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Insulin resistance as a hemorheologic disease

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Abstract

The insulin resistance syndrome is associated with hemorheologic abnormalities whose understanding is complex, since rheological properties of plasma and blood cells are to a large extent determined by the surrounding milieu: physicochemical factors, metabolism and hormones. It is thus difficult to delineate the specific role of adiposity, endothelial dysfunction, and the hormonal disturbance by its own in this complex picture. Nevertheless, low insulin sensitivity which is associated with both increased body fat and increased circulating lipids, together with impaired fibrinolysis, is characterized by a mild hyperviscosity syndrome. Those rheological alterations are more closely related to insulin resistance than to the clinical scoring of the metabolic syndrome. Overall adiposity increases plasma viscosity and RBC aggregability, while abdominal adiposity increases hematocrit. Low insulin sensitivity is associated with increased erythrocyte aggregability. When glucose tolerance declines, there is also an increase in plasma viscosity. Red cell aggregability is a marker of obesity, insulin resistance and hyperinsulinemia, while plasma viscosity seems to be more related to overall glucose tolerance than to either S_I or insulinemia.

Keywords: insulin resistance, metabolic syndrome, blood, red cell aggregation, blood viscosity, red cell deformability, plasma viscosity

1. Insulin resistance and the metabolic syndrome.

People prone to abdominal obesity are known sins Hippocrates's aphorisms to be at risk for various morbidities, including diabetes and coronary heart disease. Jean Vague introduced in 1956 the concept that abdominal adiposity was associated to impaired glucose tolerance and diabetes [1], and Gerald Reaven described in 1988 the insulin resistance syndrome or 'Syndrome X', which is a clustering of known cardiovascular risk factors, including obesity, hyperglycemia, dyslipidemia and hypertension, whose common underlying mechanism appears to be a decrease in insulin sensitivity, usually termed insulin resistance [2].

Since the measurement of insulin sensitivity requires complex procedures, several clinical definitions of a "Metabolic syndrome" have been proposed (see table 1). It should be emphasized that the most recent ones omit any mention of insulin resistance and are only based on fat distribution, blood lipids, glucose tolerance and blood pressure data [3-6]. Endothelial dysfunction and low grade inflammation are actually two other common underlying disturbances in this syndrome, associated with hypertension, diabetes, insulin resistance, obesity and hyperlipidemia [7].

As discussed further below, this issue remains confusing because the clinical definitions given on Table 1 do not select only insulin resistant patients, and that a significant percentage of insulin resistant patients are free of metabolic syndrome [8].

Table 1.

Current definitions of the metabolic syndrome (after Huang, [7]).

	NCEP ATP III (2005 revision)	**WHO (1999)**	**EGIR (1999)**	**IDF (2005)**
Absolutely required	None	Insulin resistance[a] (IGT, IFG, T2D, or other evidence of IR)	Hyperinsulinemia [c] (plasma insulin >75th percentile)	Central obesity: waist circumference[d] ≥94 cm (M) or ≥80 cm (F)
Criteria	Any three of five criteria below	Insulin resistance or diabetes, plus two of five criteria below	Hyperinsulinemia , plus two of four criteria below	Obesity, plus two of four criteria below
Obesity	Waist circumference >40 inches (M) or >35 inches (F)	Waist/hip ratio >0.90 (M) or >0.85 (F), or BMI> 30 kg/m2	Waist circumference ≥94 cm (M) or ≥80 cm (F)	Central obesity already required
Hyperglycemia	Fasting glucose ≥100 mg/dl or Rx	Insulin resistance already required	Insulin resistance already required	Fasting glucose ≥100 mg/dl
Dyslipidemia	TG ≥150 mg/dl or Rx	TG ≥150 mg/dl, or HDL-C <35 mg/dl (M) or <39 mg/dl (F)	TG ≥177 mg/dl or HDL-C <39 mg/dl	TG ≥150 mg/dl or Rx
Dyslipidemia (second, separate criteria)	HDL cholesterol <40 mg/dl (M) or <50 mg/dl (F), or Rx			HDL cholesterol <40 mg/dl (M) or <50 mg/dl (F), or Rx
Hypertension	>130 mmHg systolic or >85 mmHg diastolic, or Rx	≥140/90 mmHg	≥140/90 mmHg or Rx	>130 mmHg systolic or >85 mmHg diastolic, or Rx
Other criteria		Microalbuminuria[b]		
Refs	[3]	[4]	[5]	[6]

