Relationship Between Hemorrheologic Factors and Insulin Sensitivity in Healthy Young Men

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The present study aimed at testing a possible relationship between hemorrheologic factors, such as hematocrit, fibrinogen, and whole-blood viscosity, and insulin sensitivity in healthy humans. Twenty-one 21-year-old men were studied with the hyperinsulinemic euglycemic glucose clamp technique. We found statistically significant negative correlations between the glucose disposal rate (GDR) and calculated whole-blood viscosity at both high ($r = -.55$, $P = .01$) and low ($r = -.51$, $P = .01$) shear rates. We observed negative associations between GDR and fibrinogen ($r = -.66$, $P = .002$), GDR and hematocrit ($r = -.63$, $P = .002$), GDR and body mass index ($r = -.51$, $P = .007$), and GDR and resting heart rate ($r = -.46$, $P = .04$). Using stepwise multiple regression considering whole-blood viscosity, body mass index, mean arterial blood pressure, and heart rate as independent variables, we found that only whole-blood viscosity and body mass index were independent explanatory variables of the GDR. Together they accounted for 63% of the variability in the GDR in our subjects. These results suggest hemorrheologic, and therefore indirectly hemodynamic, factors as correlates to insulin sensitivity.

RESISTANCE to insulin-stimulated glucose disposal has been shown in subjects with essential hypertension,[1,2] and has been proposed to be a metabolic link between non–insulin-dependent diabetes mellitus, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease.[3,4]

The primary site of insulin resistance, as measured by the glucose clamp technique, is skeletal muscle.[5] Several reports suggest an association between disturbances in blood flow and insulin-stimulated glucose disposal, and recently Julius et al[6] proposed a hemodynamic link between insulin resistance and hypertension. Laakso et al[7] showed a lower increment in blood flow to skeletal muscle during a hyperinsulinemic glucose clamp in obese insulin-resistant individuals compared with insulin-sensitive controls. Reduced postprandial blood flow to skeletal muscle[8] and lower capillary density[9] are also associated with insulin resistance.

Whole-blood viscosity has been suggested in many reports to be a major independent risk factor for cardiovascular disease[10-12] and peripheral vascular disease,[13] and it is a correlate of both systolic and diastolic blood pressure.[14] During the last few years, many reports have been published on changes in viscosity, hematocrit, and other hemorrheologic factors in diabetes and hypertension, but no study has associated them directly with insulin sensitivity. We observed such associations in pilot studies, and therefore prospectively examined 21 healthy young men with the hyperinsulinemic euglycemic glucose clamp technique and calculated whole-blood viscosity. We also measured fibrinogen and plasminogen activator inhibitor (PAI-1) activity to investigate a possible association between insulin sensitivity and fibrinolytic activity, and we measured plasma catecholamine levels to assess the influence of sympathetic nervous system activity.

SUBJECTS AND METHODS

Subjects

In 1988, 3,708 18-year-old men underwent a medical examination during the military draft procedure in the city of Oslo. Attending is compulsory, and only men with severe medical disorders do not attend. Therefore, the 3,708 subjects comprise all healthy 18-year-old men in the Oslo area. Pulse, blood pressure, body weight, and height were recorded. No follow-up evaluation of the subjects was performed until the present study was undertaken.

In 1991, 39 of the young men were invited to participate in a cardiovascular risk factor screening at Ullevaal Hospital, ie, the present study. To ensure a wide range of blood pressure, we selected men at random from the 2nd (n = 13), 50th (n = 13), and 98th (n = 13) percentile of mean screening blood pressure in 1988. Twenty-one could be studied (four were excluded for medical reasons, ie, three had allergies and one had irritable colon; seven had moved abroad or to other parts of the country; three could not participate because of personal workload; and four did not respond to the written invitation). They underwent thorough physical examination and blood biochemistry evaluation including renal and liver function tests and urinalysis to exclude illness. They were all healthy, and none used regular medication. All subjects fasted and refrained from smoking for the preceding 10 hours and abstained from alcohol for the preceding 24 hours before the study. Body mass index, supine heart rate, and mean arterial blood pressure are shown in Table 1. The study was approved by the Regional Ethical Committee, and informed consent was obtained from each subject.

