CHAPTER 9

Hemorheology in Insulin Resistance

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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. Low insulin sensitivity is associated with increased erythrocyte aggregability. When low insulin sensitivity is associated with hyperinsulinemia there is an increase in plasma viscosity. Among those factors, plasma viscosity appears, in multivariate analysis, to be "independently" related to insulin resistance. Moreover, plasma hyperviscosity is corrected by insulin-sensitizing procedures (such as exercise training) and is thus to some extent a marker of this disease.

1. INTRODUCTION

Biorheology is the branch of biological sciences that studies flow and deformation of biological material under the influence of the constraints which are applied to it. The branch of biorheology focusing more specifically on blood is termed hemorheology. Its purpose is therefore to study the flow of blood, in interaction with its surrounding environment, in both macro and microcirculation. One of the historical fathers of biorheology, AL Copley, used to say that hemorheology was the "missing link" among biological science, since rheological properties of blood where modified in many physiological and pathological situations, and were also likely to play a role in most body functions.

Recent physiological and pathophysiological studies have emphasized the importance of blood rheology in microcirculatory and venous hemodynamics, while large evidence emerges for an involvement of factors of blood viscosity as vascular risk factors [1, 2].

Not surprisingly, metabolic disorders are associated with hemorheologic alterations [3], so that blood reheology has been said to represent a mirror of metabolic status [3].

2. SOME FUNDAMENTAL CONCEPTS IN HEMORHEOLOGY

When blood circulates through vessels, its flow is driven by a pressure gradient between heart and periphery, and results in a force of friction over the surface of endothelium. This force results in a shear stress τ applied on the vessel wall. Due to forces of cohesion between the wall and blood and within blood itself, the velocity of blood flow is lower in the vicinity of the endothelial surface than in the middle of the vessel, thus defining the *shear rate* $\dot{\gamma}$. This difference in velocity reflects an intrinsic resistance to flow which is termed *apparent blood viscosity* $\eta = \tau / \dot{\gamma}$.

Blood viscosity η is well described by a classical robust model, Quemada's equation [4].

$$\eta = \eta_p (1 - 1/2\, k\, \phi)^{-2}$$

where ϕ is hematocrit, η_p is plasma viscosity, and $\mathbf{k}(\dot{\gamma})$ is a shear-dependent parameter quantifying the contribution of erythrocyte rheological properties to whole blood viscosity. At high shear rate $\mathbf{k}(\dot{\gamma})$ is representative of red cell rigidity (ie, the lower $\mathbf{k}(\dot{\gamma})$, the higher is erythrocyte deformability), while at low shear rate $\mathbf{k}(\dot{\gamma})$ which tends to a maximum k_0 that is proportional to the ability to form erythrocyte aggregates (red cell aggregability).

It is beyond the scope of this review to describe the physiology of these different parameters, but the important point for our purpose is that Quemada's equation states that blood viscosity actually relies on 3 factors:
- plasma viscosity η_p, explained by plasma content in proteins;
- hematocrit ϕ, which may rapidly vary according to the area of the circulation and the physiological condition,
- red cell deformability and aggregability, which, as mentioned above, are influenced by metabolism and hormones [3] have also a marked circulatory influence in the microcirculatory bed that is beyond its physical effects on whole blood viscosity [5-6].

Therefore, our review will focus on individual factors of viscosity (η_p, , ϕ, red cell deformability and aggregability) considered separately rather than η alone.

In fact, the traditional picture of circulatory physiology provided by Hagen-Poiseuille's law involves blood viscosity as a factor of peripheral resistance that might hamper blood flow if it were not easily overcome by vasomodilation. This equation can be written as follows :
$Q = (\pi \cdot R^4 \cdot \Delta P) / (8 \cdot \eta_e \cdot L)$

Where Q is the suspension volumetric flow rate through a tube of radius R under a pressure difference ΔP over the vessel length L; η_e is an effective viscosity - i.e. the ratio of shear stress to shear rate with shear stress corresponding to the force that moves the fluid layers or laminae and shear rate corresponding to the velocity gradient in the fluid. As discussed below, terms of this equation can be re-arranged in order to describe a theoretical effect of viscosity on O_2 supply to tissues. Actually, this simplistic picture of circulation is not relevant to in vivo reality, and modern investigators like Holger Schmid-Schönbein have proposed more complex models in which the effect of blood viscosity is markedly more important, as developed below [7].