[a] IGT, impaired glucose tolerance; IFG, impaired fasting glucose; T2D, type 2 diabetes; IR, insulin resistance; other evidence includes euglycemic clamp studies. [b] Urinary albumin excretion ≥20 μg/min or albumin-to-creatinine ratio ≥30 mg/g. [c] Reliable only in patients without T2D. [d] Criteria for central obesity (waist circumference) are specific for each population; values given are for European men and women.

2. Correlations between insulin resistance measurements and factors of blood viscosity.

Relationship between insulin sensitivity (SI) and rheology have been reported since 1994, by our team [9] and others [10]. In 22 nondiabetic women (20-54 years) presenting a wide range of body mass index (from 20 to 48 kg/m²), we assessed insulin sensitivity with the minimal model procedure, over a 180 min intravenous

glucose tolerance test with frequent sampling. The insulin sensitivity index SI (i.e. the slope of the dose-response relationship between insulin increased above baseline and glucose disposal) was negatively correlated with blood viscosity, body mass index and baseline insulinemia. These correlations were independent of each other and were not explained by relationships between insulin sensitivity and fibrinogen or blood lipids.

Moan [10] performed a stepwise regression analysis in 21 young men (mean age = 21) and found two explanatory variables related to the glucose disposal rate : body mass index (even within a normal range), and whole blood viscosity. In this study only whole-blood viscosity and body mass index were independent explanatory variables of the glucose disposal rate. Together they accounted for 63% of the variability in the glucose disposal rate in the study subjects, suggesting that hemorheologic factors were correlates to insulin sensitivity. Høieggen [11-12] confirmed these findings with the euglycemic glucose clamp. They found significant negative correlations between glucose disposal rate and whole-blood viscosity. Both insulin sensitivity and blood viscosity exhibited strong correlations with serum triglyceride, total cholesterol, and cholesterol subfractions.

All these studies provide consistent results and demonstrate that insulin sensitivity, measured with the two recognized procedures, is negatively correlated to whole blood viscosity, so that the more a patient is insulin resistant, the higher is his viscosity.

3. Which are the factors of blood viscosity underlying this correlation?

The next step in these investigations was thus to determine which factor of blood viscosity is mostly impaired in insulin resistant subjects. For this purpose we investigated 108 nondiabetic subjects the relationships between insulin sensitivity measured with the minimal model and factors of blood viscosity: hematocrit, plasma viscosity, red cell deformability and red cell aggregation [13]. Across quartiles of insulin sensitivity (defined after log transformation since distribution of insulin sensitivity was not normal), hematocrit and red cell rigidity remained stable, while aggregability and plasma viscosity (η_p) increased in the lowest quartile. insulin sensitivity appeared to be correlated to only two rheological parameters: η_p and Myrenne index of red cell aggregability M1. Among SI, fasting insulin, age and BMI multivariate analysis selected only BMI as a determinant of either whole blood viscosity, and erythrocyte disaggregation threshold, only fasting insulin as determinant of M1, and a combination of BMI and insulin sensitivity for η_p .

Thus, although age and obesity are factors of hyperviscosity, the hemorheological disturbances found in insulin resistance are not fully statistically "explained" by those two factors. While hyperaggregability (measured with M1) is rather related to hyperinsulinism, η_p is influenced by SI. Therefore η_p was the hemorheological parameter that in a population of nondiabetic subjects was the more closely related to insulin-resistance, although other viscosity factors may also be modified in patients exhibiting low values of insulin sensitivity [13].

On the basis of this finding we suggested that η_p may be a simple marker for the follow up of insulin-resistant states [13].