Glucose Clamp Examination

An antecubital vein on the right arm was cannulated with a short teflon catheter (Venflon 17G, Viggo, Hälsingborg, Sweden), and the right forearm was then placed in a heating sleeve (Thermal Vascular Dilatator, Swetron, Veddesta, Sweden). The temperature was set at 52°C, and the right arm was thus used for sampling of arterialized venous blood. An antecubital vein on the left arm was also cannulated with a short teflon catheter (Venflon 18G) for later infusion of insulin and glucose. Subjects then rested supine for 20 minutes in the presence of the examining physician before baseline blood pressure and heart rate recordings and blood sampling were undertaken.

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Submitted November 16, 1992; accepted June 2, 1993.

Supported by the Norwegian Council on Cardiovascular Diseases and the Bergesen Foundation.

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0026-0495/94/4304-0005$03.00/0

Table 1. Characteristics of the Study Population (n = 21; mean ± SD)

Age (yr)	21 (all)
Body mass index (kg/m²)	23.7 ± 2.4
Heart rate (beats/min)	59 ± 12
Mean arterial blood pressure (mm Hg)	88 ± 8
Hematocrit (%)	43 ± 3
Hemoglobin (g/dL)	14.6 ± 0.9
Total plasma protein (g/L)	69.1 ± 3.8
Fasting glucose (mmol/L)	4.8 ± 0.6
Fasting insulin (mU/L)	21.5 ± 14.4
Fibrinogen (g/L)	1.7 ± 0.6
PAI-1 (U/mL)	6.6 ± 5.1
Plasma norepinephrine (nmol/L)	0.83 ± 0.3
Plasma epinephrine (nmol/L)	0.21 ± 0.1
GDR (mg/kg body weight/min)	9.1 ± 3.6
Insulin sensitivity index	8.0 ± 4.6

NOTE. Insulin sensitivity index = (GDR/mean insulin concentration during clamp) × 100, arbitrary units.

The euglycemic hyperinsulinemic glucose clamp was thereafter performed using a modification of the method described by DeFronzo et al.[15] Insulin was infused at a fixed rate of 1 mU/kg/min. Blood glucose was clamped at the subjects' fasting level (isoglycemia); this was obtained by measuring glucose concentration every 5 minutes and adjusting the rate of an intravenous infusion of glucose (concentration 240 mg/mL) according to the results. Isoglycemia was maintained for 120 minutes, and the glucose disposal rate (GDR) was calculated from the amount of glucose infused during the last 20 minutes. Average plasma insulin level during the clamp was 133.0 ± 43.3 mU/L. Because of individual differences in the metabolic clearance rate of insulin and possible continuing endogenous insulin secretion, steady-state levels of insulin varied from one person to another. We therefore also calculated the insulin sensitivity index,[15] which is a measure of the tissue sensitivity to the attained insulin concentration, ie, the amount of glucose metabolized per unit of serum insulin (GDR divided by mean level of insulin during the last 20 minutes of clamp, mg/kg body weight/min/mU/L multiplied by 100).

This technique for measuring the GDR has a day-to-day coefficient of variation of less than 5% in our laboratory.

Analytical Methods

Fasting glucose levels were determined enzymatically using a glucose dehydrogenase method and a Cobas Bio analyzer (Roche, Basel, Switzerland). We used a Reflolux II (Boehringer, Mannheim, Germany) to measure glucose concentration during the glucose clamp procedure. The Reflolux II has previously been found to be precise, in comparison to both the Beckman Glucose Analyzer (Beckman Instruments, Fullerton, CA; $r = .99$)[16] and the hexokinase method (coefficient of variation within-run, 1.9%).[17] In our laboratory, the Reflolux II rendered a correlation coefficient of .92 with the hexokinase method; within-run variation was less than 2%.

Insulin levels were determined by radioimmunoassay.[18] Hematocrit levels were determined by a laser-operated ORTHO-ELT 800/WS hematology analyzer (Ortho Diagnostic Systems, Westwood, MA). Whole-blood viscosity was calculated from hematocrit and total plasma protein level, using the regression equations proposed by de Simone et al.[19] Viscosity was calculated at shear rates of 208, 104, 52, 5.2, 0.5, and 0.1 inverse seconds (s^{-1}). These shear rates were chosen by de Simone et al[19] because they approximately encompass the velocity gradients of blood flows in the circulatory system. This method for calculating viscosity provides good predictive power of actual whole-blood viscosity at all shear rates (multiple $R > .86$), with a maximum at shear rate 5.2 s^{-1} (multiple $R = .91$).

