

RELATIONSHIPS BETWEEN METABOLIC  
AND HEMORHEOLOGIC MODIFICATIONS  
ASSOCIATED WITH OVERWEIGHT

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**ABSTRACT**

Metabolic modifications associated with the syndrome 'X' of Reaven (insulin resistance-hyperinsulinemia syndrome) might explain at least in part the rheologic changes of obesity. This hypothesis was investigated in 101 subjects (38 overweight (Ob+), 22 obese (Ob++) and 41 controls) during a standardized breakfast test. Baseline values of plasma viscosity ( $\mu\text{Pl}$ ), blood viscosity at high shear rate, RBC filterability (Hanss' hemorheometer), hematocrit, RBC aggregation (Myrenne aggregometer) serum cholesterol and triglycerides were measured. When compared to controls, obese patients Ob+ and Ob++ had a higher hematocrit ( $+2.5\%$   $p < 0.02$ ). Plasma viscosity was similar in the three groups. Blood viscosity (at both native and corrected (45%) hematocrit) is higher in Ob++ (respectively  $p < 0.01$  and  $p < 0.04$ ) while Ob+ have values similar to controls. The ratio of blood viscosity (at corrected hematocrit 45%) on plasma viscosity which is related to RBC deformability is higher in Ob++ ( $p < 0.02$ ). On the whole group of subjects ( $n = 101$ ) blood viscosity (at corrected hematocrit 45%) was correlated to baseline insulinemia ( $r = 0.225$   $p < 0.03$ ) and triglyceridemia ( $r = 0.228$   $p < 0.02$ ), but it failed to be correlated to blood pressure in obese subjects. Serum cholesterol was correlated to RBC rigidity in controls. RBC aggregation 'M' index was correlated with body mass index ( $r = 0.265$   $n = 88$   $p = 0.0124$ ), cholesterol ( $r = 0.21$   $n = 88$   $p = 0.0462$ ), baseline insulinemia ( $r = 0.37$   $n = 83$   $p = 0.0007$ ) and fibrinogen ( $r = 0.35$   $n = 40$   $p = 0.028$ ). 'M1' index was correlated to triglycerides ( $r = 0.21$   $n = 88$   $p = 0.045$ ) and baseline insulinemia ( $r = 0.24$   $n = 83$   $p = 0.0322$ ). These findings suggest that (a) the main hemorheologic disorders in obese are a higher hematocrit and RBC rigidity; (b) metabolic disorders (hyperinsulinemia, hypertriglyceridemia, i.e. signs of the "X" syndrome of Reaven) are associated with hyperviscosity; (c) thus, we hypothesize that hyperviscosity may be a mechanism involved in the vascular risk of hyperinsulinemia (or a marker of such a risk).

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**Key words:** Blood viscosity, hemorheology, erythrocyte deformability

## **INTRODUCTION**

Since the early sixties, it has been known that hyperinsulinemia is a characteristic feature of obesity (1). On the other hand, three prospective population studies on non-diabetic subjects - the Helsinki Policemen study (2), the Busselton Study (3) and the Paris prospective study (4-5) - have shown that high plasma insulin levels, either fasting or after oral glucose load, are associated with an increased risk of coronary heart disease. Interpretation of multivariate analyses including plasma insulin in these epidemiologic studies is, however, complex, owing to relatively strong correlations between plasma insulin and several other risk factors. Interaction of the predictive value of plasma insulin with other risk factors, such as obesity, plasma lipids and lipoproteins, and blood pressure also deserves consideration. For instance in the Paris study, it was found that high plasma insulin levels are predictive of increased risk of CHD in obese subjects but not in lean subjects (5). Thus, although epidemiological evidence for a pathogenetic role of hyperinsulinemia in atherogenesis has become stronger over the last years, the pathophysiologic mechanism remains uncompletely understood (5). While hyperinsulinemia has direct atherogenetic effects by its action on the cell biology of the vessel wall (6), it is known to be associated with some other atherogenetic abnormalities (increased blood pressure, impaired glucose tolerance, abdominal obesity, hyperlipidemia) which can be also responsible for the vascular risk (5). Recently, a synthesis of this situation has been proposed, with insulin resistance (not yet assessed in epidemiological studies) being the common link between all these atherogenetic disorders which become all parts of a new syndrome called "syndrome X" and more linked with the vascular risk than hyperlipidemia alone (7-8).

Most of the symptoms of this syndrome X have been shown to be associated with hemorheologic abnormalities (9). In the case of obesity, even when blood pressure, glucose and lipids are within the normal range, these rheologic modifications have been carefully described (10-24). Whether abnormal blood rheology can be considered as a symptom of syndrome X, and involved in the cardiovascular risk of this pathology, has not been yet investigated. This study was conducted in order to clarify the links between hemorheologic abnormalities of obesity and hyperinsulinemia.

