

Blood viscosity in subjects with normoglycemia and prediabetes

Running title: Blood viscosity and blood glucose

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Abstract

Objective: Blood Viscosity (BV) is higher in diabetic patients, and might represent a risk factor for the development of insulin resistance and type 2 diabetes. However, data in subjects with normal glucose or prediabetes are missing. In the present study we evaluated the relationship between BV and blood glucose in subjects with normal glucose or prediabetes.

Research Design and Methods: Enrolled subjects were divided in three groups according to blood glucose: Group A (n=74): blood glucose < 90 mg/dl; Group B (n=96): blood glucose ranging 90-99 mg/dl; Group C (n=94): blood glucose ranging 100-125 mg/dl. BV was measured at 37° C with a cone-plate viscometer at shear rates ranging 225–22.5 s⁻¹.

Results: Blood pressure, blood lipids, fibrinogen and plasma viscosity were similar in the three groups. BMI and waist were significantly increased in Group C. Hematocrit (p<0.05) and BV (p between 0.01 and 0.001) were significantly higher in Group B and C, compared to Group A. Blood glucose was significantly and inversely correlated with HDL cholesterol and directly with BMI, waist, hematocrit (r=0.134), and BV (from 225 sec⁻¹ to 22.5 sec⁻¹, r ranging from 0.162 to 0.131). BV at shear rate 225 sec⁻¹ resulted independently associated with blood glucose.

Conclusions: The present study shows a direct relationship between BV and blood glucose in non-diabetic subjects. It also suggests that, even within glucose values considered completely normal, individuals with higher blood sugar levels have increased BV comparable to that observed in subjects with prediabetes.

Blood viscosity is the force which counteracts the free sliding of the blood layers within the circulation, and depends on the internal cohesion between the molecules and the cells. Abnormally high blood viscosity can have several negative effects: the heart is overloaded to pump blood in the vascular bed and the blood itself, more viscous, can damage the vessel wall. Furthermore, according to Poiseuille's law (1), blood viscosity is inversely related to flow and might therefore reduce the delivery of insulin and glucose to peripheral tissues, leading to insulin resistance and/or diabetes (2-5).

It is generally accepted that blood viscosity is increased in diabetic patients (6-8). Although the reasons of this alteration are still under investigation, it is believed that the increase in osmolarity causes increased capillary permeability and, consequently, increased hematocrit and viscosity (9). It has also been suggested that the osmotic diuresis, consequence of hyperglycemia, could contribute to reduce plasma volume and increase hematocrit (10).

Cross-sectional studies have also supported a link between blood viscosity, hematocrit and insulin resistance (11-17). Recently, a large prospective study has demonstrated that blood viscosity and hematocrit are risk factors for type 2 diabetes mellitus. Subjects in the highest quartile of blood viscosity were over 60% more likely to develop diabetes than their counterparts in the lowest quartile (18). This finding confirms previous observations obtained in smaller and/or selected populations, in which the association between hemoglobin or hematocrit with occurrence of type 2 diabetes was investigated (19-22).

These observations suggest that the elevation in blood viscosity may be very early, well before the onset of diabetes, but definite data in subjects with normal glucose or prediabetes are missing. In the present study we evaluated the relationship between blood viscosity and blood glucose in subjects with normal glucose or prediabetes, in order to verify if alterations in viscosity are appreciable in these subjects and to which blood glucose concentration they appear.

Research Design and Methods

Subjects

Subjects were enrolled among free-living participants in a cardiovascular disease prevention program, between February 2011 and December 2012 (23,24). In order to reduce the influence of confounding factors, cigarette smoking, diabetes mellitus, plasma triglycerides above 400 mg/dl, female before menopause, and drug use (chronic treatment and any drug in the week before blood withdrawal) were exclusion criteria for the present analysis.

According to blood glucose levels, participants were divided in three groups: Group A: blood glucose < 90 mg/dl; Group B: blood glucose between 90 and 99 mg/dl; Group C: blood glucose between 100 and 125 mg/dl.

The Ethics Committee of the Azienda Policlinico Mater Domini approved the study. All recruited subjects gave their informed consent.

Methods

All subjects included in the study underwent a complete clinical examination and blood withdrawal. Standing height without shoes was measured to the nearest 0.5 cm. Weight was measured to the nearest 0.1 kg in ordinary street clothes. Body Mass Index (BMI) was computed as weight (in kg) divided by height (in m²). Waist circumference was measured midway between the lower rib margin and the iliac crest. Systolic (SBP) and diastolic (DBP) blood pressure was measured, on the right arm, after the participant had been resting for at least 5 min, with a standardized sphygmomanometer. Cigarette smoking, and ongoing drug therapies were investigated by questionnaire.