Fibrinogen levels were determined by the method of Clauss.[20] PAI-1 activity was measured in duplicate by a commercially available kit (Spectrolyse, Biopool, Umeå, Sweden). Levels of plasma catecholamines from arterialized venous blood were measured by the radioenzymatic technique of Peuler and Johnson as previously detailed.[21]

Blood pressure and heart rate were measured with an Omega 1000 Adult/Pediatric Blood Pressure Recorder (INVIVO Research Laboratories, Tulsa, OK). This device measures mean blood pressure and calculates systolic and diastolic pressures.

Statistical Analysis

Data were analyzed using the statistical package SPSS PC+ Version 3.0 (SPSS PC+, Chicago, IL) and are presented as means ± SDs. Univariate correlation coefficients (r) were calculated using the Pearson product-moment formula. Stepwise multiple regression analysis, entering the most significant variable first, was applied to compare variables independently related to the GDR. Hematocrit and plasma protein levels (and thereby also fibrinogen) have been used to calculate whole-blood viscosity, and were therefore not entered separately into the regression equation. Student's t test was used to compare smokers and nonsmokers after the variables had been checked for approximate normal distribution. The level of significance was set at P less than .05 (two-tailed).

RESULTS

Table 1 shows the hematocrit and levels of hemoglobin, total plasma protein, fasting glucose, insulin, fibrinogen, PAI-1, plasma catecholamines, and the GDR and insulin sensitivity index.

Calculated whole-blood viscosity correlated significantly and negatively with the GDR at all shear rates (Fig 1, Table 2). There was a highly significant negative correlation between the hematocrit and the GDR ($r = .63$, $P = .002$; Fig 2, Table 3).

There was also a highly significant negative correlation between the level of fibrinogen and the GDR ($r = -.66$, $P = .002$; Table 3). PAI-1 showed the same tendency, with a correlation coefficient of $-.42$ ($P = .07$). Resting heart rate ($r = -.46$, $P = .04$) and body mass index ($r = -.51$, $P = .02$) but not mean arterial blood pressure ($r = -.39$, $P = .08$) correlated significantly with the GDR. Plasma norepinephrine and epinephrine did not correlate significantly with the

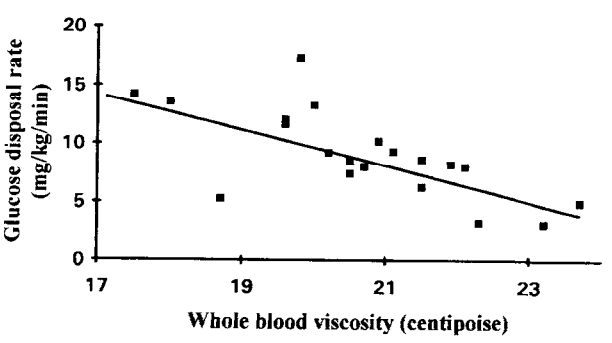

Fig 1. Correlation between the GDR and whole-blood viscosity at shear rate 5.2 s^{-1} ($r = -.69$, $P = .0005$).

Table 2. Correlation Coefficients (*r*) for Calculated WBV and the GDR at Different Shear Rates

WBV Shear Rate (s^{-1})	*r*	*P*
208	−.55	.01
104	−.53	.01
52	−.53	.01
5.2	−.69	.0005
0.5	−.49	.02
0.1	−.51	.01

Abbreviation: WBV, whole-blood viscosity.

GDR ($r = -.14, P = .6$ and $r = -.02, P = .9$, respectively). However, plasma norepinephrine correlated significantly with the hematocrit ($r = .48, P = .03$), and plasma epinephrine showed a similar tendency ($r = .26, P = .2$).

