

Editorial Focus

Beyond glucose levels in diabetic patients with coronary artery disease: Platelet activity and non-responsiveness to antiplatelet therapy

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The incidence of type 2 diabetes mellitus has reached epidemic proportions, and of concern is the fact that 80% of these patients die as a result of thrombotic complications (1). Since platelets play a key role in the development of atherothrombotic events, platelet dysfunction may play a pivotal role in the development of vascular complications related to diabetes, and may contribute to the enhanced atherothrombotic risk (2). The associated pathophysiology of platelet abnormalities in diabetes mellitus is complex and heterogeneous. For example, diabetic platelets have higher basal platelet activation as represented by elevations of intracellular Ca^{2+} and expression of various platelet activation markers (P-selectin, CD40L and CD63) (3). In addition, the overexpression of GPVI, a receptor for collagen and one of the primary platelet agonists, and that of GP IIb/IIIa, a receptor for soluble fibrinogen and von Willebrand factor, is evident in diabetes (4). Platelets are also involved in the development and maintenance of inflammation by producing the inflammatory chemokine RANTES and causing stimulation of monocytes and endothelial cells via expression of CD40L.

In this issue of *Thrombosis and Haemostasis*, Serebruany et al. (5) add to the growing amount of pathophysiological data on platelets in diabetics, by studying a large cohort of such patients with associated coronary artery disease (CAD); they demonstrate upregulation of P-selectin and GPIIb/IIIa, as well as platelets that have increased expression of a number of functionally important surface proteins, such as platelet/endothelial cell adhesion molecule-1, vitronectin receptor and thrombin protease activated receptor-1. Not surprisingly, platelets from diabetic patients were also more sensitive to aggregation by various agonists, consistent with previous studies (6). Given that diabetes represents a state of major metabolic derangement, multiple (and diverse) factors may be responsible for such platelet hyperactivation in diabetic patients, amongst which abnormalities of glucose metabolism, oxidative stress, impaired Ca^{2+} homeostasis and endothelial damage/dysfunction represent possible pathways.

In the healthy subject, insulin reduces platelet responsiveness to stimulators (e.g. thrombin, ADP, etc) (6), whilst diabetic platelets are less sensitive to the inhibitory action of insulin in result of a reduction in platelet insulin receptor numbers and affinity (one of many examples of so-called insulin resistance), especially where insulin production is also compromised (7). As glucose uptake by platelets does not depend on insulin, intra-platelet glucose concentrations are substantially elevated, thus promoting platelet activation (8). Furthermore, hyperglycemia is responsible for the non-enzymatic glycation of platelet membrane proteins that may cause changes in protein structure and conformation (9). Indeed, high HbA1c levels, which are a marker of poor glycemic control, strongly correlate with platelet expression of P-selectin and CD63 (10). Moreover, the overexpression of receptors responsible for cell-to-cell interactions such as P-selectin and GP IIb/IIIa as well as enhanced interaction with red blood cells, which release large contents of ADP, can also lead to platelet hyperreactivity (11).

Endothelial abnormalities probably play a major role in increasing platelet activation in diabetics. In these patients, the balance between constricting and dilating substances is changed and shifted towards the former. The nitric oxide (NO)/cGMP pathway is a well-established mechanism of platelet inhibition, and the dysfunctional endothelium (as in diabetics) cannot produce NO effectively. Moreover, in platelets from diabetic patients, platelet NO-synthase activity and NO expression are significantly depressed (12). In addition, high reactive oxygen species (ROS) production and lipid peroxidation in diabetics further enhance platelet activation (13). Hyperactivated platelets themselves generate ROS in abundance, further increasing the risk of thrombotic complications. Platelet-derived microparticles, small fragments of platelets released into the circulation, as a result of oxidative stress, inflammation and high shear stress have procoagulant effects and may be directly involved in the thrombotic complications associated with diabetes (14). Finally, the calcium (Ca^{2+}) signalling pathway is of great importance for

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regulation of platelet function (e.g. shape change, secretion, aggregation, and thromboxane formation) (15). Reduced plasma membrane Ca^{2+} ATPase activity and enhanced Ca^{2+} mobilization are at least partly responsible for platelet hypersensitivity to thromboxane A_2 stimulation in diabetic patients (16).

With such a wide range of pathophysiological pathways, can interventions improve things? The strict control of glucose levels has been associated with a significant reduction in lipid peroxidation and platelet activation (17). While thromboxane A_2 biosynthesis is upregulated in diabetes, tight metabolic control reduces thromboxane A_2 levels (18). However, different antiplatelet drugs are the main strategy for the prevention of thrombotic complications in diabetes, rather than simply relying on metabolic control. In the "Antithrombotic Trialists Collaboration" meta-analysis, the overall reduction in incidence of vascular events with anti-platelet therapy was only 7% in diabetic patients, which is far less than the average of 22% (19). Subgroup analysis of the Hypertension Optimal Treatment (HOT) trial found that diabetic patients benefit less from aspirin therapy than do the general patient population (20). In terms of primary prevention, aspirin use produced significant reductions in myocardial infarction risk over five years (21, 22).

Can we improve the efficacy of antiplatelet therapy in diabetics? The retrospective analysis of CAPRIE study revealed a higher clinical efficacy of clopidogrel over aspirin amongst diabetic patients (23). In the CURE study, patients on aspirin-clopidogrel combination therapy experienced a highly significant 17% reduction in the primary outcome, but in diabetics, the benefits were only of borderline statistical significance (24).

These observations may be partly attributed to the persistence of increased platelet reactivity in diabetics even with dual antiplatelet therapy use. Indeed, 'laboratory resistance' to aspirin therapy is more frequently observed in patients with diabetes mellitus (25) and in the paper by Serebruany et al. (5) they also demonstrate a compromised response to clopidogrel amongst diabetic patients with CAD. As mentioned above, diabetic patients exhibit high pretreatment platelet activity – and there are a multitude of reasons for this – and since they do not respond well to the available antiplatelet regimens when compared with similar patients without diabetes, these findings may have potential clinical implications, given the poor outcomes in this high-risk population.

What is the future of antiplatelet treatment in diabetics? Novel agents (such as prasugrel) and new groups of antiplatelet drugs (e.g. inhibitors of thromboxane A_2 synthase and/or receptor) may improve prognosis amongst diabetic patients. In the recent DAVID trial, treatment with picotamide, a dual inhibitor of thromboxane A_2 synthase and receptor, was associated with 40% reduction in a relative risk of vascular death amongst diabetic patients when compared to aspirin alone (26). Given the frantic developments in new antithrombotic drugs, things can only get better for our management options for preventing thrombotic complications in diabetes. As Serebruany et al. (5) conclude in their paper, new clinical trials in diabetes are urgently needed to define the optimal degree of platelet inhibition, and suitability for alternative (or more aggressive) antiplatelet drug regimens. We clearly have to look beyond glucose levels *per se* in our management of diabetics.

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