between DR and hemorheological variables* To evaluate the independent association between 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 glycemia, HbA<sub>1c</sub>, fibrinogen, disease duration, GFR, cardiovascular risk factors, different antidiabetic treatment, and previous cardiovascular events. As shown in Table 4 all 3 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 hemorheological 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 potentially dangerous since it affects peripheral vascular tone, increases blood pressure and causes disturbance of coagulation [17]. However, there is also evidence that low hematocrit influences negatively the prognosis of subjects with cardiovascular disease [18]. A recent published paper of Salazar-Vasquez might explain these conflicting results. He found an U-shaped relationship between Hct and blood pressure, suggesting that both lower and higher Hct values associate with higher mean arterial pressure [19].

Blood viscosity and hematocrit 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 antiatherogenic substances. Low shear stress, as well as high shear stress, reduces the protective action mediated by endothelium and influences plaque formation (see references nr. 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 remodeling 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 hematocrit 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 lower than 45 in males and 40 in females [23].

Little attention has been given to anemia as risk factor for the development or worsening of DR. Small studies have previously demonstrated that the development of severe anemia causes the progression of retinopathy to florid proliferative stage, and the treatment of anemia with erythropoietin improves visual acuity and non-proliferative retinopathy [24,25]. In a more recent cross sectional study of subjects attending a diabetic clinic, it has been found DR to be twice among patients with mild anemia (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 anemia per se causes a direct vascular injury, however there is some evidence supporting that anemia 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 the specific diabetic complications.

Possible mechanisms contributing to the onset of anemia 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].

The present study has some limitations. First, WBV has not been directly measured but calculated. However, others have previously demonstrated a very high correlation between measured and calculated viscosity [11]. Second, the present is an observational study that can not 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 hyperlipidemia, 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 anemia and low hematocrit in order to prevent possible ocular complications? Unfortunately, it is currently not possible to give an answer to this question and probably double-blind randomized clinical trials are needed to clarify this point.

In conclusion the present study demonstrates a clear inverse association between WBV, Hb, Hct, and DR, both proliferative and non-proliferative, in subjects with type 2 diabetes and without overt nephropathy, supporting the hypothesis that hemorheological 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 glycemia.

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Table 1

Hemorheological variables in controls and subjects with diabetes

<i>Hemorheological Variables</i>	<i>Control Subjects</i>			<i>Subjects with diabetes</i>		
	All	Males	Females	All	Males	Females
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&lt;0.001 vs Control

† p&lt;0.005 vs Control females

‡ p &lt;0.0001 vs Males with diabetes



Table 2

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

<i>Variables</i>	<i>Females</i>		<i>Males</i>	
	<i>With DR</i>	<i>Without DR</i>	<i>With DR</i>	<i>Without DR</i>
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 <sup>2</sup> )	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 <sub>1c</sub> (%)	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
<i>Hemorheological Variables</i>				
Fibrinogen (mg/dl)	366.0±77.8	356.8±56.3	361.7±84.4	339.2±62.3
Hemoglobin (g/L)	130±10§	135±10	139±10*	149±11
Hematocrit (%)	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

Table 3

Hemorheological variables of subjects with diabetic retinopathy DR divided according to sex and severity of DR

<i>Hemorheological Variables</i>	<i>Group 1</i>	<i>Group 2</i>	<i>Group 3</i>
Males	(n=78)	(n=18)	(n=15)
Fibrinogen (mg/dl)	339.2±62.4	344.1±82.6	381.8±97.6
Hemoglobin (g/L)	149±11†	141±10	137±08
Hematocrit (%)	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
<i>Hemorheological Variables</i>	<i>Group 1</i>	<i>Group 2</i>	<i>Group 3</i>
Females	(n=38)	(n=30)	(n=11)
Fibrinogen (mg/dl)	356.8±56.2*	349.9±78.6*	417.9±49.0
Hemoglobin (g/L)	134±10†	130±10	129±10
Hematocrit (%)	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 vs 3; † p<0.001 vs 2, 3; ‡ p<0.01 vs 3)

Table 4

Logistic regression analysis between diabetic retinopathy (DR: 0=absence; 1=presence) and Hemoglobin, Wall Blood Viscosity, and Hematocrit, evaluated separately after adjustment age, sex, HbA<sub>1c</sub>, fibrinogen, disease duration, GFR, cardiovascular risk factors, different antidiabetic treatment, and previous cardiovascular events

<i>Independent Variable</i>	<i>Odds Ratio</i>	<i>Confidence Interval</i>		<i>p</i>
		<i>95% lower</i>	<i>95% Upper</i>	
<i>Wall Blood Viscosity</i>	0.13	0.04	0.46	0.002
<i>Hematocrit</i>	0.78	0.67	0.91	0.002
<i>Hemoglobin</i>	0.64	0.44	0.94	0.02