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ABDOMINAL OBESITY, INSULIN RESISTANCE, AND ALTERATIONS IN HEMOSTASIS

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It is now well established that abdominal obesity and insulin resistance are accompanied by alterations in hemostasis leading to a pro-thrombotic state. The latter could favour the development of atherothrombosis and deep vein thrombosis. Hemostatic abnormalities can occur at any stage of the system (Figure 1).

Abdominal Obesity and Platelet Hyperactivity

Platelet hyperactivity has been described in many studies and may be associated with insulin resistance, inflammation, and adipokines. Platelets from obese subjects are resistant to the hypoaggregating effect of insulin [1]. Urinary thromboxane metabolite excretion, which reflects platelet activation, is increased in obese women and is mainly determined by insulin resistance. It decreases after weight loss or pioglitazone treatment [2].

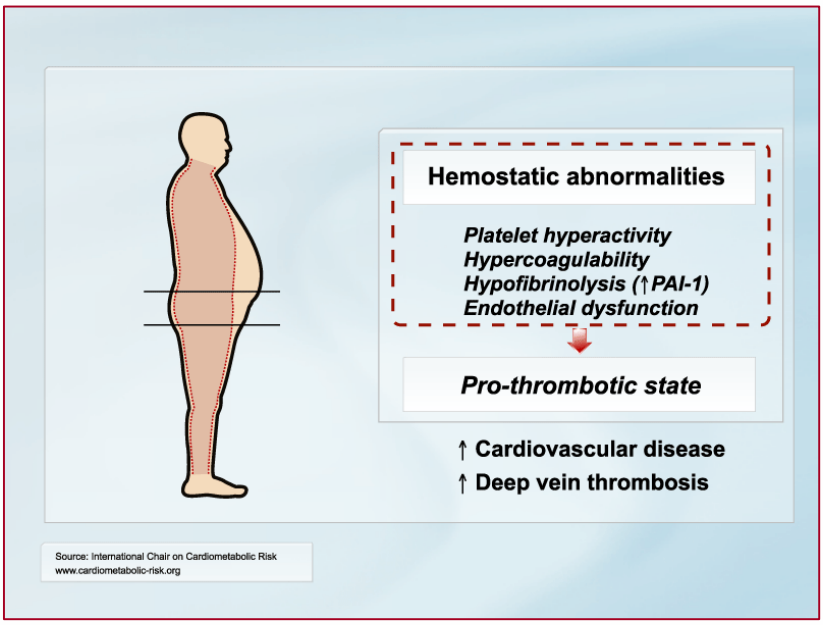

Figure 1: The metabolic syndrome and abdominal obesity

Hypertriglyceridemia and increased concentration of free fatty acids induce a proaggregating effect in vitro, and hypo-HDLemia may also influence platelet aggregation. Moreover, products of adipose tissue have been shown to modulate platelet function. Leptin promotes platelet activation [3, 4], and results obtained in adiponectin knockout mice clearly indicate that adiponectin acts as an endogenous hypoaggregating agent [5].

Platelets play a major role in the development of atherothrombosis, and their pharmacological inhibition is at the center of active cardiovascular disease and the secondary prevention of cardiovascular events. Platelet response to antiaggregating agents is variable, with some patients being resistant to the drug effect [6]. Platelet hyperactivity, which is present in patients with abdominal obesity, cannot be excluded as the cause of the heterogeneity of response to treatment. Indeed, obesity is associated with a lower sensitivity to aspirin, with a negative correlation between maximal aggregation induced by arachidonic acid, and insulin sensitivity [7] (Figure 2). Obesity is also associated with a lower sensitivity to clopidogrel [8], and the presence of type 2 diabetes decreases the biological efficiency of the aspirin-clopidogrel association [8].

