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IM - COMMENTARY

Platelets, oxidative stress and preservation of the vascular endothelium: is it a matter of fat?

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Endothelial dysfunction is a systemic and early event in the natural history of atherosclerosis [1]. The mechanisms eliciting endothelial dysfunction are still incompletely known, although an involvement of oxidative stress and reactive-oxygen species generating enzymes, such as NADPH oxidase, as well as nitric oxide bioavailability, have been implicated [2, 3].

The interaction between endothelial dysfunction and visceral fat is not novel: in this regard, it has been recently reported that flow-mediated dilatation (FMD) is blunted after modest weight gain and recovers after restoration of normal weight [4], thus suggesting the reversibility of the process and its dependence on visceral fat.

The originality of the manuscript by Angelico et al. [5], published in this issue of IEM, stands in the clinical setting where this issue was challenged, i.e. metabolic syndrome (MS), and in their effort to dissect the underlying pathogenic cascade. Indeed, this study provides a mechanistic explanation for the association between MS and FMD, described in a large group of 2,123 Framingham Offspring Cohort participants [6]. In this US cohort, endothelial dysfunction progressively deteriorates with an increasing number of MS components. In the study by Angelico et al., patients with MS were compared with patients not fulfilling the criteria for MS. The choice of a control group of "non-healthy" subjects, encompassing different degrees of cardiovascular burden, instead of healthy subjects, further strengthens the relevance of the biochemical abnormalities found in patients presenting with the clustering of MS perturbations in the cross-sectional comparison.

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The authors postulate that NOX-2, the catalytic core of NADPH oxidase, is overactivated in MS, elicits oxidative stress, as reflected by enhanced isoprostane formation, and that NOX-2-generated oxidative stress, in turn, impairs endothelial function. This pathway is reversible, at least in part, by successful weight loss achieved with a restricted-calorie, Mediterranean-type diet. A small in vitro study on platelets of healthy subjects unravelled an involvement of adiponectin up-regulation associated with weight loss [7] in the reversal of oxidative stress, and thereby, of endothelial dysfunction. Interestingly, platelets have been suggested to play a central role as triggers of the entire process. In fact, previous observations by the same group, show that adiponectin reduces translocation of p47 subunit of NADPH oxidase to platelet membrane, thus decreasing NOX-2 activation [8], and that about one-third of circulating NOX-2 stems from platelet activation, with ensuing release of NOX-2 in the medium. These findings, coupled with the inverse relationship between adiponectin and NOX-2 in MS patients, prompted the authors to assess the effect of physiologic concentrations of adiponectin on NADPH oxidase activation, showing that adiponectin dose-dependently lowers NOX-2 cleavage from platelet membrane and NOX-2 concentration in the supernatant of arachidonic acid-activated platelets.

It is of interest that both platelet activation and endothelial dysfunction are early events in the natural history of atherosclerosis. The cross talk between platelets and endothelial cells dates back to the bone marrow, where haematopoietic precursors, megakaryocytes, and sinusoidal endothelium interact directly [9]. The hypothesis that platelet oxygen free radicals may trigger a cascade of events ultimately leading to endothelial dysfunction is supported by previous observations by the same authors showing a progressive decrease in platelet formation of