3. CORRELATIONS BETWEEN INSULIN SENSITIVITY AND HEMORHEOLOGY

Relationship between insulin sensitivity (SI) and rheology have been reported since 1994, by our team [8-9] and others [10]. 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, and therefore indirectly hemodynamic, factors were correlates to insulin sensitivity.

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) ranges between 0.1 and 20.1 x 10(-4) min-1/microU/ml) i.e all the range of insulin sensitivity. SI was negatively correlated with blood viscosity ($r = -0.530$ $p < 0.02$), body mass index ($r = 0.563$ $p < 0.01$) and baseline insulinemia ($r = 0.489$ $p < 0.05$). These correlations were independent of each other and were not explained by relationships between insulin sensitivity and fibrinogen or blood lipids. Thus, we concluded that blood fluidity was correlated with insulin sensitivity when it is measured with an accurate technique, suggesting that blood hyperviscosity is a symptom of insulin resistance that might be involved in the cardiovascular risk of this syndrome.

Further works by Høieggen [11-12] confirmed these earlier findings. These authors measured whole blood viscosity in 105 healthy blood donors and found that it correlated with systolic blood pressure, cholesterol, cholesterol/HDL cholesterol ratio, triglycerides, body mass index and waist-hip ratio.

Interestingly, subjects with systolic blood pressure > 130 mmHg had higher whole blood viscosity than those with lower blood pressure [11].

In another study in healthy young men they performed a hyperinsulinemic isoglycemic glucose clamp, and found statistically significant negative correlations between glucose disposal rate and whole-blood viscosity. Both insulin sensitivity and blood viscosity exhibited strong correlations with lipid parameters (serum triglyceride, total cholesterol, cholesterol subfractions.

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

However, whole blood viscosity is an in vitro measurement that is not by itself relevant to in vivo hemodynamics. It should be analyzed as indicated above in terms of hematocrit, plasma viscosity, red cell deformability and red cell aggregation. These correlations cannot demonstrate any pathophysiological relationship, and have the only interest to point out an overall tendency to worsen blood rheology when insulin sensitivity decreases.

4. WHICH FACTOR OF VISCOSITY?

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 ($p=0.009$) and insulin sensitivity ($p=0.007$) 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].

5. INSULIN RESISTANCE OR 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]. This applies at least to the NCEP-ATPIII definition [16], since we are not aware of a similar study using the IDF definition [17]. Some degree of discrepancy exists between these two definitions, so that this needs to be studied also with the IDF definition.

At this stage of the investigation, it thus appeared that the 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 [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.

6. INSULIN RESISTANCE OR HYPERINSULINEMIA?

Even more, there is another confusing issue due to the fact 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 and insulinemia on the database of the European Group for the study of Insulin Resistance (EGIR). Using clamp-derived insulin sensitivity and fasting plasma insulin concentrations available in 1308 non-diabetic subjects with a wide range of age and body mass index, they were able to define three situations. In this cohort, 40% of the whole 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]. In this study we aimed at defining the specific hemorheologic profile of insulin resistance and hyperinsulinemia by separating a sample of 81 subjects 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 or insulinemia.

This study, consistent with the classification proposed by Ferranini and Balkau, shows thus that hyperinsulinemia and insulin resistance induce hyperviscosity syndromes which are somewhat different, although they are associated most of the time. Low insulin sensitivity increased red cell aggregation while hyperinsulinemia increases plasma viscosity.

It should be emphasized that this picture [29] was somewhat different from our first findings where plasma viscosity appeared to be the factor of blood viscosity that was the most specifically related to insulin resistance [13]. The reason for this discrepancy in studies performed on similar samples performed with the same methods of measurement of insulin, insulin sensitivity and blood rheology is unclear.

7. FIBRINOGEN AND INSULIN SENSITIVITY

Since fibrinogen is a major determinant of blood theology, 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 [30-32].

8. IMPROVING INSULIN SENSITIVITY AND BLOOD RHEOLOGY

Since exercise is one of the key treatments of the metabolic syndrome [33] and is a major insulin sensitizer [34], and in addition is one of the stronger available tools for improving blood rheology [35-37] we studied the specific effect of endurance training on the hemorheological aspects of the metabolic syndrome [38-39].