## **SUBJECTS AND METHODS.**

### **Subjects**

One hundred and one subjects were studied (31 males, 70 females, age: 22-61). Sixty were obese patients undergoing a nutritional and metabolic check-up in our outpatient unit before they were given a diet. The 41 others were healthy subjects with normal weight who were volunteers for making up a large control group for our standardized breakfast test. The sixty obese subjects were divided as follows: 38 had moderate overweight (body mass index between 25 and 31 kg/m<sup>2</sup>) and constituted the group Ob+. Twenty-two had a marked overweight (body mass index of 31 kg/m<sup>2</sup> or more) and constituted the group Ob++.

### Protocol

No alimentary restriction was imposed; however, subjects were asked to fast for 12 hr before commencement of the test at 8:30 A.M. A cannula was placed in the cephalic vein at the level of the cubital fossa for blood sampling at various times. They ate a standardized breakfast containing 2070 kilojoules with 9.1 % proteins, 27.5 % lipids, and 63.4 % carbohydrates. The meal was composed of bread (80 g), butter (10 g), jam (20 g), skimmed concentrated milk (80 ml), sugar (10g) and powder coffee (2,5 g). Blood samples were drawn twice before the meal and at 15, 30, 45, 90, 120, 150 and 180 min following the onset of the meal.

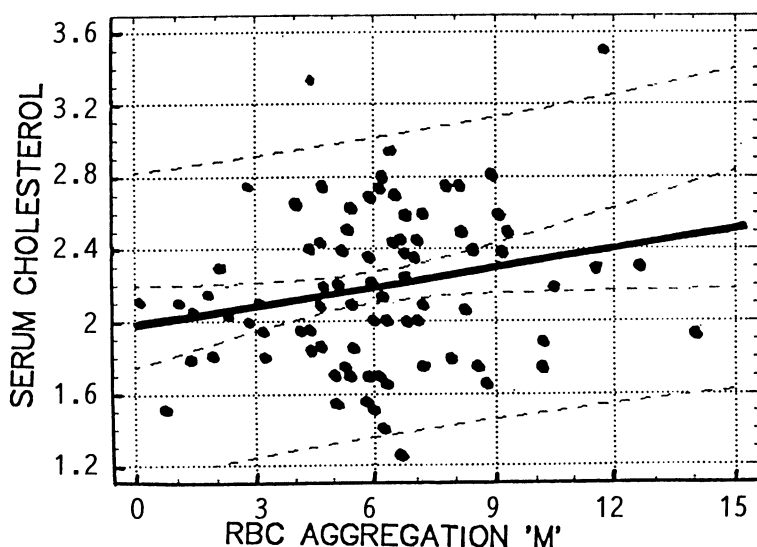


FIG.1

*Correlation between RBC aggregation index 'M' and serum cholesterol.  $r=0.21$   
 $p=0.04663$ .*

### Laboratory measurements

All samples were analyzed for insulin by a radioimmunoassay (kit SB-INSI-1 from the international CIS) and glucose with a Beckman glucose analyzer. The within assay coefficient of variation (CV) for insulin was determined by repetitive measurements of the same sample and was between 8.6% (low values) and 9.7% (high values). The between assay CV for insulin was between 12.5% (low values) and 14.4% (high values). The sensitivity (lowest detectable value) was 2  $\mu$ U/ml. Blood samples for hemorheological measurements (7 ml) were obtained with a large bore needle (Luer adaptor Venoject, set into the catheter) to avoid shear damage to erythrocytes. A

vacuum tube was used for blood withdrawal, with potassium EDTA as the anticoagulant. No tourniquet was used for sample drawing in order to minimize venous stasis. Viscometric measurements were performed at high shear rate ( $1000 \text{ s}^{-1}$ ) with a falling ball viscometer (MT 90 Medicatest, 37 rue de l'Ermitage F-86280 Saint Benoit) (25-27). Accuracy of the measurements was regularly controlled with the Carrimed Rheometer 'CS' (28) (Rhéo, 19 rue Ambroise Croizat, 91120 Palaiseau, France). The coefficient of variation of this method ranges between 0.6 and 0.8% (10 repetitive measurements of the same sample). We measured with this device apparent viscosity of whole blood at native hematocrit, plasma viscosity, and blood viscosity at corrected hematocrit (45%) according to the well known equation of Quemada (29):

$$\mu_b = \mu_{pl} \cdot (1 - 1/2 k \cdot h)^{-2}$$

where  $\mu_s$  is blood viscosity,  $\mu_{pl}$  plasma viscosity,  $h$  the hematocrit and  $k$  a shear dependent intrinsic viscosity of the red cells according to Quemada.