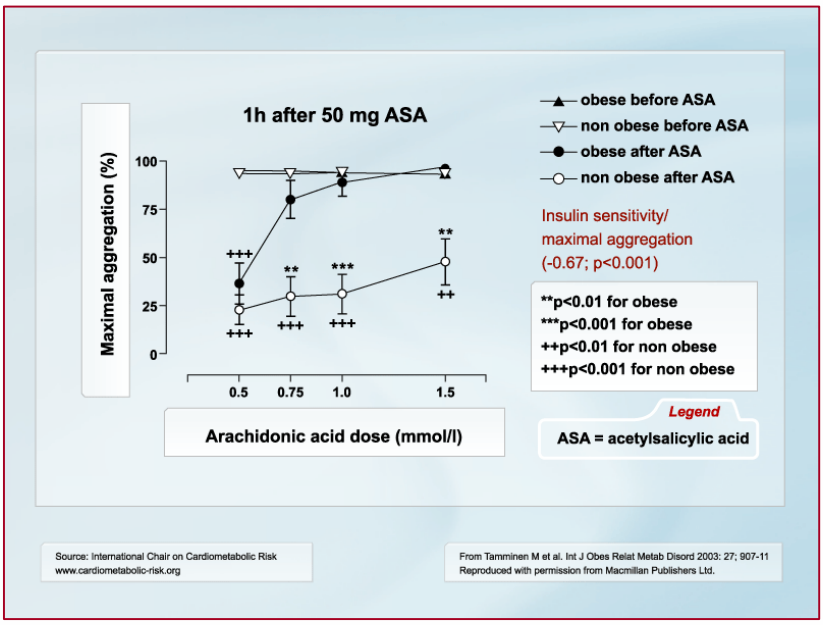

Figure 2: Is the metabolic syndrome at the origin of the aspirin resistance?

The therapeutic consequences of platelet hyperactivity are not yet well defined. Do patients with abdominal obesity need higher doses of antiaggregating agents in acute situations? Do they need twice-a-day administration? New recommendations may be forthcoming in the near future.

Abdominal Obesity and Hypercoagulability

Abdominal obesity is accompanied by coagulation abnormalities that may favour thrombus propagation.

Tissue factor (TF), the key initiator of coagulation (Figure 3), is widely expressed in atherosclerotic plaques and is found in macrophages, smooth muscle cells, extracellular matrix, and acellular lipid-rich core. The blood-borne TF encrypted on the circulating microparticles derived from vascular cells is a marker of vascular injury and a source of procoagulant activity. Evidence indicates that elevated levels of blood-borne or circulating TF have been associated with the metabolic syndrome and type 2 diabetes. Treating insulin resistance through weight loss or thiazolidinediones decreased circulating TF levels. Adipose tissue may participate in the TF pool increase when the metabolic syndrome is present. Indeed, homogenates of human adipose tissue expressed TF on macrophages and smooth muscle cells. This elevated TF expression may result from various stimulants such as hyperinsulinemia. In human volunteers, a 24-hour hyperinsulinemic clamp pro-

duces a strong increase in TF procoagulant expression in circulating monocytes with a parallel increase in plasma thrombin-antithrombin complexes and other markers of thrombin generation [9].

Plasma concentrations of vitamin K-dependent proteins are increased in obesity and decreased after weight loss [10]. These results could be explained by a potentiation of hepatic synthesis of vitamin K-dependent proteins during obesity, as a strong relationship has been reported between circulating levels of vitamin K-dependent proteins and the hepatic enzyme gamma glutamyl transferase [11]. It has also been reported that VLDL produced in excess during abdominal obesity supports activation of factor VII by the Xa/Va complex; this could slow down the clearance of factor VII.