4. Is high blood viscosity rather a symptom of insulin resistance or a symptom of metabolic syndrome?

What makes a little confusing the issue of "Metabolic syndrome", "Insulin resistance syndrome" and "Syndrome X", is that there are three possibilities to define it : on the basis of a measurement of insulin sensitivity, on the basis of a surrogate of insulin sensitivity, or on the basis of a purely clinical classification that does no longer take into account the insulin and insulin sensitivity status. Clearly, these three approaches do not select the same patients [14]. Initially, G. Reaven [15] defined an "insulin resistance syndrome" as a cluster of abnormalities responsible of higher cardiovascular risk. However, further definition of the 'Metabolic Syndrome', although they aimed at refer to the same clinical entity, did no longer mention insulin resistance in the criteria [16, 17] and it became rapidly obvious that this later approach did not select only insulin resistant patients, while some insulin resistant patients were not classified as suffering from the metabolic syndrome. Despite the simplicity of use of the new definition, some leading authors still insisted on the fact that insulin resistance is really the core of a cluster of deleterious abnormalities. A defect in insulin action associated with a compensatory increase in insulin secretion, and therefore hyperinsulinemia, results in impaired glucose tolerance or type 2 diabetes, obesity, dyslipidemia, coronary artery disease and hypertension [18, 19]. Therefore, insulin resistance and metabolic syndrome are two distinct, although closely related, concepts.

We tried to delineate the combined effects of obesity, insulin resistance, and hyperinsulinemia in 157 nondiabetic subjects divided in 6 groups according to BMI (cut-off point 25 kg/m²) and insulin sensitivity measured with the minimal model and divided into quartiles (lowest quartile, highest quartile, and the two middle quartiles put together). Thus, we investigated the effect of varying levels of insulin sensitivity with or without obesity. Results showed that both obesity and insulin resistance impair blood rheology by inducing alterations in on red cell rigidity and plasma viscosity. Whole blood viscosity at high shear rate reflects rather obesity than insulin resistance. In this sample erythrocyte aggregation seemed to be rather a marker of hyperinsulinemia [20].

In another study, we classified a sample of 90 subjects into 4 subgroups according to the clinical score "NCEP-ATPIII" of metabolic syndrome. Results show no significant changes of blood rheology across classes of NCEP score despite a borderline rank correlation between erythrocyte aggregability and the score. This study thus suggested that the hyperviscosity syndrome of the metabolic syndrome is not proportional to its clinical scoring. By contrast we found the classical correlations between blood viscosity and blood lipid profile, suggesting that the individual items of the syndrome are better correlates of blood rheology than its clinical scoring [21].

Therefore, factors of blood viscosity are correlated to insulin resistance but not to the score of the metabolic syndrome, consistent with the discrepancy between the two concepts that was pointed out by several authors [8, 14, 18]. All this can be summarized by the statement that blood rheology is likely to be a marker of insulin resistance rather than a marker of the metabolic syndrome. Obviously, lipid abnormalities, that directly influence erythrocyte rheology [3] play a major role in this story, as does obesity.

5. Is high blood viscosity rather a symptom of insulin resistance or hyperinsulinemia?

Another confusing issue is that insulin resistance is associated with a compensatory increase in insulin secretion, and thus hyperinsulinemia, due to the physiological feedback loop between insulin sensitivity and insulin secretion pointed out by the team of RN Bergman [22-23]. This physiological relationship underlies the validity of 'surrogates of insulin sensitivity' that have been developed in order to easily measure insulin resistance without performing a dynamic test [24]. Actually indices based on fasting insulin have been demonstrated to correctly fit with insulin sensitivity measurements in some situations like polycystic ovary syndrome or nondiabetic obesity, suggesting that they really could help to evaluate insulin sensitivity over a wide range of clinical situations. However, there are clearly situations of complete discrepancy between insulin sensitivity and indices based on insulin, such as trained athletes, reactive hypoglycemia, and diabetes,

so that the general use of insulin as a mirror of insulin sensitivity should not be recommended outside of conditions where its validity has been well demonstrated [25]. However, although hyperinsulinemia and insulin resistance are reciprocally related to one another, the association is not constant [26]. Therefore, some studies showing relationships between insulin resistance and other parameters, when they use these surrogates rather than a dynamic measurement of insulin sensitivity, actually reflect a relationship of these parameters with hyperinsulinemia.

