

# Type 2 diabetics with higher plasma viscosity exhibit a higher blood pressure

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**Abstract.** Among hemorheologic parameters, plasma viscosity is one of the most studied in epidemiology, so that it has emerged as an independent risk factor. In diabetes, plasma viscosity is frequently elevated. For this reason we tried to define characteristics of non-insulin dependent diabetics with high plasma viscosity ( $>1.45$  mPa.s) and whether they were more insulin resistant and/or exhibited other hemorheologic disturbances. 12 subjects (age  $56.1 \pm 11.7$ ; BMI  $28.6 \pm 4.8$ ) were thus found to have a value of plasma viscosity  $>1.45$  mPa.s. They were compared to 20 age and BMI-matched NIDDMs. Patients have similar insulin sensitivity, HbA1c, and fibrinogen. RBC aggregation, rigidity and hematocrit were not significantly different. Whole blood viscosity at high shear rate was slightly higher ( $p = 0.05$ ). When corrected for hematocrit whole blood viscosity is no longer different. However, hematocrit was not lower in subjects with  $hpl >1.45$ . By contrast blood pressure was markedly higher (systolic:  $177.5 \pm 2.5$  mmHg vs  $140 \pm 8$  mmHg,  $p < 10^{-8}$ ; diastolic  $110 \pm 14$  vs  $83 \pm 9$  mmHg,  $p < 10^{-9}$ ; mean  $132 \pm 18$  mmHg vs  $102 \pm 7$  mmHg  $p < 10^{-9}$ ). Therefore, in NIDDM, higher plasma viscosity, regardless insulin resistance and adiposity, is strongly related to blood pressure.

**Keywords:** Blood viscosity, plasma viscosity, hemorheology, erythrocyte deformability, erythrocyte aggregability, insulin sensitivity, insulin resistance, minimal model, arterial hypertension

## 1. Introduction

Among hemorheologic parameters, plasma viscosity is one of the most studied in epidemiology, so that it has emerged as an independent risk factor [1,2]. On the other hand, in type 2 (non-insulin dependent) diabetes, plasma viscosity is frequently elevated [3,4], due to alterations in the plasma protein content [4,5]. In this disease, there is a close statistical relationship between values of plasma viscosity and the development of vascular complications [6,7].

However, it remains difficult to extrapolate from such studies clear conclusions on the pathophysiological involvement of plasma viscosity in hemodynamic disturbances and in vascular complications, due to the fact that plasma viscosity is a complex integrated reflect of lipoprotein and inflammatory status [4,5], which are by their own “classical” risk factors for vascular complications [8].

Even more interestingly, in patients suffering from the insulin resistance syndrome, plasma viscosity was found to be an independent statistical marker of insulin resistance [9].

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The aim of this study was thus to delineate the metabolic and clinical profile of type 2 diabetics whose plasma viscosity is situated in the upper range of the distribution, with special reference to their insulin sensitivity.

## 2. Subjects and methods

### 2.1. Study subjects

According to our previous works, 1.45 mPa.s is with our technique the lower boundary of the highest quartile of plasma viscosity, and may be thus used to define high plasma viscosity [9]. We selected in our database of outpatients explored for type 2 diabetes and in whom both hemorheological parameters and insulin sensitivity had been assessed a group of 12 subjects (6 male and 6 female) who were found to have a value of plasma viscosity  $>1.45$  mPa.s. These patients were compared to an other group of twenty age and body mass index (BMI)-matched NIDDMs. Arterial pressure was measured according to the usual guidelines with a sphygmomanometer and mean arterial pressure was evaluated as usual with the formula mean arterial pressure = diastolic arterial pressure +  $0.33 \times (P_{\text{systolic}} - P_{\text{diastolic}})$ .

Subjects' clinical characteristics are shown in Table 1.