Venous blood for routine and viscosity analyses was collected in the morning before the breakfast after overnight fasting, in order to avoid the influence of post-prandial lipid increase on haemorheological parameters (25).

Attention was paid to avoid venous stasis and the haemostatic loop, when used, was immediately removed after cannulation of the vein. Blood glucose and lipids were measured by routine methods. Subjects with blood glucose lower than 100 mg/dl were classified as non diabetic, those with values between 100 and 125 mg/dl were classified as prediabetic, and those with blood sugar above 125 mg/dl were classified as diabetic and excluded from the present analysis.

Blood and plasma viscosity were measured within 2 hours from blood withdrawal; the blood specimen was added with heparin (35 I.U./mL). Viscosity measurement was performed at 37° C with a cone-plate viscometer (Wells-Brookfield DV-III, Stoughton, U.S.A.) equipped with a cp-40 spindle. Blood viscosity was recorded at shear rates ranging 225 – 22.5 s⁻¹. For plasma viscosity the average of measurements at shear rates of 225 and 90 s⁻¹ was calculated. The coefficient of variation for blood and plasma viscosity was below 3%. Micro-haematocrit was measured without correction for plasma trapping. The coefficient of variation for micro-haematocrit was ~1%.

Erythrocyte rigidity was evaluated according to Dintenfass's formula: $Tk = (\mu r^{0.4} - 1) \cdot (\mu r^{0.4} \cdot h)^{-1}$, where h is hematocrit and μr is the relative blood viscosity (blood viscosity / plasma viscosity).

Statistical analysis

All statistical analyses were performed by SPSS 17.0 for Windows. All studied variables, but triglycerides, had normal distribution. Triglycerides were log transformed before analyses. One-way ANOVA and LSD post-hoc test were used to test the difference in studied variables between groups with different blood glucose concentration. Pearson's correlation coefficient was used to test the correlation between continuous variables. Multiple linear regression analysis was performed to evaluate the independent association of clinical and biochemical variables with blood glucose.

Results

The clinical, biochemical and haemorheological characteristics of the 264 participants are shown in Table 1. Seventy-four subjects had blood glucose lower than 90 mg/dl (Group A), 96 subjects blood glucose ranging 90 - 99 mg/dl (Group B) and 94 had blood glucose ranging 100 - 125 mg/dl (Group C). Blood pressure, blood lipids, fibrinogen and plasma viscosity were similar in the three groups. BMI and waist were significantly increased in subjects with prediabetes (Group C) compared to the other two groups ($p < 0.05$). Subjects with high normal blood glucose were younger ($p < 0.05$) compared to the other two groups. Hematocrit ($p < 0.05$) and blood viscosity (p between 0.01 and 0.001) were significantly higher in subjects with prediabetes and in those with blood glucose ranging 90 - 99 mg/dl, compared to subjects with blood glucose less than 90 mg/dl. Erythrocyte rigidity was similar in the three groups.

In simple correlation analysis in the whole population, blood glucose was significantly and inversely correlated with HDL cholesterol ($r = -0.123$) and directly with BMI ($r = 0.142$), waist ($r = 0.180$), hematocrit ($r = 0.134$), and blood viscosity (from shear rate 225 sec^{-1} to shear rate 22.5 sec^{-1} , r ranging from 0.162 to 0.131). No correlation was found with age, total cholesterol, triglycerides, plasma viscosity, fibrinogen, and erythrocyte rigidity. All the above variables significantly correlated with blood glucose, and age significantly different between groups at ANOVA, were tested for independent association with blood glucose in stepwise multiple regression analyses (age, HDL cholesterol, BMI, waist, and hematocrit were constantly in the model, while the viscosities at different shear rates were introduced one at a time). Only blood viscosity at shear rate 225 sec^{-1} resulted independently associated with blood glucose, while blood viscosity at lower shear rates was not (Table 2).

Two additional stepwise multiple regression analyses were performed to identify the variables independently associated to the viscosity at high shear rate (225 sec^{-1}) and low shear rate (22.5 sec^{-1}). All variables significantly correlated to these two viscosities were included as independent variables (for blood viscosity at shear rate 225 sec^{-1} (correlation coefficients): age (-0.178), total cholesterol (0.258), triglycerides (0.185), HDL-cholesterol (-0.202), blood glucose (0.162), hematocrit (0.440), plasma viscosity (0.438) and Tk (0.294); for blood viscosity at shear rate 22.5 sec^{-1} : age (-0.148), total cholesterol (0.219), hematocrit (0.207), plasma viscosity (0.355) and Tk (0.377)). The results indicate that hematocrit, plasma viscosity and erythrocyte deformability are the only variables independently associated to the viscosity in these subjects.