Recently, Ferrannini and Balkau [26] investigated the issue of the separate effect of insulin sensitivity measured with glucose clamp and insulinemia in 1308 non-diabetic subjects with a wide range of age and body mass index. They defined three situations. 40% of the population had insulin resistance and/or hyperinsulinemia. In this subgroup 60% of subjects had the two abnormalities, but there were subjects with insulin resistance but without hyperinsulinemia and others with hyperinsulinemia but without insulin resistance. Their clinical phenotypes were slightly different. Subjects with 'pure' insulin resistance had a more central fat distribution and presented evidence of excessive lipolysis and endogenous glucose production. Subjects with 'pure' hyperinsulinemia had suppressed lipolysis, endogenous glucose production and insulin clearance, higher values of systolic blood pressure and lower values of serum HDL-cholesterol concentrations. The only abnormality common to both phenotypes was the presence of raised serum triglycerides concentrations. This study supported the idea of three different subgroups of individuals in a non-diabetic population, and suggested that hyperinsulinemia and insulin resistance carry distinct pathogenic potential in terms of the components of the insulin resistance syndrome [26].

Actually, this classification of patients can be criticized and considered rather as a sequence of steps than separate phenotypes (RN Bergman, personal communication). According to Bergman's *'portal hypothesis'* of insulin resistance [27-28], the natural history of this syndrome can involve a first stage of purely hepatic insulin resistance with compensatory hyperinsulinism (ie the phenotype of 'pure' hyperinsulinemia), followed by a generalized insulin resistance with compensatory hyperinsulinism (the phenotype of insulin resistance plus hyperinsulinemia), and then due to beta-cell progressive failure, a situation of 'pure' insulin resistance, in which insulin resistance is no longer compensated by hyperinsulinemia.

Notwithstanding, this leaded us to investigate the same issue for blood rheology, ie, are they different pictures according to the insulin status ('pure' hyperinsulinemia, 'pure' insulin resistance, insulin resistance plus hyperinsulinemia) [29]. A sample of 81 subjects swas divided into 4 subgroups according to quartiles of insulin sensitivity (SI) (measured with the minimal model) and baseline insulin. Results show that (1) values of insulin sensitivity within the upper quartile are associated with low blood viscosity and plasma viscosity; (2) that low insulin sensitivity regardless insulinemia is associated with increased erythrocyte aggregation indexes; (3) that when low insulin sensitivity is associated with hyperinsulinemia (insulin the upper quartile and insulin sensitivity in the lower) there is a further increase in blood viscosity due to an increase in plasma viscosity. Interestingly, hematocrit was not related to insulin sensitivity nor insulinemia.

This study shows thus that low insulin sensitivity is associated with increased red cell aggregation while hyperinsulinemia is associated with increased plasma viscosity.

We further reassessed this issue in a larger series of 335 subjects of both genders [30] with the intravenous glucose tolerance test. Minimal model analysis allows the calculation of SI, insulin response, and an overall glucose tolerance parameter termed "disposition index" (DI) that measures whether insulin response is adequate or not for the level of insulin sensitivity. SI was only correlated (negatively) with red cell aggregation. Fasting insulin was also correlated (positively) with red cell aggregation disaggregation thresholds. Fasting DI (Si x fasting insulin) is negatively correlated to red cell aggregation but also positively to whole blood viscosity and hematocrit. Stimulatory DI (Si x insulin peak) fails to be correlated with any parameter of red cell aggregation but is negatively correlated to whole blood viscosity and plasma viscosity.

This study confirms that red cell aggregability is associated with insulin resistance and hyperinsulinemia, but plasma viscosity seems to be more related to overall glucose tolerance than to either SI or insulinemia.

6. Fibrinogen and insulin sensitivity

Since fibrinogen is a major determinant of blood rheology, we also studied the relationships between insulin sensitivity and plasma fibrinogen. We found that there was a fair negative correlation between insulin sensitivity and plasma fibrinogen. Using partial correlation analysis, the negative relation between insulin sensitivity and fibrinogen was maintained independently from the body mass index [31-32].

