

Hemorheological disturbances correlate with the lipid profile but not with the NCEP-ATPIII score of the metabolic syndrome.

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## 1. Abstract

The metabolic syndrome, which is associated with an high risk for diabetes and atherothrombosis, is associated with hemorheologic abnormalities. These abnormalities seem more and more to be explained by its various symptoms than by insulin resistance which represents theoretically the core of the syndrome. In this study we aimed at defining the specific hemorheologic profile of insulin resistance and hyperinsulinemia by separating a sample of 90 subjects into 4 subgroups according to the clinical score « NCEP-ATPIII » which is the best recognized standardized definition of the syndrome. Results show no significant changes of blood rheology across classes of NCEP score despite a borderline rank correlation between RBC aggregability « M1 » and the score. Whole blood viscosity was mostly correlated to HDL-cholesterol ( $r=-0.353$   $p=0.007$ ) and triglycerides ( $r=0.574$   $p=0.0001$ ). Plasma viscosity was correlated with total cholesterol ( $r=0.3359$   $p=0.02$ ) and with LDL-cholesterol ( $r=0.357$   $p=0.03$ ). Red blood cell rigidity « Tk » was negatively correlated to HDL-cholesterol ( $r=-0.430$   $p=0.007$ ). Aggregability « M » was correlated to total cholesterol ( $r=0.356$   $p=0.01$ ) and « M1 » to HDL-cholesterol ( $r=-0.406$   $p=0.006$ ). Thus, despite previously described correlations with glucose disposal parameters, the hyperviscosity syndrome of the metabolic syndrome is not proportional to its clinical scoring and is strongly dependent upon the lipid profile.

**Key-words:** Insulin resistance, insulin sensitivity, minimal model, metabolic syndrome, hemorheology, plasma viscosity, erythrocyte aggregability

## **2. Introduction**

The metabolic syndrome is a constellation of chronic disorders (hypertension, abnormalities of blood clotting, low HDL and high LDL cholesterol levels, high triglyceride levels) that collectively result in an increased risk for cardiovascular disease and premature death [1-2]. The chief abnormality present in this syndrome seems to be insulin resistance, which occurs primarily in the liver as a result of fat accumulation in the portal territory [3]. As a result, insulin levels become elevated in the body's attempt to overcome the resistance to insulin. The elevated insulin levels lead, directly or indirectly, to the other metabolic abnormalities seen in these patients.

This syndrome is associated with hemorheologic abnormalities [4], which seem more and more explained rather by its various symptoms than by insulin resistance that represents theoretically the core of the syndrome [5].

Due to the technical difficulty and cost to correctly measure insulin resistance, standardized scores have been proposed for the diagnosis of this disease. One of the most widely employed of these scores is the « NCEP-ATPIII » score [6]. In this study we aimed at defining the specific hemorheologic profile of insulin resistance and hyperinsulinemia by separating a sample of 90 subjects into 4 subgroups according to this standardized classification.

## **3. Materials and Methods**

In this study we investigated a sample of 90 subjects classified according to the clinical score « NCEP-ATPIII ». Subjects were outpatients attending our unit of exploration of metabolic diseases. Their characteristics are shown on Table 1.

Based on the guidelines from the 2001 National Cholesterol Education Program Adult Treatment Panel (ATP III), any three of the following traits in the same individual meet the criteria for the metabolic syndrome: (a) Abdominal obesity: a waist circumference over 102 cm (40 in) in men and over 88 cm (35 inches) in women. (b) Serum triglycerides 150 mg/dl or above. (c) HDL cholesterol 40mg/dl or lower in men and 50mg/dl or lower in women. (d) Blood pressure of 130/85 or more. (e) Fasting blood glucose of 110 mg/dl or above. Therefore, it is very easy to score an individual according to this list of symptoms between 0 and 5. [6]. In this study we thus used this score to stratify into 4 subgroups the group of subjects.

#### *Laboratory measurements*

Samples were analysed for serum lipids with standard routine techniques. 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 Medicatest, F-86280 Saint Benoit) [7]. The coefficient of variation of this method ranged between 0.6 and 0.8% [7]. 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 [8]. Dintenfass' 'Tk' index of erythrocyte rigidity was calculated [9]. RBC aggregation was

assessed with the Myrenne aggregometer [10] 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  $600\text{ s}^{-1}$ ).