The training procedure employed in this work requires some comments. It 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 [42]. Interestingly, the ability to oxidize lipids at exercise seems to be associated with lower blood viscosity and thus a favorable hemorheologic profile [43]. Correlations found between erythrocyte deformability and the ability to oxidize at exercise more lipids may be due to effects of endurance training on lipid oxidation which may in turn modify both lipid metabolism and free radical generation, thus influencing erythrocyte rheology [43].

A first study was performed on thirty-two obese insulin resistant subjects that were tested before and after 2 months. Twenty-one of them were trained (3x45 min/wk) at the LIPOXmax and eleven served as controls. Blood rheology was unchanged in the control group while training markedly improved plasma viscosity whose mean values decrease from 1.43 mPa.s down to 1.35 mPa.s. There was no change in either hematocrit red cell rigidity or red cell aggregation. Besides, training improved body composition

with a mean weight loss of 2.5 kg that was totally explained by a loss in fat mass (-2.7 kg) while fat free mass remained unchanged, and the balance of substrates oxidation shifted towards a higher use of lipids.

Relationship among these variuos exercise-induced alterations were investigated in a second study that employed the same training protocol in 24 patients, all submitted to training [39]. This study showed that variations of whole blood viscosity at high shear rate were explained by two statistically independent determinants: hematocrit and red cell rigidity. Whole blood viscosity decreased in 16 subjects, but increased in 8, due to a rise in hematocrit. 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. Red cell aggregability reflected both the circulating lipids (Cholesterol and its fractions HDL and LDL) and the ability to oxidize lipids at exercise. Factors associated to a post-training decrease in erythrocyte aggregability were weight loss and more precisely decrease in fat mass, improvement in lipid oxidation, rise in HDL-Cholesterol, and decrease in fibrinogen. On the whole the major determinant of hemorheologic improvement was an increase in cardiorespiratory fitness ($VO_{2\ max}$), correlated with a decrease in plasma viscosity, rather than an improvement in lipid metabolism, although erythrocyte aggregability and deformability exhibited clear relationships with lipid metabolism. For which reason hematocrit increased in 30% of the patients during this kind of training remains unclear at present.

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, i.e. 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.

Another approach of the impact of therapeutic of insulin resistance on blood rheology is shown by Aksnes [43] who compared the effect of vasodilating agents on levels whole blood viscosity in the same 21 hypertensive patients with cardiovascular risk factors. Patients were randomized double-blindly to additional treatment with amlodipine 5 mg or losartan 100 mg and after 8 weeks of treatment, all patients were crossed over to the opposite treatment regimen for another 8 weeks. Although no significant differences in whole blood viscosity and blood pressure were observed between the 2 treatment regimens, a consistent trend toward lower viscosity was found at all shear rates as vasodilatory treatment was intensified (baseline to amlodipine 5 mg to amlodipine 10 mg to losartan 100 mg + amlodipine 5 mg). The author hypothesized that whole blood viscosity changes could explain improved insulin sensitivity seen on AT1-receptor blockade.

9. CONCLUSIONS: EGG OR CHICKEN?

At present there is no information to discuss whether hemorheology is by itself 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. Such a mechanism has been hypothesized [43] and cannot be ruled out. However, the bulk of 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.

10. REFERENCES

[1] Tzoulaki I, Murray GD, Lee AJ, Rumley A, Lowe GD, Fowkes FG. Inflammatory, haemostatic, and rheological markers for incident peripheral arterial disease: Edinburgh Artery Study. Eur Heart J. 2007;28(3): 354-62.