When we analyzed the data using stepwise multiple regression with whole-blood viscosity, body mass index, heart rate, and mean arterial blood pressure as variables, both viscosity and body mass index were independently and significantly correlated with the GDR, whereas heart rate and mean arterial pressure did not reach the level of statistical significance (Table 4). The R^2 coefficient expresses the amount of variability accounted for by each of the variables when the most significant variable is entered first, ie, changes in whole-blood viscosity accounted for 48% of the variation in GDR, whereas viscosity and body mass index together explained 63%. Since viscosity is calculated from the hematocrit and plasma protein concentration, entering these variables separately instead of viscosity would provide the same level of explanation—ie, 40% of the variability of the GDR is accounted for by variations in hematocrit, and 9% by variations of total plasma protein. We chose viscosity because this provides an integrated measure, and used calculated viscosity at shear rate 5.2 s^{-1} for this analysis since this gives the best correlation with actual viscosity.[19]

The level of hyperinsulinemia during the clamp showed considerable interindividual variation (mean, 133; range, 77 to 221 mU/L). We therefore calculated the insulin sensitivity index[15] to determine whether the correlations were dependent on attained insulin concentration during the glucose clamp examination. We found that the insulin sensitivity index conveyed essentially the same information as the GDR (Table 3), and have based the discussion on the latter.

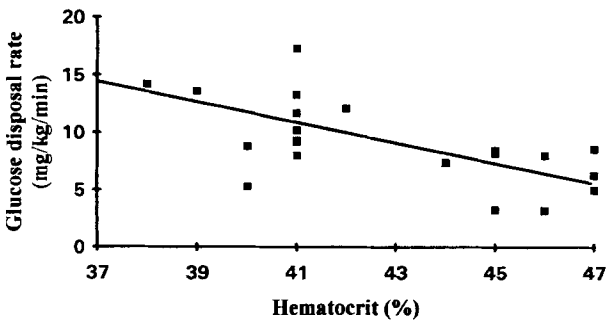

Fig 2. Correlation between the GDR and hematocrit ($r = -.63$, $P = .002$).

Table 3. Correlations With Insulin-Mediated Glucose Disposal

	GDR		GDR/I	
	r	*P*	*r*	*P*
Hematocrit	−.63	.002	−.65	.001
Body mass index	−.51	.02	−.64	.002
Heart rate	−.46	.04	−.31	.13
Mean arterial blood pressure	−.39	.08	−.31	.18
Total plasma protein	−.28	.22	−.22	.33
Fibrinogen	−.66	.002	−.50	.02
PAI-1	−.42	.07	−.34	.15
Plasma norepinephrine	−.14	.6	−.15	.5
Plasma epinephrine	−.02	.9	−.12	.6

Abbreviation: GDR/I, insulin sensitivity index ([GDR/mean insulin concentration during clamp] × 100).

Six subjects were reported to be daily smokers. Compared with nonsmokers, they tended to have higher hematocrit (45% ± 3% *v* 42% ± 3%, $P = .08$) and fibrinogen (2.0 ± 0.4 *v* 1.6 ± 0.6 g/L, $P = .08$), lower plasma protein (66 ± 2 *v* 70 ± 3 g/L, $P = .03$), and similar whole-blood viscosity (20.8 ± 0.3 *v* 20.6 ± 1.8, $P = .6$). The GDR (8.0 ± 1.2 *v* 9.5 ± 4.1 mg/kg body weight/min, $P = .2$) and the insulin sensitivity index (6.6 ± 2.0 *v* 8.4 ± 5.1, $P = .2$) also tended to be lower in the smokers. However, omitting smokers from the analysis did not change the strength of the correlations between the GDR and hematocrit ($r = -.66$), fibrinogen ($r = -.65$), or whole-blood viscosity ($r = -.69$).

DISCUSSION

The present study demonstrates a rather strong and independent negative relationship between the hematocrit/whole-blood viscosity and the GDR in healthy young men. To our knowledge, this is the first report associating insulin sensitivity with the hematocrit and whole-blood viscosity, and our data may suggest the existence of an important link between these cardiovascular risk factors.

The mechanism for this association is not clear. Insulin resistance has been linked both to processes taking place at the receptor[22] and postreceptor level.[23] Blood flow and glucose delivery to skeletal muscle have also been shown to be modulators of glucose uptake.[24] Blood flow is determined by arterial blood pressure and peripheral vascular resistance, which is a function of the size and geometry of the resistance vessels and also of blood viscosity.[25] The hematocrit is the most important single determinant of whole-blood viscosity, since viscosity increases directly with the hematocrit throughout its normal range.[14] Therefore, a

Table 4. Cumulative Multiple *r* and R^2 (amount of variablity in GDR explained) When GDR Is Considered the Dependent Variable

	Cumulative Multiple *r*	Cumulative Multiple R^2
Whole-blood viscosity	.69	.48 ($P = .0005$)
Body mass index	.79	.63 ($P = .0001$)*
Heart rate	.82	.67 (NS)
Mean arterial blood pressure	.82	.67 (NS)

*This level of significance is for the influence of whole-blood viscosity and body mass index together.

possible explanation for the relationship between hematocrit/viscosity and insulin resistance may be hemodynamic, ie, a higher hematocrit and whole-blood viscosity decrease the blood flow and thereby decrease glucose delivery to skeletal muscle.