### 2.2. Hemorheological measurements

Blood samples for hemorheological measurements (7 ml) were drawn with potassium EDTA as the anticoagulant in a vacuum tube (Vacutainer). Viscometric measurements were done at high shear rate ( $1000 \text{ s}^{-1}$ ) with a falling ball viscometer (MT 90 Mediatest, F-86280 Saint Benoit) [10]. The coefficient of variation of this method ranged between 0.6 and 0.8% [10]. With this device we measured apparent viscosity of whole blood at native hematocrit, plasma viscosity and blood viscosity at corrected hematocrit (0.45) according to the equation of Quemada [11]. Dintenfass' 'Tk' index of erythrocyte rigidity was calculated [12]. RBC aggregation was assessed with the Myrenne aggregometer [13] which gives two indices of RBC aggregation: 'M' (aggregation during stasis after shearing at  $600 \text{ s}^{-1}$ ) and 'M1' (facilitated aggregation at low shear rate after shearing at  $600 \text{ s}^{-1}$ ).

### 2.3. Frequently sampled intravenous glucose tolerance test (FSIVGTT)

A cannula was placed in the cephalic vein at the level of the cubital fossa for blood sampling at various times, while glucose was administered via the contralateral cephalic vein. Glucose ( $0.5 \text{ g.kg}^{-1}$ , solution at 30%) was slowly injected over 3 min. Insulin ( $0.02 \text{ units/kg}^{-1}$  body weight, i.e. 1–2 units)

Table 1  
General characteristics of study subjects (mean  $\pm$  SEM)

	$\mu\text{pl} < 1.45$ ( $n = 20$ )	$\mu\text{pl} > 1.45$ ( $n = 12$ )
Age (years)	$56.1 \pm 11.7$	$55.6 \pm 7.5$
Weight (kg)	$81.6 \pm 15.3$	$82.5 \pm 9.2$
Height (m)	$1.69 \pm 0.09$	$1.64 \pm 0.08$
BMI ( $\text{kg/m}^2$ )	$28.6 \pm 4.8$	$31.1 \pm 4.7$
Sex ratio (m/f)	5/15	6/6

Abbreviations: BMI: body mass index (= weight/height<sup>2</sup>).

was injected into the vein contralateral to the one used for sampling, immediately after 19 min. Blood samples were drawn twice before the glucose bolus and at 1, 3, 4, 6, 8, 10, 15, 19, 20, 22, 30, 41, 70, 90 and 180 min following glucose injection.

#### 2.4. Glucose disposal coefficient ( $K_g$ )

The least square slope of the log of the absolute glucose concentration, between 4 and 19 minutes after the glucose bolus, was used as an index of glucose tolerance,  $K_{g4-19}$ . This  $K_g$  value describes glucose disposal by tissue and depends on three factors: insulin release, insulin sensitivity, and glucose effectiveness independent of insulin.

#### 2.5. Measurement of insulin sensitivity and glucose effectiveness

Minimal model analysis of FSIVGTT was according to Bergman [14] with the home-made software “TISPAG”, which uses a nonlinear least square estimation, from the Department of Physiology, University of Montpellier I [15–18]. This program gave the values of insulin sensitivity (SI) and glucose effectiveness (Sg). SI is a measurement of the influence of plasma insulin to change glucose’s own effect on glucose concentration. Sg is the fractional disappearance rate of glucose, independent of any insulin response. This parameter Sg was actually broken down into its two components: the contribution of hyperglycemia *per se* to tissue glucose utilization and the effect of basal insulin on glucose uptake. The basal insulin component of Sg is termed the basal insulin effect (BIE) and can be calculated as the product of basal insulin,  $I_b$ , and SI. Thus the contribution of non-insulin-dependent glucose uptake (glucose effectiveness at zero insulin, GEZI) to glucose uptake is the difference between total Sg and BIE.

$$GEZI = Sg - I_b \times SI.$$

According to Welch et al. [19] glucose uptake rates normalized to a plasma glucose level of 11 mmol/l were also calculated from the minimal model data. Insulin-mediated glucose uptake (IMGU) at any level of insulin can be calculate from SI as follows:

$$IMGU = SI \times G_{200} \times I_{200} \times V_D,$$

where  $G_{200}$  and  $I_{200}$  are glucose and insulin values interpolated from individual determinations bracketing 200 mg/dl for each patient, usually no more than 1–2 min from the 200 mg/dl value.  $V_D$  is the glucose distribution space and is assumed to be 1.6 dl/kg. Similarly, non-insulin-mediated glucose uptake (NIMGU) can be calculated as follows:

$$NIMGU = GEZI \times G_{200} \times V_D.$$

The sum of NIMGU and IMGU represented total glucose uptake (TGU). All these values (IMGU, NIMGU and TGU) were corrected by body weight and thus expressed as  $\text{mg} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$  body weight.