[2] Lowe GD. Virchow's triad revisited: abnormal flow. Pathophysiol Haemost Thromb. 2003; 33(5-6): 455-7.
[3] Brun JF. Hormones, metabolism and body composition as major determinants of blood rheology: potential pathophysiological meaning. Clin Hemorheol Microcirc. 2002; 26(2):63-79.
[4] Quemada D. Rheology of concentrated disperse systems. II. A model of non newtonian shear viscosity in steady flows. Rheol Acta 1978; 17 : 632-642
[5] Baskurt OK, Meiselman HJ.Blood rheology and hemodynamics. Semin Thromb Hemost. 2003; 29(5): 435-50.
[6] Baskurt OK.In vivo correlates of altered blood rheology. Biorheology. 2008;45(6):629-38.
[7] Gaudard A, Varlet-Marie E, Bressolle F, Mercier J, Brun JF. Hemorheological correlates of fitness and unfitness in athletes: moving beyond the apparent "paradox of hematocrit"? Clin Hemorheol Microcirc. 2003;28(3):161-73.
[8] Brun JF Brun, C Dupuy-Fons, JF Monnier, JP Micallef, D Bouix, C Peyreigne and A Orsetti. Blood viscosity is negatively correlated to insulin sensitivity. Biorheology 32 (1995), 387-388
[9] Brun JF, Monnier JF, Kabbaj H, Orsetti A. La viscosité sanguine est corrélée à l'insulino-résistance. J Mal Vasc (Paris) 21 (1996), 171-174.
[10] Moan, G. Nordby, I. Os, K.I. Birkeland and S.E. Kjeldsen, Relationship between hemorrheologic factors and insulin sensitivity in healthy young men, Metabolism 1994; 43: 423-427.
[11] Fossum E, Høieggen A, Moan A, Nordby G, Velund TL, Kjeldsen SE. Whole blood viscosity, blood pressure and cardiovascular risk factors in healthy blood donors. Blood Press. 1997 ; 6(3): 161-5.
[12] Høieggen A, Fossum E, Moan A, Enger E, Kjeldsen SE. Whole-blood viscosity and the insulin-resistance syndrome. J Hypertens. 1998; 16(2):203-10.
[13] Perez-Martin A, Dumortier M, Pierrisnard E, Raynaud E, Mercier J, Brun JF. Multivariate analysis of relationships between insulin sensitivity and blood rheology: is plasma viscosity a marker of insulin resistance? Clin Hemorheol Microcirc. 2001;25(3-4): 91-103.
[14] Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. Endocrinol Metab Clin North Am. 2004; 33(2):283-303
[15] Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988; 37(12): 1595-607.
[16] Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; 285:2486-2497.
[17] Alberti, KG, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition, Lancet 366 (9491) (2005), pp. 1059–1062
[18] Reaven G. Why a cluster is truly a cluster: insulin resistance and cardiovascular disease. Clin Chem. 2008; 54(5): 785-7
[19] Kashyap SR, Defronzo RA.The insulin resistance syndrome: physiological considerations. Diab Vasc Dis Res. 2007; 4(1): 13-9.
[20] Brun JF, Aloulou I, Varlet-Marie E. Hemorheological aspects of the metabolic syndrome: markers of insulin resistance, obesity or hyperinsulinemia? Clin Hemorheol Microcirc. 2004;30(3-4):203-9
[21] Aloulou I, Varlet-Marie E, Mercier J, Brun JF. Hemorheological disturbances correlate with the lipid profile but not with the NCEP-ATPIII score of the metabolic syndrome. Clin Hemorheol Microcirc. 2006;35(1-2):207-12.
[22] Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, et al.Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function.Diabetes. 1993; 42(11):1663-72.
[23] Bergman RN. Pathogenesis and prediction of diabetes mellitus: lessons from integrative physiology. Mt Sinai J Med. 2002; 69(5):280-90.
[24] Wallace TM, Levy JC, Matthews DR.Use and abuse of HOMA modeling. Diabetes Care. 2004; 27(6): 1487-95
[25] Brun JF, Raynaud E, Mercier J. Homeostasis model assessment and related simplified evaluations of insulin sensitivity from fasting insulin and glucose. Diabetes Care. 2000; 23(7):1037-8
[26] Ferrannini E, Balkau B. Insulin: in search of a syndrome. Diabet Med. 2002;19(9):724-9.
[27] Bergman RN and Ader M. Free fatty acids and pathogenesis of type 2 diabetes mellitus. Trends Endocrinol Metab 11: 351–356, 2000
[28] Kabir M, Catalano KJ, Ananthnarayan S, Kim SP, Van Citters GW, Dea MK, Bergman RN. Molecular evidence supporting the portal theory: a causative link between visceral adiposity and hepatic insulin resistance. Am J Physiol Endocrinol Metab. 2005; 288(2):E454-61.
[29] Aloulou I, Varlet-Marie E, Mercier J, Brun JF. The hemorheological aspects of the metabolic syndrome are a combination of separate effects of insulin resistance, hyperinsulinemia and adiposity. Clin Hemorheol Microcirc. 2006; 35(1-2):113-9.
[30] Worth H. Comparison of hydrofluoroalkane-beclomethasone dipropionate autohaler with budesonide Turbuhaler in asthma con-trol. Respiration 2001; 68: 517-26.
[31] Raynaud E, Brun JF, Perez-Martin A, Orsetti A, Solère M. Negative correlation between plasma fibrinogen and insulin sensitivity measured with the minimal model technique. Clin Hemorheol Microcirc. 1998 ; 18(4): 323-30.
[32] Raynaud E, Brun JF, Perez-Martin A, Mercier J. Association between fibrinogen levels and insulin resistance. Diabetes Care. 1998; 21(11): 2040-1

