

Hemorheological aspects of the metabolic syndrome: markers of insulin resistance, obesity or hyperinsulinemia?

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Abstract. The metabolic syndrome is a major health problem in western countries, due to the deleterious metabolic consequences of sedentarity and rich diet in the large part of the population who exhibits the so-called “thrifty phenotype”. This syndrome, which is at high risk for diabetes and atherothrombosis is associated with hemorheologic abnormalities. Initially, insulin resistance was considered as the core of the syndrome. However, it becomes clear that the syndrome is a cluster in which the combined effects of obesity, insulin resistance, and hyperinsulinemia can be inconstantly associated. Thus, we investigated in 157 nondiabetic subjects (53 males and 104 females, age 35.6 ± 1.1 yr, mean BMI 29.2 ± 0.6 kg/m²) the respective importance of each of these factors. Subjects were divided in 6 groups according to BMI (cut-off point 25 kg/m²) and insulin sensitivity (SI) measured with the minimal model (lowest quartile SI $< 1.1 \text{ min}^{-1}/(\mu\text{U/ml}) \cdot 10^{-4}$, highest quartile SI > 9.5 , middle zone between 1.1 and 9.5). Results show that whole blood viscosity at high shear rate is higher in obese subjects ($p < 0.01$). Plasma viscosity is also higher in obese subjects 1.41 ± 0.02 vs 1.34 ± 0.012 ($p < 0.01$), and, in addition, in lean subjects, is lower when SI is in the upper quartile. RBC rigidity index “Tk” is higher in obese subjects. A worsening effect of insulin resistance (SI < 1.1) on Tk is found only in obese subjects. The aggregability index “M1” is increased when SI < 1.1 in both obese and nonobese subjects. No clear effect of either SI or obesity on hematocrit is observed. On the whole, obesity and insulin resistance both impair blood rheology by acting on red cell rigidity and plasma viscosity. Whole blood viscosity at high shear rate reflects rather obesity than insulin resistance. Myrenne “M1” aggregation is rather a marker of hyperinsulinemia. Thus, the hemorheologic picture of the metabolic syndrome is far to be only a reflect of insulin resistance alone.

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

1. Introduction

The metabolic syndrome is a clustering of risk factors, including elevated triglycerides, decreased high-density lipoprotein cholesterol, hyperinsulinemia, and hypertension [1]. This syndrome, which is at high risk for diabetes and atherothrombosis is associated with hemorheologic abnormalities [2]. Initially, insulin resistance was considered as the core of the syndrome [3]. However, it becomes clear that the syndrome is an heterogeneous cluster in which the combined effects of obesity, insulin resistance, and hyperinsulinemia can be inconstantly associated [4].

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Insulin resistance is defined as a value of insulin sensitivity in the lower quartile of distribution. Since insulin sensitivity (i.e., the slope of the dose-response relationship between insulinemia and glucose disposal) is a continuously distributed variable, the definition of a cut-off value is somewhat arbitrary [5]. However, it is clearly demonstrated that low insulin sensitivity is associated with both increased body fat and increased circulating lipids, together with impaired fibrinolysis [6]. Each of these abnormalities may explain by its own why there is a mild hyperviscosity syndrome in this situation. More recently, a sub-clinical inflammatory reaction has been shown to precede the onset of type 2 (non-insulin-dependent) diabetes [7].

Several reports underlined quite close correlations between insulin resistance and impaired rheology, so that plasma viscosity appears, in multivariate analysis, to be “independently” related to insulin resistance [8]. Moreover, plasma hyperviscosity is corrected by insulin-sensitizing procedures (such as exercise training [9]) and is thus to some extent a marker of this disease [8].

The most “specific” (88%) hemorheologic “marker” of insulin resistance appears thus, in our studies, to be plasma viscosity, although the sensitivity of this marker is rather poor (40%) [8]. Such a finding may have a clinical relevance, since this hemorheological parameter has been found to be statistically related to cardiovascular risk in several studies and emerges as a new “risk factor” [10–12].