## 2.6. Laboratory measurements

Samples were analyzed for plasma insulin by radioimmunoassay (kit SB-INSI-5 from the international CIS). The within-assay coefficient of variation (CV) for insulin was determined by repetitive measurements of the same sample and was 6.6%; the between-assay CV was 6.2%. The sensitivity (lowest detectable value) was  $<1 \mu\text{U/ml}$ . Plasma glucose was measured with a Beckman glucose analyzer, with coefficients of variation of 8.3% (within-assay) and 7.9% (between-assay). Fibrinogen was measured with the Clauss method.

## 2.7. Statistics

Data are expressed as means  $\pm$  SD. To detect differences between parameters represented by a single measurement, non-parametric tests for unpaired (Mann–Whitney) and paired (Wilcoxon) data were used as appropriate. Correlations were performed by Pearson analysis and multiple regression analysis.  $p < 0.05$  was considered significant.

## 3. Results

As shown on Tables 1–4, patients have similar age, weight, body mass index, and HbA1c. They are thus grossly matched for adiposity, age and glycemic control. While plasma viscosity was of course very significantly higher in the group defined by values of this parameter higher than 1.45 mPa.s, the other hemorheological parameters (RBC aggregation, RBC rigidity and hematocrit) were not significantly different. Whole blood viscosity at high shear rate was slightly higher ( $p = 0.05$ ), but when corrected for hematocrit with the equation of Quemada, whole blood viscosity was no longer different.

Table 2  
Minimal model measurements of glucose disposal in the 32 subjects of the study

	$\mu\text{pl} < 1.45 (n = 20)$	$\mu\text{pl} > 1.45 (n = 12)$
Baseline insulin ( $\mu\text{U/ml}$ )	$12.25 \pm 7.61$	$10.25 \pm 3.39$
Peak insulin $I_{1+3}$ ( $\mu\text{U/ml}$ )	$30.9 \pm 27.25$	$29.5 \pm 12.15$
Kg ( $\text{min}^{-1} \times 10^{-2}$ )	$0.76 \pm 0.34$	$0.83 \pm 0.31$
Sg ( $\text{min}^{-1} \times 10^{-2}$ )	$1.61 \pm 0.86$	$1.44 \pm 0.43$
SI ( $\text{min}^{-1}/(\mu\text{U/ml}) \times 10^{-4}$ )	$1.74 \pm 2.68$	$0.84 \pm 0.96$

Kg: glucose tolerance, Sg: glucose effectiveness, SI: insulin sensitivity.

Table 3  
Minimal model measurements of glucose disposal in the 32 subjects of the study

	$\mu\text{pl} < 1.45 (n = 20)$	$\mu\text{pl} > 1.45 (n = 12)$
BIE ( $\text{min}^{-1} \times 10^{-2}$ )	$0.18 \pm 0.27$	$0.07 \pm 0.08$
GEZI ( $\text{min}^{-1} \times 10^{-2}$ )	$1.44 \pm 0.93$	$1.37 \pm 0.44$
IMGU ( $\text{mg} \cdot \text{min}^{-1} \text{kg}^{-1}$ )	$2.85 \pm 4.42$	$1.12 \pm 1.54$
NIMGU ( $\text{mg} \cdot \text{min}^{-1} \text{kg}^{-1}$ )	$3.52 \pm 1.65$	$3.91 \pm 1.33$
TGU ( $\text{mg} \cdot \text{min}^{-1} \text{kg}^{-1}$ )	$5.75 \pm 2.64$	$5.03 \pm 1.9$

Abbreviations: BIE: basal insulin effect; GEZI: glucose effectiveness at zero insulin; IMGU: insulin-mediated glucose uptake; NIMGU: non-insulin-mediated glucose uptake; TGU: total glucose uptake.