Discussion

The present study shows, for the first time, a direct relationship between blood viscosity and blood glucose in non-diabetic subjects. It also suggests that, even within glucose values considered completely normal, individuals with higher blood sugar levels have increases in blood viscosity comparable to those observed in subjects with prediabetes.

Many studies have so far investigated blood viscosity in patients with diabetes mellitus (26). Usually, however, these studies were performed in small groups of patients, often only at few shear rates and sometimes did not demonstrate any difference between diabetic and control subjects (27,28). Some findings have suggested a role for the increase in blood viscosity as pathogenetic factor for the development of microvascular complications (29,30). Important increases in blood viscosity have been reported in diabetic retinopathy and it has been hypothesized that these changes lead to a prolonged reduction in the supply of oxygen and nutrients to the capillaries, causing the development of angiopathy (31,32). Once the retinopathy has developed, its progression may be favored by a reduction in blood viscosity and hemoglobin (33). Overall, changes in viscosity in diabetic patients are accepted as common and as a result of the disease. However, the relationship between blood glucose, diabetes mellitus and viscosity may be much more complex. First, it is useful to underline that the blood is a non-Newtonian fluid, in that its viscosity varies with the flow velocity. Specifically, when the flow velocity is high, the cellular component of blood (red cells, white cells and platelets) is concentrated at the center of the vessel, while the plasma flows in the periphery. In conditions of low flow velocities, the cellular component occupies the entire column of flowing blood, causing an increase in viscosity. Blood viscosity at high shear rates ($\geq 90 \text{ sec}^{-1}$, corresponding to in vivo systolic flow condition) is strongly influenced by erythrocyte deformability, while at lower shear rates (representing in vivo diastolic flow condition) red cell aggregation plays the most important role (34). The deformability and the aggregation of erythrocytes are, in turn, driven by different characteristics of the erythrocytes and the plasma. Furthermore, factors such as cigarette smoking, hyperlipidemia, and hyperfibrinogenemia, which are very frequent in patients with diabetes mellitus, may alter blood viscosity. In light of this it is evident that further studies are needed to clarify the relationship between diabetes mellitus and blood viscosity.

The importance of blood viscosity was recently highlighted following the observation that it increases the risk of developing diabetes in normoglycemic subjects participating in the ARIC Study (18). In that study, the authors have not directly measured blood viscosity but used two validated formulas, one for the shear rate 208 sec^{-1} and the other for the shear rate 0.5 sec^{-1} (35). The findings of our study are in line with the conclusions of the ARIC Study and further demonstrate that the blood viscosity of the subjects with prediabetes or high normal blood glucose is significantly higher compared to that of subjects with low normal blood glucose, at all considered shear rates. This supports the hypothesis that the alterations are very early and present in any flow condition. Furthermore, these findings are also in line with the results of a previous study which showed that the blood viscosity in patients with prediabetes was comparable to that of diabetic subjects with complications (36), and significantly higher than that of healthy control subjects. If increased viscosity somehow alters the supply of oxygen and nutrients to the tissues, then the observed changes may contribute to the development of peripheral insulin resistance (by reduced glucose utilization in the muscle) and, in the long term, diabetes mellitus. It cannot be excluded that

a slight increase in blood glucose, secondary to other conditions of insulin resistance as aging, inflammation, physical inactivity, etc., can cause increased blood viscosity, thereby creating a vicious circle. Clearly, this requires further study for a more exact definition. The observation that the change in viscosity is already evident at blood glucose values above 90 mg/dl seems very important. This allows understanding why in some studies no difference was observed between diabetics and controls (27,28). Probably the controls had high normal blood sugar levels or were prediabetic. In a previous study, conducted in a small population of diabetic patients and a control group, we found no difference in blood viscosity measured at shear rate of 225 sec^{-1} (37). The controls, however, had a mean blood glucose of more than 95 mg/dl, and although non-diabetics, they probably already had increased blood viscosity. Furthermore, the value of 90 mg/dl would suggest a greater attention in subjects that exceed this threshold in terms of correction of the conditions that can cause increased viscosity.