## Statistics

Data are expressed as means  $\pm$  SEM. Correlations were performed by Pearson analysis and multiple regression analysis. Normality of parameters was assessed with the normality test of Kolmogorov and Smirnov. This test gives a K-S Distance and a p value that allow concluding that the test "passes" or "fails". A test that fails indicates that the data varies significantly from the pattern expected if the data was drawn from a population with a normal distribution. A test that passes indicates that the data matches the pattern expected if the data was drawn from a population with a normal distribution.  $P < 0.05$  was considered significant.

## 4.Results.

Results (see table 2) show no significant changes of blood rheology across classes of NCEP score despite a borderline rank correlation between RBC aggregability « M1 » and the score.

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Whole blood viscosity was mostly correlated to HDL-cholesterol ( $r=-0.353$   $p=0.007$ ) and triglycerides ( $r=0.574$   $p=0.0001$ , see Fig.1). Plasma viscosity was correlated with total cholesterol ( $r=0.3359$   $p=0.02$ ) and with LDL-cholesterol ( $r=0.357$   $p=0.03$ ). RBC rigidity « Tk » was negatively correlated to HDL-cholesterol ( $r=-0.430$   $p=0.007$ , see Fig.2). Aggregability « M » was correlated to total cholesterol ( $r=0.356$   $p=0.01$ ) and « M1 » to HDL-cholesterol ( $r=-0.406$   $p=0.006$ ).

## 5. Discussion

This study thus shows no significant changes of blood rheology across classes of NCEP score despite a borderline rank correlation between RBC aggregability « M1 » and the score. By contrast several correlations between the lipid profile and blood rheology are evidenced. While triglycerides are strongly correlated to whole blood viscosity, total cholesterol and LDL cholesterol are correlated to plasma viscosity and RBC aggregability. Besides, HDL-cholesterol is negatively correlated to whole blood viscosity, RBC rigidity and RBC aggregability.

These findings of strong correlations between all these viscosity factors and the lipid profile are not new. The major effect of lipoprotein subfractions has been studied in vitro [12] and was found to be a major determinant of erythrocyte aggregation. In primary hyperlipoproteinemias [13] their effect on plasma viscosity has been demonstrated. In

common obesity [14] we have reported relationships between lipid profile and hemorheologic modifications associated with overweight, and this has also been shown in children, in whom weight loss has a correcting effect [15]. In type II hyperlipoproteinemia, LDL cholesterol levels have been shown to impair blood rheology and this effect is reversed by the HMG-CoA inhibitors lovastatin [16], atorvastatin [17] and simvastatin [17]. Another study on severe hypertriglyceridemia has shown that a decrease in triglycerides lowers plasma viscosity [18].

Actually, a critical review of all the studies on the influence of circulating lipids and lipoproteins on red cell rheology and plasma viscosity would probably be interesting, since all these clinical situations include a wide variety of lipid disorders and are generally associated with slightly different hemorheologic profiles.

Since the NCEP-ATPIII score includes the major clinical components of the metabolic syndrome (abdominal obesity, serum triglycerides, HDL cholesterol, high blood pressure, hyperglycemia) and that all of these disorders are well known to impair blood rheology, it is surprising to find no correlation between this scoring and the hemorheologic profile. One could expect that all the correlations discussed above would result in a progressive increase in blood viscosity across the NCEP-ATPIII score classes. However, we are unable to evidence a significant relationship between this score and the hemorheologic profile. Since our sample of subjects is not very large, this may be due to a type-2 error, but the results suggest that if such a relationship exists, it is surely very weak. An explanation for this weakness could be that the effects of abdominal obesity, serum triglycerides, cholesterol, high blood pressure, and hyperglycemia on blood rheology are not adding their separate influence on hemorheological profile but that the hemorheologic effects of abdominal obesity and hyperglycemia are mostly explained by their association with a deleterious lipid profile.

Thus, despite previously described correlations with glucose disposal parameters, the hyperviscosity syndrome of the metabolic syndrome is not proportional to its clinical scoring, and is found to be mostly related to the lipid profile.

## **6. References.**

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**Table 1**

General characteristics of study subjects (mean $\pm$ SEM). Abbreviations: BMI: body mass index (=weight/height<sup>2</sup>); WHR: waist to hip ratio.

| AGE        | WEIGHT     | HEIGHT     | BMI                  | WHR         | FAT MASS   |
|------------|------------|------------|----------------------|-------------|------------|
| (years)    | (kg)       | (m)        | (kg/m <sup>2</sup> ) |             | (kg)       |
| 52.7       | 85.5       | 1.63       | 32.9                 | 0.87        | 35.57      |
| $\pm 1.25$ | $\pm 1.98$ | $\pm 0.01$ | $\pm 0.9$            | $\pm 0.013$ | $\pm 1.37$ |