Table 4  
Biological and hemorheologic parameters in the 32 subjects of the study

	$\mu\text{pl} < 1.45$ ( $n = 20$ )	$\mu\text{pl} > 1.45$ ( $n = 12$ )
Blood viscosity $\mu\text{b}$ at $1000 \text{ s}^{-1}$ (mPa.s)	$2.58 \pm 0.35$	$2.86 \pm 0.39$
Plasma viscosity $\mu\text{pl}$ (mPa.s)	$1.28 \pm 0.09$	$1.47 \pm 0.07^{***}$
Venous hematocrit (%)	$40.7 \pm 4.5$	$42.41 \pm 4.27$
Erythrocyte rigidity 'Tk'	$0.59 \pm 0.10$	$0.54 \pm 0.12$
Erythrocyte aggregation 'M'	$8.17 \pm 5.59$	$8.53 \pm 3.09$
Erythrocyte aggregation 'M1'	$12.15 \pm 7.2$	$11.8 \pm 4$
Fibrinogen (g/l)	$3.57 \pm 1.1$	$3.43 \pm 0.96$
Serum triglycerides (g/l)	$3.57 \pm 1.1$	$3.57 \pm 1.1$
Serum HDL-cholesterol (g/l)	$0.42 \pm 0.08$	$0.39 \pm 0.1$
Serum LDL-cholesterol (g/l)	$1.56 \pm 0.39$	$1.35 \pm 0.59$
HbA1c (%)	$8.71 \pm 2.3$	$8.62 \pm 2.3$

\*\*\*  $p < 0.01$ .

Table 5

Mean values ( $\pm$  SD) of blood pressure in the 32 subjects of the study.  
Values are given in mm Hg

	$\mu\text{pl} < 1.45$ ( $n = 20$ )	$\mu\text{pl} > 1.45$ ( $n = 12$ )
Systolic	$140 \pm 8$	$177.5 \pm 2.5^{***}$
Diastolic	$83 \pm 9$	$110 \pm 14^{****}$
Mean	$102 \pm 7$	$132 \pm 18^{****}$

\*\*\*  $p < 10^{-8}$ ; \*\*\*\*  $p < 10^{-9}$ .

It is interesting to notice that high plasma viscosity did not define a subgroup of patients with more severe insulin resistance, since values of all minimal model parameters were not significantly different. Similarly, lipid parameters and fibrinogen were not different.

By contrast, as shown in Table 5, blood pressure was markedly higher in the subgroup whose plasma viscosity was higher than 1.45 mPa.s. This was true for systolic blood pressure ( $p < 10^{-8}$ ) and even more for diastolic blood pressure ( $p < 10^{-9}$ ) and mean blood pressure ( $p < 10^{-9}$ ).

We tried to find correlations among those various parameters but were unable to find any interesting one.

#### 4. Discussion

In this study we tried to define the characteristics of non-insulin dependent diabetics with high plasma viscosity ( $>1.45$  mPa.s) and to look whether they were more insulin resistant and/or exhibited other hemorheologic disturbances. Results show that blood pressure was markedly higher in the subgroup whose plasma viscosity was higher than 1.45 mPa.s. By contrast, patients had similar insulin sensitivity, body mass index, fibrinogen and lipids.

As reminded above, according to our previous works, 1.45 mPa.s is with our technique the lower boundary of the highest quartile of plasma viscosity, and may be thus used to define high plasma viscosity [9]. The sensitivity of plasma viscosity  $>1.45$  mPa.s for detecting insulin resistance in a sample of 108 nondiabetic subjects was 40.9%, the specificity 88.4%, the positive predictive value 47.4% and the negative predictive value 85.4%. In this population, 35% of subject with plasma viscosity  $>1.45$  mPa.s

were insulin resistant (SI in the lower quartile) while only 12.5% of subjects with plasma viscosity  $<1.45$  mPa.s had such a low SI. Presumably, such findings may be also relevant to diabetes, but in this case the picture is likely to be considerably obscured by a lot of other variables. Since we find no significant association here between insulin resistance and plasma viscosity, we cannot comment this issue. However, there is a nonsignificant tendency towards a lower SI and IMBGU value in patients who plasma viscosity exceeds 1.45 mPa.s so that a type 2 error cannot be ruled out. Theoretically, both SI plasma viscosity are likely to be related to arterial pressure.