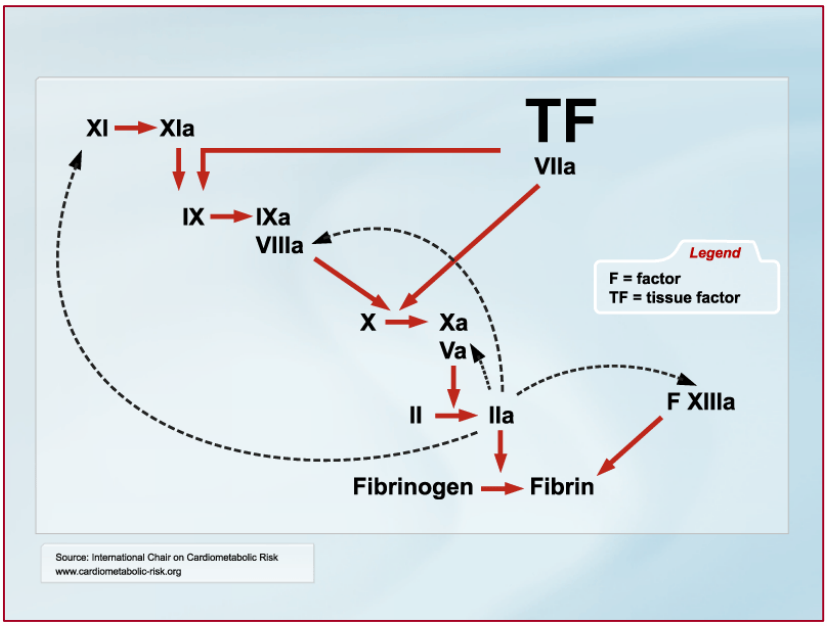

Figure 3: Tissue factor as a key initiator of coagulation

Plasma factor VIII and fibrinogen levels correlate with measures of obesity [12]. Plasma concentration of fibrinogen depends more on the fat mass than on fat repartition. It has been proposed that the increase in interleukin (IL)-6 produced by macrophages of adipose tissue and adipocytes themselves is responsible for the slight increase in hepatic synthesis of fibrinogen in obese persons [13]. Interestingly, HDL was shown to attenuate the expression of tissue factor and down regulate thrombin generation by enhancing the anticoagulant protein C pathway.

In summary, the increase in local and systemic TF concentration, factor VIII, vitamin K-dependent proteins, and fibrinogen levels in patients with the metabolic syndrome may support an exacerbated tendency to thrombosis. Abdominal obesity may be independently involved, either directly or indirectly, through its capacity to produce hemostatic factors or inflammatory mediators and its association with several other well known cardiovascular risk factors such as insulin resistance and dyslipidemia.

Abdominal Obesity and Hypofibrinolysis

Hypofibrinolysis, due to an increased level of plasminogen activator inhibitor-1 (PAI-1), is the most important and visible change in the hemostatic system in the metabolic syndrome (for review see [14]). Plasma PAI-1 levels may increase by a factor of 2 to 3 in patients with a severe meta-

bolic syndrome compared to normal subjects. Fifty percent of plasma PAI-1 variability is explained by BMI, waist-to-hip ratio, and triglyceride levels.

PAI-1 is the predominant inhibitor of the fibrinolytic system (Figure 4). Increased concentration of PAI-1 in the circulation impairs the removal of thrombi from the vascular system and may influence the development of atherosclerotic lesions as well. In large epidemiological studies, elevated plasma levels of PAI-1 proved to be predictors of myocardial infarction. Remarkably, the predictive ability of PAI-1 disappears after adjustment for markers of the metabolic syndrome [15]. These results suggest that the presence of abdominal obesity and insulin resistance are a prerequisite for the increased PAI-1 levels in patients at risk of atherothrombosis and have led to the proposal that increased PAI-1 levels can be considered a true component of the metabolic syndrome [14, 16].