However, it is clear that almost all the abnormalities that cluster with insulin resistance in the metabolic syndrome are likely to impair blood rheology by their own, so that it is extremely difficult to delineate the pathophysiological interrelationships of parameters such as inflammation, low insulin sensitivity, obesity, hypertriglyceridemia, hyperviscosity, etc.

The aim of this study was thus to perform a multivariate analysis of the respective influence of low insulin sensitivity, obesity, hyperinsulinemia on hemorheological parameters.

2. Subjects and methods

2.1. Subjects

We investigated 157 nondiabetic subjects (53 males and 104 females, age 35.6 ± 1.1 yr, mean BMI 29.2 ± 0.6 kg/m²) which were divided in 6 groups according to BMI (cut-off point 25 kg/m²) and insulin sensitivity (SI) measured with the minimal model (lowest quartile SI $< 1.1 \text{ min}^{-1}/(\mu\text{U/ml}) \times 10^{-4}$, highest quartile SI > 9.5 , middle zone between 1.1 and 9.5). These subjects were explored in our outpatients unit for a precise assessment of their insulin sensitivity for various reasons (obesity, hypoglycemia, familial antecedents of diabetes, personal antecedents of gestational diabetes, etc.) but were not found to exhibit overt abnormalities of glucoregulation according to the current standards.

2.2. Laboratory measurements

Blood samples for hemorheological measurements (7 ml) were drawn with potassium EDTA as the anticoagulant in a vacuum tube (Vacutainer) as specified by the International Committee for Standardization in Haematology [12]. Measurements were performed within 2 h after venepuncture. Blood viscosity and plasma viscosity were measured at very high shear rate (1000 s^{-1}) with a micro-method. Measurements were performed on the MT 90 falling ball viscometer (Mediatest, F-86280 Saint Benoit) [13,14]. Accuracy of the measurements was regularly controlled with the Carrimed Rheometer “CS” (purchased from Rhéo, 91120 Palaiseau, France) [15]. The coefficient of variation of this method ranges between 0.6 and 0.8%. The results of viscometric measurements were expressed as apparent viscosity of whole

blood at native hematocrit μ_b , plasma viscosity μ_{pl} , blood viscosity at corrected hematocrit (45%) μ_{45} according to the equation of Quemada [16], and RBC rigidity index “Tk”. Hematocrit (packed cell volume) was evaluated by a microhematocrit technique on a Hellige autocrit centrifuge.

RBC aggregation was assessed with the Myrenne aggregometer [17] which gives two indices of RBC aggregation: “M” (aggregation during stasis after shearing at 600 s^{-1}) and “M1” (falicitated aggregation at low shear rate after shearing at 600 s^{-1}).

2.3. Intravenous glucose tolerance test (IVGTT) protocol

After a 12 hr fast, at 9:00 A.M., a cannula was placed in the cephalic vein at the level of the cubital fossa for blood sampling. A glucose injection (0.5 g/kg, solution at 30%) was administered in the contralateral cephalic vein, slowly over precisely three minutes. Blood samples were drawn twice before the glucose bolus and at 1, 3, 4, 8, 10, 15, 19, 20, 22, 30, 41, 70, 90 and 180 min following glucose injection. Insulin (0.02 units/kg body weight i.e. 1 or 2 units) was injected intravenously immediately after the 19 min sample. The 1 and 3 min samples were used for the determination of insulin early secretory phase [18]. The other samples were necessary for minimal model calculations.

2.4. Measures of insulin sensitivity (SI)

Minimal model analysis of the IVGTT was performed according to Bergman’s method [19–21] with the software “TISPAG” from the Department of Physiology of the University of Montpellier I, France [22,23] which uses a non-linear least square estimation. SI was calculated from the following equations:

$$dG(t)/dt = -(p_1 + X(t))G(t) + p_1 G_b, \quad (1)$$

$$G(0) = G_0, \quad (2)$$

$$dX(t)/dt = -p_2 X(t) + p_3 (I(t) - I_b), \quad (3)$$

$$X(0) = 0, \quad (4)$$

where $G(t)$ and $I(t)$ are plasma glucose and insulin concentrations, $X(t)$ is the insulin in a compartment remote from plasma (“insulin action”), and p_1 – p_3 are model parameters. G_0 is the glucose concentration that one would obtain immediately after injection, if there were instantaneous mixing in the extra cellular fluid compartment. G_b and I_b are basal values of glucose and insulin. Parameter p_1 represents S_g , i.e. the fractional disappearance rate of glucose, independent of any insulin response. p_3 and p_2 determine the kinetics of insulin transport, into and out of (respectively) the remote insulin compartment where insulin action is expressed. SI is an index of the influence of plasma insulin to change glucose’s own effect on glucose concentration. Thus, SI is equal to $-p_3/p_2$.

2.5. Statistics

Values are presented as mean \pm standard error (SE) of the mean. Comparison was made with analysis of variance after verification of the normality of the sample with the Kolmogorov–Smirnov test. Significance level was defined as $p < 0.05$.

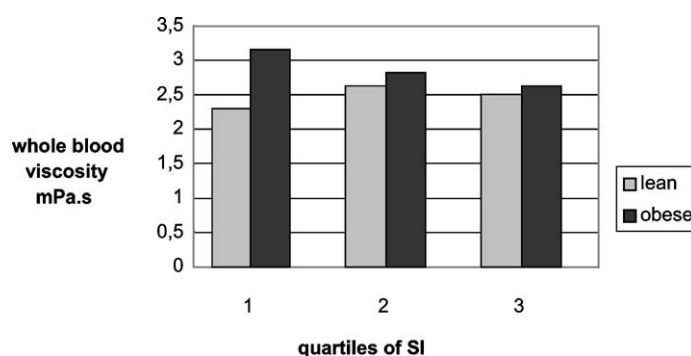


Fig. 1. Mean values of whole blood viscosity (shear rate 1000 s^{-1}) in the 4 quartiles of distribution of insulin sensitivity (SI) according to the BMI status ($<$ or $> 25 \text{ kg/m}^2$). Left: insulin resistance ($\text{SI} < 1.1 \text{ min}^{-1}/(\mu\text{U/ml}) \cdot 10^{-4}$); middle: two middle quartiles put together; right: high insulin sensitivity. (SI highest quartile $\text{SI} > 9.5 \text{ min}^{-1}/(\mu\text{U/ml}) \cdot 10^{-4}$.) Whole blood viscosity at high shear rate is higher in overweight subjects ($p < 0.01$) regardless SI status.

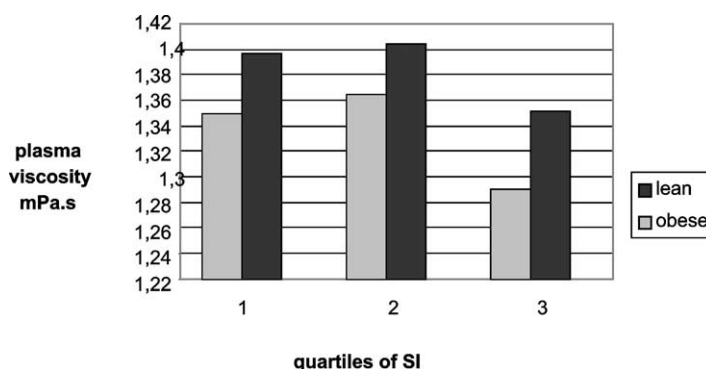


Fig. 2. Mean values of plasma viscosity in the 4 quartiles of distribution of insulin sensitivity (SI) according to the BMI status ($<$ or $> 25 \text{ kg/m}^2$). Left: insulin resistance ($\text{SI} < 1.1 \text{ min}^{-1}/(\mu\text{U/ml}) \cdot 10^{-4}$); middle: two middle quartiles put together; right: high insulin sensitivity. (SI highest quartile $\text{SI} > 9.5 \text{ min}^{-1}/(\mu\text{U/ml}) \cdot 10^{-4}$.) Plasma viscosity is also higher in overweight subjects 1.41 ± 0.02 vs 1.34 ± 0.012 ($p < 0.01$), and, in addition, in lean subjects, it is lower when SI is in the upper quartile ($p < 0.05$).