**Table 2**

Hemorheological parameters across the NCEP-ATPIII score classes. No significant difference can be detected.

| Score                                    | 1 (n=14)  | 2 (n=22)  | 3 (n=7)   | 4 (n=11)   |
|------------------------------------------|-----------|-----------|-----------|------------|
| $\eta_b$ 1000 s <sup>-1</sup><br>[mPa.s] | 2.68±0.12 | 2.84±0.11 | 3.16±0.30 | 3.04±0.22  |
| Hct (%)                                  | 41.4±1.3  | 40.9±1    | 44.4±1.9  | 42.8±1.5   |
| $\eta_p$ mPa.s                           | 1.41±0.03 | 1.43±0.03 | 1.36±0.05 | 1.41±0.03  |
| Tk                                       | 0.57±0.05 | 0.58±0.02 | 0.6±0.04  | 0.605±0.04 |
| M                                        | 5.4±0.4   | 5.1±0.3   | 5.6±0.4   | 6.1±0.4    |
| M1                                       | 10.0±0.5  | 10.2±0.8  | 10.5±0.5  | 11.3±0.5   |

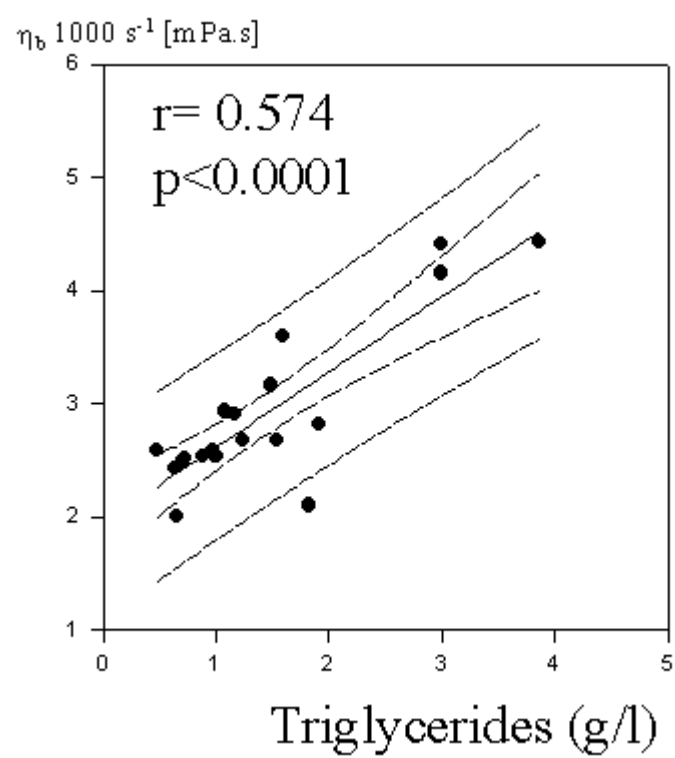


Fig. 1

Correlation between whole blood viscosity and triglycerides.

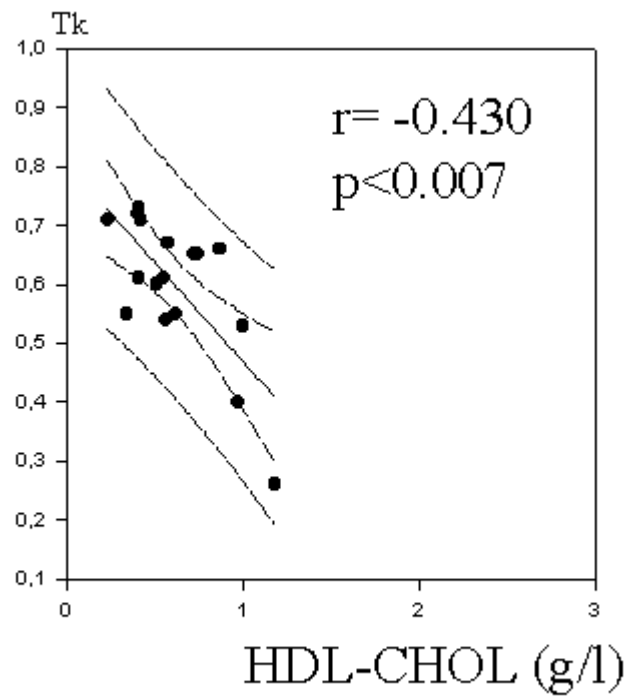


Fig. 2

Negative correlation between Dintenfass's viscometric red cell rigidity index "Tk" and high density lipoprotein cholesterol.