7. Improving insulin sensitivity improves blood rheology

Exercise is one of the key treatment of the metabolic syndrome [33] and is a major insulin sensitizer [34]. In addition it is one of the stronger available tools for improving blood rheology [35-37]. We performed two studies about the effects of endurance training on the hemorheological aspects of the metabolic syndrome [38-39]. The training procedure was based on Brooks and Mercier's "crossover concept" [40] and thus on the notion of a power intensity that elicits a maximal rate of lipid oxidation (LIPOXmax) that can be determined with graded exercise calorimetry [41]. Exercise is targeted at this level, resulting in a selective improvement in the ability to oxidize fats at exercise [41]. Interestingly, the ability to oxidize lipids at exercise seems to be associated with lower blood viscosity and thus a favorable hemorheologic profile [42]. Changes in erythrocyte rigidity appeared to reflect weight loss and decrease in LDL cholesterol. Plasma viscosity was related to cholesterol and its training-induced changes are related to those of the maximal aerobic capacity $VO_{2\,max}$, but not to lipid oxidation. These two studies show that, consistent with observations in athletes, the metabolic and ergometric improvements induced by training reduces plasma viscosity in sedentary, insulin resistant patients, ie the parameter that appeared in our first studies to be more related to insulin resistance itself. Plasma viscosity appears to mirror metabolic disturbances, since it is correlated to cholesterol levels. Its training-induced changes are related to those of the maximal aerobic capacity $VO_{2\,max}$, but not to lipid oxidation. Lipid oxidation seems to be rather related to erythrocyte rheology.

Besides, at those low levels training the response in hematocrit that reflects a beneficial phenomenon of "autohemodilution" [35-37] is not evidenced. Probably a longer period or a stronger training intensity is required to observe these classical hematocrit changes. [43]

8. Which comes first: insulin resistance or hyperviscosity?

At present there is no information to discuss whether hemorheology by itself is a factor governing insulin sensitivity, due to vascular effects, according to A. Baron's findings that insulin is an important muscular vasodilator [44] and that a decrease in its action in the vascular bed accounts for a significant part of glucose disposal impairment in insulin resistance. Studies presented here shows that metabolic alterations found in the metabolic syndrome and more or less associated with insulin resistance are potent modifyers of blood rheology, while the correlations between insulin resistance itself are less elusive. Since the lipid disorders typically associated with the metabolic syndrome are unequivocally able to impair by their own blood rheology, we believe that the most obvious conclusions that can be drawn from these studies is that the metabolc disturbances associated to lowered insulin sensitivity and/or hyperinsulinemia result in hemorheologic disturbances. Whether those hemorheologic disturbances are in turn able to impair insulin sensitivity via vascular effects is an attractive hypothesis but, as far as we know, poorly supported until now by the literature.

As emphasized in a recent review [7] insulin-mediated increases in endothelial NO synthase (eNOS) activity and NO production lead to increased blood flow and functional capillary recruitment that results in increased

delivery of insulin and glucose to skeletal muscle and fat, which contributes to insulin-mediated glucose uptake. Thus, when endothelial dysfunction occurs and vascular redistribution effects of insulin are blunted, there is a vicious cycle that results in further reduction in the metabolic effects of insulin in peripheral tissues owing to decreased delivery of glucose and insulin to the tissues. In addition eNOS-derived NO stimulates mitochondrial biogenesis [44-47] through a cyclic GMP-dependent mechanism [48]. A reduction in bioavailability of eNOS-derived NO might thus result in increased fat storage. In addition, eNOS-knockout mice are model ofmetabolic syndrome [45] because they combine many of its defining features, including hypertension, endothelial dysfunction, insulin resistance and obesity.

Given the hemorheologic and hemodynamic effects of NO [49] endothelial release by NO is likely to prodide a link between insulin resistance and hyperviscosity, together with the more classical lipid disorders and with the low grade inflammation that are classically described in this situation [15]. Thus, blood rheology appears more and more as an integrated reflect of the consequences of low insulin sensitivity on various body functions.

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