3. Results

When the 157 nondiabetic subjects were divided in 6 groups according to BMI (cut-off point 25 kg/m^2) and insulin sensitivity (SI) measured with the minimal model (lowest quartile $\text{SI} < 1.1 \text{ min}^{-1}/(\mu\text{U/ml}) \times 10^{-4}$, highest quartile $\text{SI} > 9.5$, middle zone between 1.1 and 9.5) as indicated above, the following results were observed on the various parameters of blood viscosity:

As shown in Fig. 1, mean values of whole blood viscosity at high shear rate were the same across quartiles of SI but were higher in each class of SI when the BMI exceeded 25 kg/m^2 ($p < 0.01$).

Figure 2 shows that plasma viscosity is also higher when the BMI exceeds 25 kg/m^2 . Mean values are $1.41 \pm 0.02 \text{ mPa.s}$ in overweight subjects vs 1.34 ± 0.012 in lean ones ($p < 0.01$). In addition, in lean subjects, plasma viscosity is lower when SI is in the upper quartile.

Figure 3 shows that the mean values of the RBC rigidity index “Tk” are higher when the BMI exceeds 25 kg/m^2 regardless of SI status. However a worsening effect of insulin resistance ($\text{SI} < 1.1$) on “Tk” is found, but only in subjects whose BMI $> 25 \text{ kg/m}^2$.

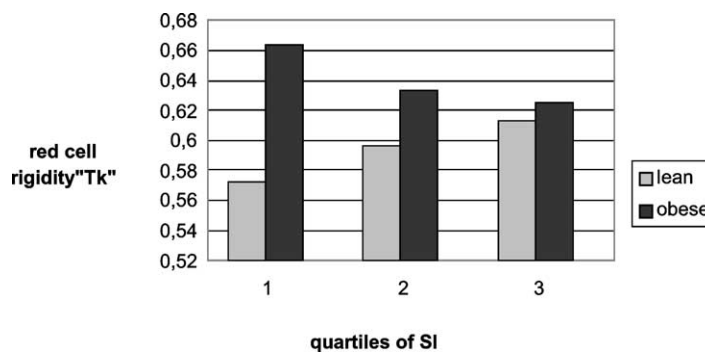


Fig. 3. Mean values of The RBC rigidity index “Tk” in the 4 quartiles of distribution of insulin sensitivity (SI) according to the BMI status ($<$ or $>$ 25 kg/m^2). Left: insulin resistance ($\text{SI} < 1.1 \text{ min}^{-1}/(\mu\text{U/ml}) \cdot 10^{-4}$); middle: two middle quartiles put together; right: high insulin sensitivity. (SI highest quartile $\text{SI} > 9.5 \text{ min}^{-1}/(\mu\text{U/ml}) \cdot 10^{-4}$). The RBC rigidity index “Tk” is higher in obese subjects put together compared to the lean ones ($p < 0.05$). A worsening effect of insulin resistance ($\text{SI} < 1.1$) on Tk is found only in overweight subjects ($p < 0.05$).