Two indices of erythrocyte rigidity (Dintenfass' 'Tk' and Quemada's 'k') were calculated from blood viscosity, hematocrit and plasma viscosity measured at time 0 with equations derived from those given above:

$$k = 2 \cdot (1 - \mu_r^{-0.5}) \cdot h^{-1}$$

and:

$$Tk = (\mu_r^{0.4} - 1) \cdot (\mu_r^{0.4} \cdot h)^{-1} \quad (30)$$

Where  $\mu_r$  is relative blood viscosity  $\mu_b / \mu_{pl}$ .

In addition, relative blood viscosity at fixed hematocrit 45% ( $\mu_{45r}$ ) was used as an index of RBC rigidity.

The hematocrit/viscosity ratio, an index of oxygen supply to tissues, was calculated according to Chien (31) and Stoltz (32), with  $h$  (as percentage) divided by  $\mu_b$  value at high shear rate which was determined as described above.

Erythrocyte rigidity was measured by filtration of red cells resuspended at 8% hematocrit in Tris-Albumin buffer, with the Hemorheometre MK-1 (from IMH, 2, allée du Jardin de la Cure, 95470 Saint Witz, France). This apparatus measures the the initial flow rate of a suspension of red cells (33) through  $5 \mu\text{m}$  Nuclepore sieves. Results were expressed as a relative viscosity of filtration ( $\mu_{fr}$ ) and corrected by hematocrit:

$$\mu_{fr} = (t_s/t_b)/h$$

where  $t_s$  is the time of passage of the suspension of red cells at 8% hematocrit,  $t_b$  the time of passage of the buffer alone, and  $h$  the packed cell volume (%).

### Statistics

Correlations were tested by linear regression analysis. Results are presented as mean  $\pm$  the SE of the mean. A value of  $p < 0.05$  was considered as significant. Correlations were performed using the method of least squares. Variables in the two groups were compared using the two tailed nonparametric test of Mann-Whitney for unpaired data. Significance was defined as  $p < 0.05$ . The choice of nonparametric tests was done in order to adhere the guidelines of J. Stuart (34) and the ICSH expert panel for blood rheology (35), since hemorheological parameters usually appear to exhibit a nonnormal distribution.

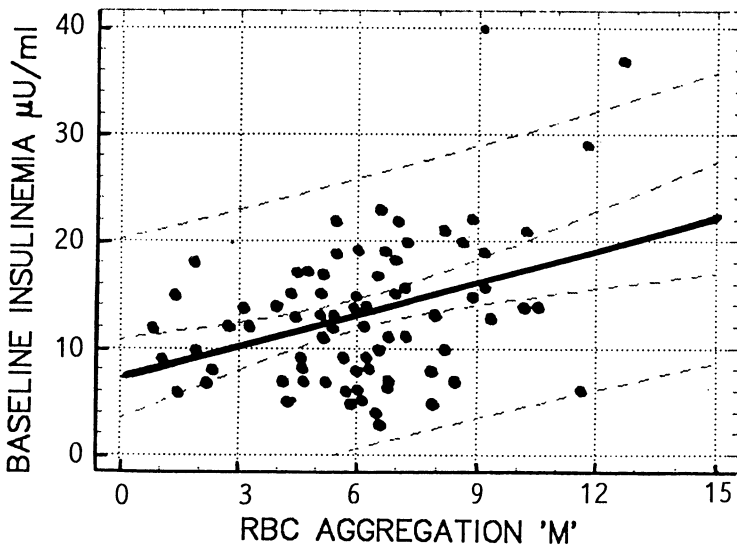


FIG.2

Correlation between baseline insulinemia and RBC aggregation index 'M'.  $r=0.37$   
 $p=0.0007$ .

### RESULTS

Table I shows the values of blood glucose, blood lipids, and fibrinogen in the three groups.

Table II shows the hemorheologic parameters measured in the three groups. Blood viscosity at native hematocrit was higher in group Ob++ than in controls ( $p<0.01$ ). Whole blood viscosity at corrected hematocrit 45% was higher in Ob+ ( $p<0.04$ ) and in the whole group of obese (Ob+ and Ob++  $p<0.05$ ) when compared to controls. Hematocrit was higher than controls in Ob+ ( $p<0.001$ ) as well as in the whole group of obese (Ob+ and Ob++ put together  $p<0.02$ ). Relative viscosity at corrected hematocrit ( $\mu_{45r}$ ) was higher than in controls in Ob++ ( $p<0.02$ ) and in the whole sample of obese ( $p<0.05$ ). It was higher in Ob++ than in Ob+ ( $p<0.02$ ). There was no statistical difference in the subgroups for plasma viscosity, WBC count, Tk and RBC filterability measured with the hemorheometre. However, a nonsignificant tendency to increase in the obese subjects was found for the two latter measurements.