In this regard, it is intriguing to try to identify the factors which influence the viscosity. Changes in osmolality or osmotic diuresis have been suggested as factors able to modify blood viscosity (9,10). While these factors may play a role at very high blood glucose concentrations, it seems unlikely they may affect blood viscosity within normal or slightly increased blood glucose values. Among the variables considered in our study, hematocrit, plasma viscosity and erythrocyte deformability are the factors independently associated with high and low shear rates blood viscosity, confirming recently published data (38). The gradual increase in plasma viscosity, hematocrit, and erythrocyte rigidity, even within levels considered completely normal, leads to increased blood viscosity. It is possible to hypothesize that gradually increasing concentrations of blood glucose can directly affect the red blood cells, possibly resulting in impaired deformability and aggregation. If confirmed in larger and prospective studies, these results could indicate the need for very early intervention on these factors in an attempt to prevent the development of diabetes mellitus.

The plasma viscosity was slightly higher in Groups B and C compared to Group A, but only close to statistical significance. The plasma viscosity is strongly influenced by the levels of fibrinogen and other plasma proteins, and to a lesser extent by obesity and blood lipids (38,39). In the present study, subjects with high normal blood glucose or prediabetes have higher values of BMI, and slightly of blood lipids, and this may explain why plasma viscosity tends to higher values, thus contributing to the increase in whole blood viscosity.

The present study has, in our opinion, some limitations. Insulin resistance has not been evaluated, since insulin was not measured. Similarly, data on inflammation and plasma proteins are lacking, although the careful selection of the subjects, with the exclusion of those taking drugs, may have limited the impact of these factors. The subjects were classified on the basis of a single fasting glucose, and HbA1c was not available in this population; therefore it is possible that a few subjects were classified inappropriately. We believe that this potential bias might have affected only a few subjects and therefore does not invalidate the results. Finally, the erythrocyte deformability was calculated, and not directly measured. Therefore, the data on erythrocyte deformability should be interpreted with caution.

Conclusions

In conclusion, the main finding of the study is that blood viscosity significantly increases already at high-normal blood sugar levels, independently of other common determinants of hemorheology. Intervention studies are needed to verify whether changes in blood viscosity are able to influence the development of type 2 diabetes.

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Author contributions:

Concetta Irace: Researched data and wrote the manuscript

Claudio Carallo: Researched data and wrote the manuscript

Faustina Scavelli: Researched data

Maria Serena De Franceschi: Contributed to the discussion and reviewed the manuscript

Teresa Esposito: Researched data

Agostino Gnasso: Researched data and wrote the manuscript

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Table 1. Clinical, biochemical and rheological characteristics of subjects (Group A: blood glucose < 90 mg/dl; Group B: blood glucose 90-99 mg/dl; Group C: blood glucose 100-125 mg/dl).

	Group A	Group B	Group C	p≤
Number	74	96	94	
Age (yrs)	56.2±12.4	52.8±10.8	57.2±10.0	0.02
Cholesterol (mg/dl)	209±41	220±40	213±40	0.23
Triglycerides (mg/dl)	116±51	132±64	141±74	0.09
HDL-cholesterol (mg/dl)	53±17	51±15	49±12	0.27
Glucose (mg/dl)	85±5	95±3	108±7	---
BMI (kg/m ²)	28.3±4.1	28.0±4.5	29.9±4.9	0.01
Waist (cm)	91±10	91±13	96±10	0.01
SBP (mmHg)	139±22	136±19	139±24	0.60
DBP (mmHg)	86±10	85±10	87±10	0.59
Hematocrit (%)	42.6±3.9	44.0±3.5	43.8±3.4	0.05
Blood viscosity ₂₂₅ (cP)	4.58±0.60	4.98±0.73	4.90±0.72	0.01
Blood Viscosity ₉₀ (cP)	5.38±0.76	5.95±1.07	5.79±0.99	0.01
Blood Viscosity ₄₅ (cP)	6.08±1.01	6.94±1.82	6.78±1.58	0.01
Blood Viscosity _{22.5} (cP)	7.40±1.35	8.61±2.87	8.41±2.51	0.01
Plasma Viscosity (cP)	1.48±0.15	1.54±0.16	1.55±0.16	0.06
Fibrinogen (mg/dl)	323±86	337±85	318±82	0.33
Tk	0.85±0.06	0.85±0.08	0.83±0.07	0.18

Abbreviations: HDL-cholesterol: High Density Lipoprotein-Cholesterol; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; Tk: Erythrocyte rigidity

Table 2. Stepwise multiple regression analysis.

Dependent variable: Blood glucose			
	β coefficient	t	p
Blood viscosity 225 sec ⁻¹	2.421	2.179	0.031
<i>Variables not in the model</i>			
Age	0.144	1.870	0.063
HDL-Cholesterol	-0.109	-1.386	0.168
BMI	0.055	0.718	0.474
Waist	0.096	1.256	0.211
Hematocrit	0.061	0.711	0.478

Abbreviations: HDL: High Density Lipoprotein-Cholesterol; BMI: Body Mass Index