Arterial pressure is a major concern in type 2 diabetes. The UKPDS study [20] clearly demonstrated its strong influence on the occurrence of diabetic complications, independent of glycemetic control. In most cases the ideal aim is less than 140/80. In our subgroup with  $\mu\text{pl} > 1.45$  mPa.s its mean values are 177/110, i.e. clearly in the pathologic range.

It is well known that there is a higher incidence of hypertension in diabetes. The exact occurrence has been a matter of controversy since definitions of threshold values have been changing during the time. With the most recent definitions given by the WHO (systolic  $\geq 140$  mmHg or diastolic  $\geq 90$  mmHg one can consider that 42% of insulin dependent and 71% of NIDDMs are hypertensive). The metabolic and genetic background, and more specifically the underlying insulin resistance, are likely to explain most of this hypertension, regardless the glycemetic control itself [21].

It is not surprising to find in this population a relationship between plasma viscosity and hypertension. Such a relationship is also classical in nondiabetic hypertensives [22–26].

Actually, it remains difficult to understand whether hemorheologic alterations in hypertension are cause or consequence of the hemodynamic abnormality [27]. Recently, Bogar [28] suggested that abnormal hemorheology and hypertension are not directly linked but that they share the same inductive genetic and/or environmental factors like obesity, chronic mental stress, physical inactivity and cigarette smoking.

In physiological experiments, plasma viscosity, which is not influenced by shear and flow rate, is able to exert hemodynamic effects. Whether such hemodynamic effects can play a pathogenetic role is more and more suggested by recent clinical investigations. In a longitudinal study on nondiabetic hypertensives, Levenson's team demonstrated that plasma viscosity was associated with the incidence of CHD events in middle-aged men [29]. It is thus logic to find plasma viscosity associated in diabetes with hypertension which is a major actor in the development of vascular complications.

However, it could be expected to find plasma viscosity closely related to insulin resistance, lipid disorders, obesity, and high fibrinogen [9], all factors that may be also associated to hypertension and thus explain the link between blood pressure and hemorheology. Interestingly, in our study, lipid parameters and fibrinogen are not abnormal, and are thus similar in both groups, so that they cannot explain such a link. The same remark can be done with insulin resistance, age and body mass index.

In the conditions of this study, the link between blood pressure and plasma viscosity appears to be to some extent "independent" of covariables such as insulin resistance, lipid disorders, obesity, and high fibrinogen.

Concerning blood rheology, it is interesting to notice two things. First, high plasma viscosity is not associated with other hemorheologic disturbances which are frequently found in this situation, for example, red cell hyperaggregability. Obviously a tendency to higher whole blood viscosity is observed, but it is weak and it disappears when hematocrit is fixed at 45%. In this sample of subjects high plasma viscosity can be studied regardless the other hemorheologic parameters, as an isolated disorder. On the other hand, there is no "viscoregulatory" decrease in hematocrit in order to compensate for this high

plasma viscosity, as usually found in many hyperviscosity syndromes [30,31], including apparently diabetes in which we reported lowered hematocrit values when poor control or vascular complications increase viscosity factors [32].

On the whole, this study gives an opportunity to evidence the “isolated” relationship between plasma viscosity and blood pressure. It shows that, regardless adiposity, age, fibrinogen, triglycerides, cholesterol, insulin and insulin sensitivity, hematocrit, red cell rheology, and whole blood viscosity, type 2 diabetic patients whose plasma viscosity is higher than 1.45 mPa.s exhibit a markedly higher blood pressure.

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