TABLE I.

*Values of blood glucose, blood lipids, fibrinogen and insulin in the three groups. Values are given as mean (SEM).*

	CONTROLS	Ob+	Ob++
baseline glucose mmol/l	4.61(0.09)	5.08(0.15)	5.75(0.18)
peak glucose mmol/l	7.45(0.16)	9.24(1.01)	8.91(0.36)
triglycerides g/l	0.737(0.06)	1.17 (0.06)	1.51(0.14)
cholesterol g/l	1.842(0.07)	2.28(0.06)	2.12(0.08)
Albumin g/l	44.95(1.1)	44.17(0.81)	42.75(0.85)
fibrinogen g/l	3.5(0.15)	3.68(0.18)	3.77(0.25)
sex ratio M/F	12/29	11/27	7/15
baseline insulin $\mu$ U/ml	7.72(0.7)	11.6(0.76)	18.76(1.71)
peak insulin $\mu$ U/ml	52.61(5.37)	93.49(5.95)	94.5(10.25)

The following statistical correlations were found. Whole blood viscosity at corrected hematocrit was correlated to serum triglycerides in the whole group of subjects ( $r=0.228$   $p<0.04$ ). Cholesterol was correlated to RBC rigidity index 'Tk' only in controls (32 values,  $r=0.427$   $p<0.02$ ). This correlation was no longer found in obese patients ( $r=0.02$  n.s.) neither it was in the whole 101 subjects ( $r=0.118$  n.s.). Red cell rigidity index obtained by filtration correlated with cholesterol neither in obese ( $r=0.201$  n.s.) nor in controls ( $r=0.103$  n.s.) and was also decorrelated in the whole population studied ( $r=0.167$  n.s.). Corrected blood viscosity at hematocrit 45 was correlated with baseline insulinemia ( $r=0.255$   $p<0.03$ ). RBC aggregation showed the following significant correlations: 'M' index was correlated with body mass index ( $r=0.265$   $n=88$   $p=0.0124$ ), cholesterol ( $r=0.21$   $n=88$   $p=0.0462$ ), baseline insulinemia ( $r=0.37$   $n=83$   $p=0.0007$ ) and fibrinogen ( $r=0.35$   $n=40$   $p=0.028$ ). 'M1' index was correlated to 'M' ( $r=0.673$   $n=88$   $p=0.0124$ ), triglycerides ( $r=0.21$   $n=88$   $p=0.045$ ), baseline insulinemia ( $r=0.24$   $n=83$   $p=0.0322$ ) and serum free thyroxine concentration ( $r=0.38$   $n=30$   $p=0.0386$ ). There was a tendency to a correlation between hematocrit and fibrinogen ( $r=-0.289$   $n=40$   $p=0.07$ ). Plasma viscosity was correlated to fibrinogen ( $r=0.327$   $n=40$   $p=0.039$ ) and glycemia at baseline ( $r=0.238$   $p=0.05$ ). Blood pressure was not correlated with rheologic parameters in this study.

## DISCUSSION

The standardized breakfast test which has been used in this study is derived from the test developed by the team of P.J. Lefèbvre (36). We introduced some modifications in meal composition (37) in order to fit with average french habits. The quantity of glucids (76g) was chosen in order to obtain a similar increase in blood glucose than during oral glucose tolerance test (75g). We reported elsewhere preliminary evidence that this breakfast test, in obese subjects, can give similar informations than OGTT with a more physiological procedure (37). It does not suppress all the psychological and sensorial background of normal meals (38). Thus, it is both more physiological and better tolerated than classical OGTT for the assessment of glucose tolerance. In such a study dealing with the 'Syndrome X' we postulated that it was the accurate tool for the metabolic check-up of patients.