A reverse mechanism may also be considered. Insulin, as a growth factor, may stimulate erythropoiesis to increase the hematocrit or stimulate the synthesis of plasma proteins. Insulin resistance has been associated with elevated levels of insulin-like growth factor-1 (IGF-1),[26] and IGF-1 may stimulate erythropoiesis.[27,28] The role of insulin or IGF-1 on plasma protein synthesis is less established.

The strength of the correlation between mean arterial blood pressure and insulin resistance in our study corresponds well with findings in previous reports,[1] although the correlation did not reach the level of statistical significance. This could be due to the relatively low number of study subjects (type II error), but probably not to a narrow range of blood pressure (SD of ±10 mmHg, Table 1). Concomitant increases in heart rate and blood pressure are characteristic features of the sympathetic nervous system influence on cardiovascular adjustments,[29,30] and thus the negative correlations between resting heart rate, blood pressure, and the GDR could point to sympathetic nervous system involvement.

Mental stress can increase the hematocrit,[31,32] and an epinephrine infusion that increases plasma epinephrine to levels that are found during mental stress increases the hematocrit (Kjeldsen SE, et al, unpublished data) and decreases insulin-stimulated glucose utilization.[33,34] We observed positive associations between plasma catecholamines and the hematocrit. However, plasma catecholamines did not correlate directly with the GDR.

The observed association between body mass index and insulin resistance has been described in non-obese individuals,[1] but is not a consistent finding.[35] Obesity is conventionally defined as a body mass index greater than 27 kg/m^2; in our study, the range of body mass index was 17.3 to 28.5 kg/m^2, with only two subjects exceeding 27.0 kg/m^2. When we re-analyzed the data excluding these two subjects, the association was no longer statistically significant ($r = -.33$, $P = .16$). Unless this is a type II error, our data are then not in support of an independent relation between body mass index and insulin resistance in non-obese individuals.

Elevated levels of fibrinogen and PAI-1 have previously been associated with decreased insulin-mediated glucose disposal[36] and hyperinsulinemia.[37] We observed a similar association with respect to PAI-1 activity (although it was not statistically significant), whereas fibrinogen was more closely related to the GDR in our study. This provides further evidence for the association between insulin resistance and decreased fibrinolytic activity.

People living at high altitude have higher levels of hematocrit and may, according to our hypothesis, be postulated to have impaired insulin-mediated glucose disposal. In fact, there are two studies demonstrating concomitant increases in serum glucose and insulin on short-term ascent to high altitude,[38,39] changes that could reflect the appearance of an acute insulin-resistant state.

Smoking may induce insulin resistance,[40,41] although the mechanism remains unclear. Smoking increases hemoglobin concentration[42] and the hematocrit,[43] and this is a possible explanation for the relationship between smoking and insulin resistance. The smokers in our study had higher levels of hematocrit and fibrinogen but significantly lower total plasma protein, an observation that also has been made in a population-based study.[44] Because of the influence of plasma protein level, calculated whole-blood viscosity was similar in smokers and nonsmokers. Excluding the smokers left the strength of the correlations in our study unchanged, indicating that hemorrheologic factors affect insulin-mediated glucose disposal independent of smoking status.

The present data suggest that hemorrheologic factors, which are established risk factors for cardiovascular disease, are associated with insulin resistance. This may support a hemodynamic basis for insulin resistance.

ACKNOWLEDGMENT

We thank the staff of the Department of Clinical Chemistry and the Laboratory of Hematology at Ullevaal University Hospital, and of the Joint Norwegian Medical Services, Head Quarters Defence Command, Norway, for their generous cooperation. Ruth Amundsen is acknowledged for expert technical assistance with the catecholamine assay.

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