[33] Raynaud E, Pérez-Martin A, Brun JF, Aissa Benhaddad A, Fédou C, Mercier J. Relationships between fibrinogen and insulin resistance. Atherosclerosis 2000; 150 (2): 365-370

[34] Dumortier M, Brandou F, Perez-Martin A, Fedou C, Mercier J, Brun JF. Low intensity endurance exercise targeted for lipid oxidation improves body composition and insulin sensitivity in patients with the metabolic syndrome. Diabetes Metab. 2003; 29(5):509-18.

[35] Manetta J, Brun JF, Maimoun L, Callis A, Préfaut C, Mercier J. Effect of training on the GH/IGF-I axis during exercise in middle-aged men: relationship to glucose homeostasis. Am J Physiol Endocrinol Metab. 2002; 283(5):E929-36.

[36] Brun JF, Khaled S, Raynaud E, Bouix D, Micallef JP, Orsetti A.The triphasic effects of exercise on blood rheology: which relevance to physiology and pathophysiology? Clin Hemorheol Microcirc. 1998; 19: 89-104

[37] Brun JF. Exercise hemorheology as a three acts play with metabolic actors: is it of clinical relevance? Clin Hemorheol Microcirc. 2002;26(3):155-74.

[38] Brun JF, Bouchahda C, Chaze D, Benhaddad AA, Micallef JP, Mercier J. The paradox of hematocrit in exercise physiology: which is the "normal" range from an hemorheologist's viewpoint? Clin Hemorheol Microcirc. 2000; 22(4):287-303.

[39] Dumortier M, Pérez-Martin A, Pierrisnard E, Mercier J, Brun JF. Regular exercise (3x45 min/wk) decreases plasma viscosity in sedentary obese, insulin resistant patients parallel to an improvement in fitness and a shift in substrate oxidation balance. Clin Hemorheol Microcirc. 2002;26(4):219-29.

[40] Aloulou I, Varlet-Marie E, Mercier J, Brun JF.Hemorheologic effects of low intensity endurance training in sedentary patients suffering from the metabolic syndrome. Clin Hemorheol Microcirc. 2006; 35(1-2):333-9.

[41] Brooks GA, Mercier J. Balance of carbohydrate and lipid utilization during exercise: the "crossover" concept. J Appl Physiol. 1994; 76(6): 2253-61

[42] Brun JF, Jean E, Ghanassia E, Flavier S, Mercier J.Metabolic training: new paradigms of exercise training for metabolic diseases with exercise calorimetry targeting individuals. Ann Readapt Med Phys. 2007; 50(6): 528-34

[43] Brun JF, Varlet-Marie E, Cassan D, Manetta J, Mercier J. Blood fluidity is related to the ability to oxidize lipids at exercise. Clin Hemorheol Microcirc. 2004; 30(3-4): 339-43.

[44] Aksnes TA, Seljeflot I, Torjesen PA, Höieggen A, Moan A, Kjeldsen SE. Improved insulin sensitivity by the angiotensin II-receptor blocker losartan is not explained by adipokines, inflammatory markers, or whole blood viscosity. Metabolism. 2007; 56(11): 1470-7.

[45] Baron AD. Hemodynamic actions of insulin. Am J Physiol. 1994 ; 267(2 Pt 1): E187-202.