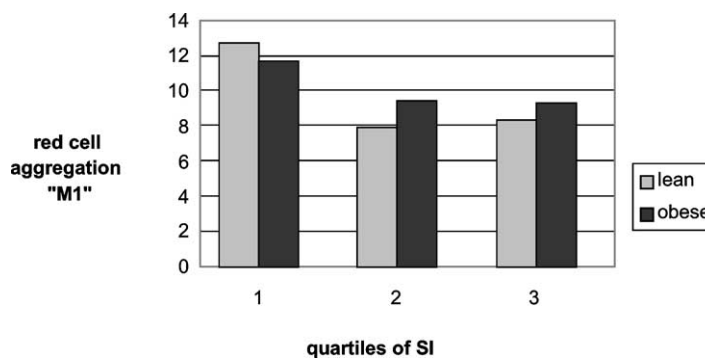


Fig. 4. Mean values of the aggregability index “M1” across the 4 quartiles of distribution of insulin sensitivity (SI) according to the BMI status ($<$ or $>$ 25 kg/m^2). Left: insulin resistance ($\text{SI} < 1.1 \text{ min}^{-1}/(\mu\text{U/ml}) \cdot 10^{-4}$); middle: two middle quartiles put together; right: high insulin sensitivity. (SI highest quartile $\text{SI} > 9.5 \text{ min}^{-1}/(\mu\text{U/ml}) \cdot 10^{-4}$). “M1” is increased when $\text{SI} < 1.1$ ($p < 0.05$) in both obese and nonobese subjects.

No clear effect of either SI or obesity on hematocrit is observed (data not shown). No significant effect on “M” aggregation index (data not shown).

As shown in Fig. 4, the aggregability index “M1” is increased when $\text{SI} < 1.1$ in both overweight and lean subjects, i.e., regardless adiposity status.

4. Discussion

Results show that both obesity and insulin resistance impair blood rheology by acting on red cell rigidity and plasma viscosity. Whole blood viscosity at high shear rate reflects rather obesity than insulin resistance. Myrenne “M1” aggregation is increased when SI is located in the range of insulin resistance, regardless the body mass index status.

On the whole, it is clear that the hemorheologic picture of the metabolic syndrome is far to be only a reflect of insulin resistance alone. First of all, whole blood viscosity at high shear rate appears in this study to reflect obesity rather than insulin resistance itself and does not seem to be a marker of insulin

resistance. This is consistent with our previous study [8] although in an older one [24–26] on a reduced number of subjects the only correlation between blood rheology and we were able to find was actually a nonlinear negative one between SI and whole blood viscosity. Our interpretation at that time was that whole blood viscosity was an integrated index reflecting a host of associated abnormalities, so that it appeared to be more sensitive to changes in SI status [24].

However, in a larger sample [8], we clearly evidenced that plasma viscosity was the only “independent” correlate of SI. This is consistent with the data in Fig. 2 which show that plasma viscosity, in lean subjects, is lower when SI is in the upper quartile. However, plasma viscosity seems to be also sensitive to obesity since it appears to be higher in the group of subjects whose BMI is higher than 25 kg/m².

Interesting data concerning the red cell rigidity “Tk” index are also found. This index is higher in obese subjects, evidencing an influence of adiposity itself. However, it is also increased when SI is in the range of insulin resistance (SI < 1.1), but this finding is only significant in the subgroup of obese subjects. Presumably, both adiposity and insulin resistance are likely to increase by separate mechanisms red cell rigidity.

Concerning red cell aggregability, the index “M” does not change across subgroups of body mass index or SI. By contrast, the aggregability index “M1” is increased when SI < 1.1 in both obese and nonobese subjects. This may suggest that M1 is a marker of insulin resistance, but we have already clarified this issue by multivariate analysis [8] and demonstrated that M1 is in fact a correlate of hyperinsulinemia rather than insulin resistance. It is interesting nonetheless to evidence a situation where M and M1 exhibit a different behavior. Although in most clinical studies those two parameters are strongly correlated and give almost the same information, M is supposed to reflect fibrinogen-induced aggregation (that occurs at low shear rate in venules) while M1 rather measures the aggregating effect of α 2-macroglobulin (that occurs at higher shear rates on the arteriolar side of the microcirculatory bed) [17].

On the whole, put together with those of our previous paper on this subject [8] our findings indicate that both obesity and insulin resistance impair blood rheology by acting on red cell rigidity and plasma viscosity. Whole blood viscosity at high shear rate reflects rather obesity than insulin resistance. Red cell rigidity is higher in insulin resistant individuals only when they are overweight. Finally, the Myrenne “M1” aggregation index is increased in the case of insulin resistance but is actually rather a marker of hyperinsulinemia than insulin resistance. Plasma viscosity appears again to be the only variable “independently explained” by SI, but it may also depend on obesity itself, regardless SI status.

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