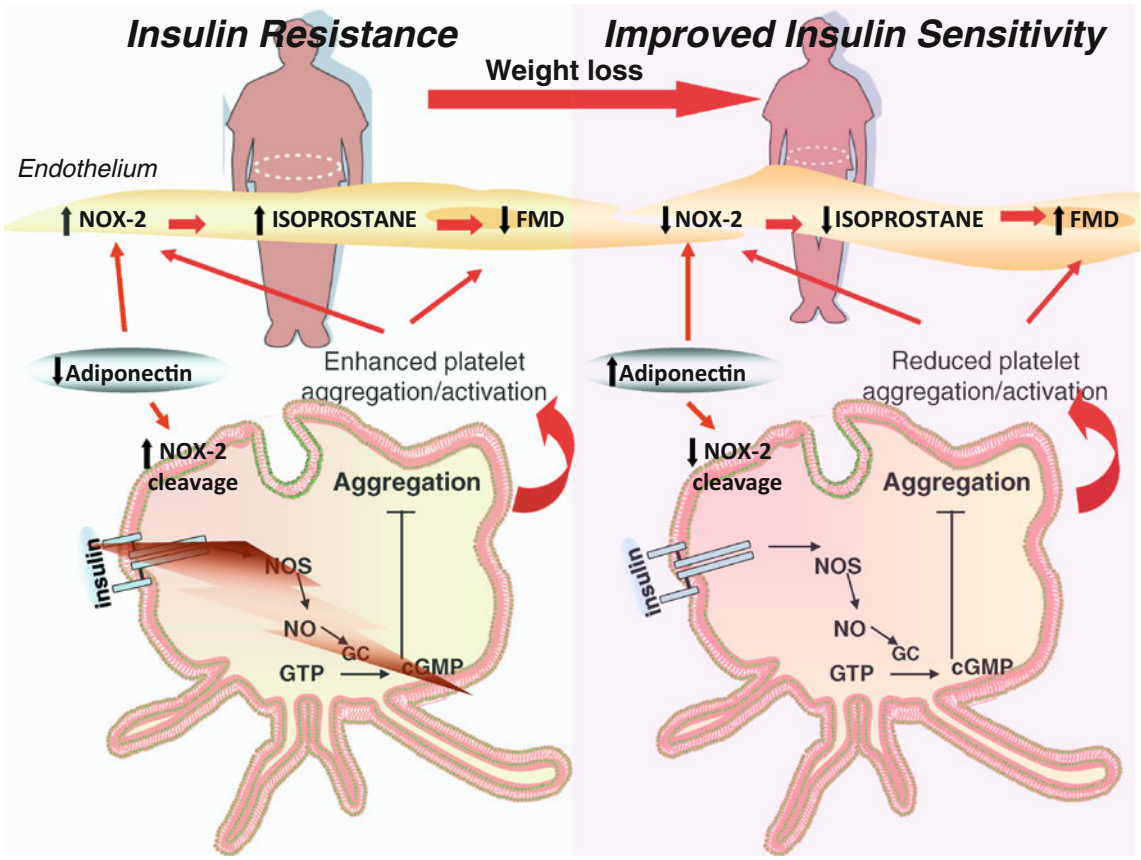

Fig. 1 NOX-2, the catalytic core of NADPH oxidase, is over-activated in MS, elicits oxidative stress—as reflected by enhanced isoprostane formation—and NOX-2-generated oxidative stress, in turn, impairs endothelial function [flow-mediated dilation (*FMD*)]. Adiponectin dose-dependently lowers NOX-2 cleavage from platelet membrane. Since platelets are a pivotal source of systemic NOX-2, it is conceivable that they are the initiators of this detrimental cascade in settings of persistently enhanced platelet activation, such as obesity and MS. Insulin resistance may be the primitive abnormality associated, on the one hand, with adiponectin down-regulation, leading to un-contrasted NOX-2 activation, and, on the other hand, with platelet resistance to insulin, which translates into reduced ability of insulin to increase NO (endothelial dysfunction) and reduced sensitivity of platelets to anti-aggregating stimuli. The resulting enhanced platelet aggregation/activation further triggers NOX-2-mediated pathogenesis. The entire pathway is reversible, at least in part, by successful weight loss achieved with a restricted-calorie, Mediterranean-type diet, in association with improved insulin sensitivity

nitric oxide moving from patients with hereditary deficiency in gp91phox (NOX-2) to obese patients [10]. Thus, vascular tone is modulated by NADPH oxidase-generated oxidative stress, affecting nitric oxide generation. Since platelets are a pivotal source of systemic NOX-2, it is conceivable that they are the initiators of this detrimental cascade in settings of persistently enhanced platelet activation, such as obesity and MS [11, 12]. A large body of evidence supports the notion that in obesity and obese type 2 diabetes, platelets are sites of insulin resistance. A multistep resistance to anti-aggregation has been characterized, including the ability of insulin to increase NO, the ability of NO to increase cyclic guanosine monophosphate (cGMP), the ability of cGMP to reduce platelet calcium and thus aggregation and the ability of prostacyclin to increase cyclic adenosine monophosphate (cAMP) and the cAMP ability to reduce platelet function [13]. Recently, weight loss has been reported to restore platelet sensitivity to nitric oxide and prostacyclin as well as in vivo platelet activation, as assessed by soluble P-selectin and CD40L [14, 15]. Subsequent in vivo observations yield the concept that insulin resistance per se is a major determinant of increased platelet activation in obesity, independent of underlying inflammation [16]. Successful weight loss or the insulin-sensitizer pioglitazone, are associated with a concomitant improvement in insulin sensitivity and platelet activation.

Consistently, in the group of patients with MS evaluated in this study, HOMA-IR, reflecting the degree of insulin resistance, is the only independent predictor of FMD values at baseline. In addition, successful weight loss is associated with a statistically significant decrease of mean HOMA-IR, even though the between-group comparison between patients achieving and not achieving weight loss does not

reach formal statistical significance. Based on these considerations, it is possible to speculate that, in MS, insulin resistance is the primitive abnormality associated, on the one hand, with adiponectin downregulation, leading to uncontrasted NOX-2 activation, and, on the other hand, with platelet resistance to insulin, which translates into reduced ability of insulin to increase NO (endothelial dysfunction) and reduced sensitivity of platelets to anti-aggregating stimuli (enhanced platelet aggregation/activation triggering NOX-2-mediated pathogenesis) (Fig. 1). This hypothesis warrants confirmation with intervention studies addressing the reversal of this detrimental cascade by selectively targeting insulin resistance in MS patients.

A similar pathway of adiponectin-mediated pathogenesis has been recently described [8] in hyper-cholesterolemic patients, demonstrating that this pathway may be favourably modulated by atorvastatin. Hypercholesterolemia is also characterized by documented persistent platelet activation and isoprostane formation [17], and statins have been shown to revert these biochemical abnormalities [18]. The fact that the described detrimental cascade is shared by different clinical settings raises the question whether a single, prevalent metabolic perturbation rather than a clustering of multiple abnormalities is responsible for endothelial dysfunction. In this regard, since successful weight loss in the present study is able to concurrently affect BMI, cholesterol levels, haemoglobin A_{1c}, it would be interesting to assess which of these clinical factors percent change is the main determinant of the percent change in FMD, adiponectin and isoprostane formation. This would be useful information to assess the main contributor to this perturbation in MS, and to test the efficacy of further interventions targeting the prevalent metabolic perturbation, on top of a dietary strategy, in this clinical setting.

Conflict of interest None.

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