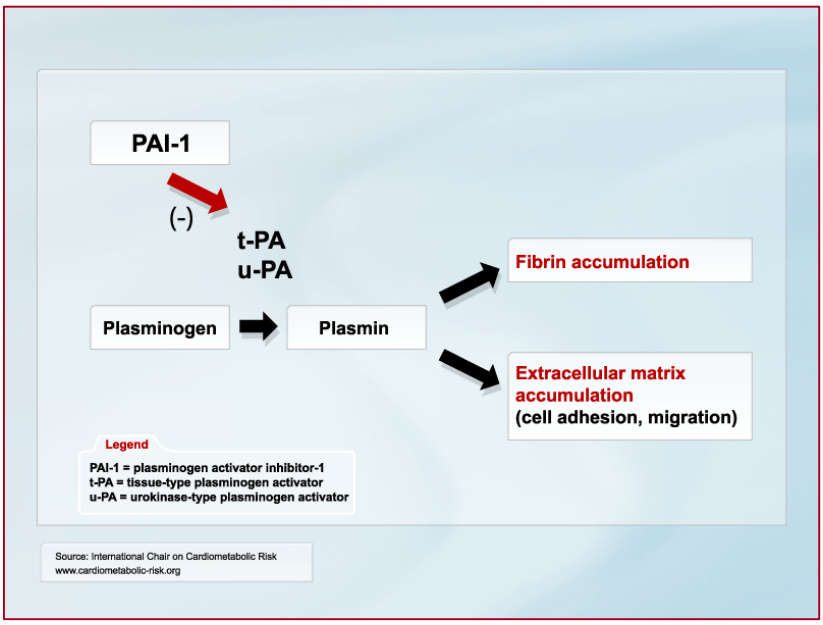

Figure 4: The fibrinolytic cascade

The increase in plasma PAI-1 levels associated with abdominal obesity may be attributed to PAI-1 production by ectopic adipose tissues. Macrophages infiltrating adipose tissue express PAI-1, as do adipocytes in response to PAI-1 inducers. Ectopic fat accumulation in liver is also associated with strong PAI-1 expression close to the fat cells. Overall, these findings suggest that circulating PAI-1 levels reflect fat redistribution and may be considered a biomarker of ectopic fat storage disease.

Tissue expression of PAI-1 is not constitutive but mainly inducible. Many inducers of PAI-1 synthesis during obesity have been identified that may exert their effect locally or more remotely. The causes of PAI-1 overexpression in metabolic syndrome are complex, with much interference between biological systems. Identifying inflammation or oxidative stress at the macrophage level as fundamental precursors is tempting and may yield interesting approaches to elucidate the link between atherosclerosis and metabolic syndrome.

Circulating PAI-1 levels predict development of type 2 diabetes, suggesting that PAI-1 may be causally related to development of obesity [17]. Recently, in vivo and in vitro studies in mice supported the role of PAI-1 in obesity development and in metabolic disorders (review in [14]) and therefore support the concept that PAI-1 inhibition has the potential to reduce obesity and improve

insulin sensitivity and may represent a new therapeutic target. This requires confirmation in different experimental models, and the mechanisms involved should be precisely defined.

Abdominal Obesity and Endothelial Dysfunction

Endothelial dysfunction contributes to cardiovascular disease, including hypertension and coronary artery disease.

It has become clear that the metabolic syndrome is associated with endothelial dysfunction [18], with inadequate vasodilatation and/or paradoxical vasoconstriction in coronary and peripheral arteries in response to stimuli that release nitric oxide (NO). In healthy conditions, insulin promotes glucose disposal and stimulates the endothelial production of NO, which, in turn, through NO-dependent increases in blood flow to skeletal muscle, may account for 25% to 40% of the increase in glucose uptake in response to insulin stimulation. A physiologic increment in plasma insulin concentration particularly increases microvascular blood volume, consistent with a capillary recruitment mechanism.

Metabolic insulin resistance is characterized by imbalance between production of NO and secretion of endothelin-1, which leads to decreased blood flow and worsens insulin resistance [19].

In parallel with inadequate vasodilatation, endothelial cells in obesity develop a proinflammatory phenotype with increased expression of vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and E-selectin; the release of microparticles [20] and shedding products; and an increased synthesis and release of Von Willebrand Factor (VWF). The latter plays a major role in the adhesion of platelets to the vascular wall. VWF levels are correlated with parameters of the insulin resistance syndrome [12] and inflammatory parameters [21].

Interestingly, some recent clinical studies have demonstrated that non-pharmacological and pharmacological strategies targeting obesity and/or insulin resistance ameliorate endothelial function and low-grade inflammation, whereas improving endothelial function ameliorates insulin resistance [19]. This underscores the reciprocal connection between endothelial dysfunction and insulin resistance.

Conclusion

Abdominal obesity is accompanied by important changes in the hemostatic system that favour the development of arterial as well as venous thrombosis [22]. Hyperactivity of platelets and hypercoagulability favour platelet and fibrin deposits, and hypofibrinolysis due to excess PAI-1 prevents their elimination. The increased PAI-1 expression that accompanies abdominal obesity is the main abnormality in hemostasis, with an original regulation. As PAI-1 could also be directly involved in the physiopathology of obesity, it represents an original target for preventing both the vascular and metabolic risks.

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