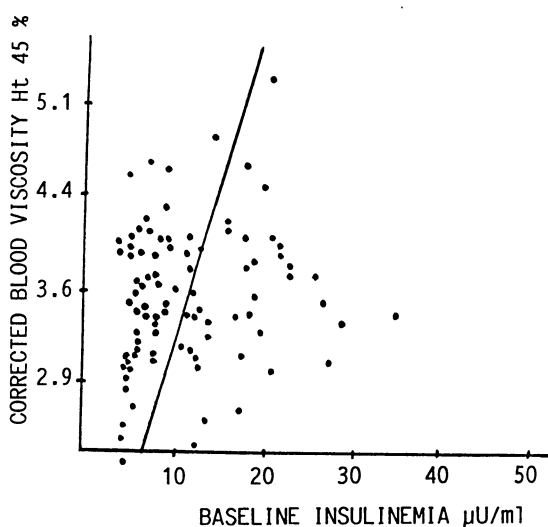


FIG. 3

*Correlation between baseline insulinemia and corrected blood viscosity at Ht 45%.  $r=0.225$   $p<0.03$ .*

Our finding of hemorheologic abnormalities in obese patients when compared with normal weight control subjects is in agreement with several previous papers (12, 17, 16-18, 20). It has been generally reported that they existed even in 'isolated' obesities, i.e. in patients with overweight and without any other sign of syndrome X (impaired glucose tolerance, hyperlipidemia, hypertension, coronary heart disease), suggesting that they were not a sign of a disease associated to obesity but rather a consequence of

overweight (20). However, in these isolated obesities, relationships with the plasma protein pattern (20, 24) and with hyperinsulinism (21-22) have been reported, even when these parameters are not abnormal enough to be considered as pathologic.

Karam et al (1) in 1963, reported increased plasma insulin concentrations in obese subjects compared with lean controls. Subsequent studies have shown that the hyperinsulinism of obese subjects is due, in part, to a decreased response of the tissues to insulin (39). However, the mechanisms responsible for hyperinsulinemia in obese subjects are incompletely understood (40). Evidence is growing that hyperinsulinism and insulin-resistance (which may potentiate each other in a positive vicious circle) are responsible for the various signs of the syndrome X (2-8) which appears to be a common finding in obesity (7). Thus, the correlations we report in this paper between insulin and various hemorheologic parameters may support the following pathogenetic scheme: hyperinsulinism/insulin resistance, both cause and/or consequence of overweight, induces a metabolic pattern with hyperlipidemia and impaired glucose tolerance. This pattern could be responsible for the hemorheologic abnormalities which could in turn be an additional risk factor for cardiovascular disease (41-42).

TABLE II.

*Values of hemorheological parameters in the three groups. Values are given as mean (SEM). Comparison vs controls \*\*  $p < 0.02$ . \*\*\*  $p < 0.01$ . Test of Mann Whitney.*

	CONTROLS	Ob+	Ob++
blood viscosity mPa.s.	2.9(0.06)	2.97(0.08)	3.22(0.12)***
plasma viscosity mPa.s	1.27(0.017)	1.22(0.02)	1.26(0.04)
RBC rigidity $\mu$ r	0.25(0.02)	0.706(0.26)	2.22(1.84)
RBC rigidity Tk	0.52(0.01)	0.55(0.02)	0.56(0.07)
RBC rigidity $\mu$ 45r	1.906(0.05)	1.98(0.03)	2.11(0.04)**
Hematocrit %	38.47(0.72)	41.82(0.65)***	39.45(1.41)
WBC count	7195(378)	6872(312)	7283(633)
h/ $\mu$	0.161 (0.006)	0.155(0.003)	0.175 (0.02)
RBC aggregation M	5.35(0.96)	6.02(0.33)	6.36(0.63)
RBC aggregation M1	9.48(1.27)	10.61(0.92)	10.25(0.93)

In this study we did not find a correlation between fibrinogen and insulinemia. This is in agreement with a paper stating that hepatic fibrinogen synthesis is not insulin dependent, whereas albumin synthesis is increased by insulin (43). If increased fibrinogen is also found (in some studies) associated to hyperinsulinic states (and probably involved in the cardiovascular risk) it is probably dependent on other mechanisms such as low fibrinolysis (19).

It should be stressed that insulin profiles before and during oral glucose tolerance tests or breakfast tests are probably not a good marker of insulin resistant states (2-8) although they have been yet the only used in epidemiological studies. Other more sophisticated methods using glucose clamp or intravenous glucose tolerance tests with appropriated mathematical modelling will be required to assess the relationships between insulin sensitivity in se and blood rheology. Such investigations are in progress in our department.



Notwithstanding, this study suggests that hyperviscosity, as a consequence of the metabolic pattern of hyperinsulinism (and presumably insulin resistance) in isolated obesity, may be a novel symptom of the 'syndrome X'. We plan to further characterize in a more large series of patients the 'hierarchy' of the interrelationships between overweight, hyperinsulinism, lipid and sugar minor abnormalities, and blood rheology, as well as the influence of insulin sensitivity measured by more specific tests on rheologic parameters.

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