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Mini Review

The "sweet" relations between diabetes and platelets

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Atherosclerosis is the most important factor that leads to the high risk of atherothrombotic cases in patients with diabetes mellitus (DM). High morbidity and mortality in these patients are firstly caused by cardiovascular disease, mostly coronary artery disease (CAD) along with acute coronary syndrome (ACS) [1]. It is reported 20 years ago that patients with DM but without CAD have similar cardiac-related mortality risk to patients without DM with myocardial infarction (MI) history [2]. Moreover, cardiovascular disease has a poorer prognosis in patients with DM than the non-DM patients due to the increased risk of complications and recurrent atherothrombotic events [3]. Actually, in an ACS situation, the DM patient has a high possibility to have recurrent ischaemic events and finally die [4]. After all, the presence of several factors and comorbidities has a negative impact on ACS outcomes in DM patients [5]. The increased coagulation along with impaired fibrinolysis, endothelial dysfunction, and platelet hyperreactivity are the main factors that are involved in the prothrombotic condition of DM patients [6,7]. Among them, platelet hyperreactivity is of particular importance, since thrombi formed, developed and sustained with the platelet's crucial contribution [8]. Platelets of DM patients are becoming hyperreactive, by dysregulation of several signaling pathways, leading to intensified adhesion and aggregation [6,9-12]. Additionally, a hyperreactive platelet may end in an unsatisfactory response to antiplatelet agents [13,14]. Several factors such as hyperglycemia, insulin deficiency resistance, other associated metabolic conditions, and cellular abnormalities (Table 1) intrigue multiple mechanisms that cause the increased platelet reactivity seen in patients with DM [15]. Furthermore, inflammatory activity plays an important role in diabetes and platelet dysfunction. IL-1β secreted by inflammatory cells causes changes to platelet function due to their binding to platelets. This cytokine is critically involved in abnormal clot formation, erythrocyte pathology, and platelet hyper-activation [16].

Hyperglycaemia	Associated Metabolic Conditions	Deficient Insulin Action	Endothelial Dysfunction	Platelet
•Increased P-selectin expression •Osmotic effect •Activation of prot. kinase C •Decreased membrane fluidity by glycation of surface protein	•Obesity •Dyslipidaemia •Inflammation	•Impaired response to nitric oxide and prostacyclin •insulin receptor substrate-dependent factors: increased intracellular calcium and degranulation	•Increased production of Tissue Factor •Decreased nitric oxide and prostacyclin production	•Increased platelets turnover •Increased intracellular calcium •Upregulation of $P2Y_{12}$ signaling •Oxidative stress •Increased P-selectin and glycoprotein expression

Table 1: Mechanisms contributing to platelet dysfunction in patients with diabetes mellitus (DM).

The fact that the platelet function can be modified in many ways by the diabetic environment explains the failure of glycaemic control alone to decrease the risk of atherothrombotic events in DM patients. Indeed, the increased platelet hyperreactivity is the result of complex inter-regulated pathways (Figure 1). Additionally, bearing in mind that DM platelets show resistance to antiplatelet therapy, it is necessary to find new therapeutical approaches to correct platelet function in diabetes. The comprehension of the molecular pathways that lead to platelet hyperreactivity in DM patients may put the basis for targeted antiplatelet treatment strategies in this high-risk cohort. For example, the fact that calpain, which is elevated in DM patients, plays a significant role in platelet activation, makes it attractive to suggest the Ca2+- activated proteases as a favorable therapeutic target to inhibit thrombotic complications in DM patients.

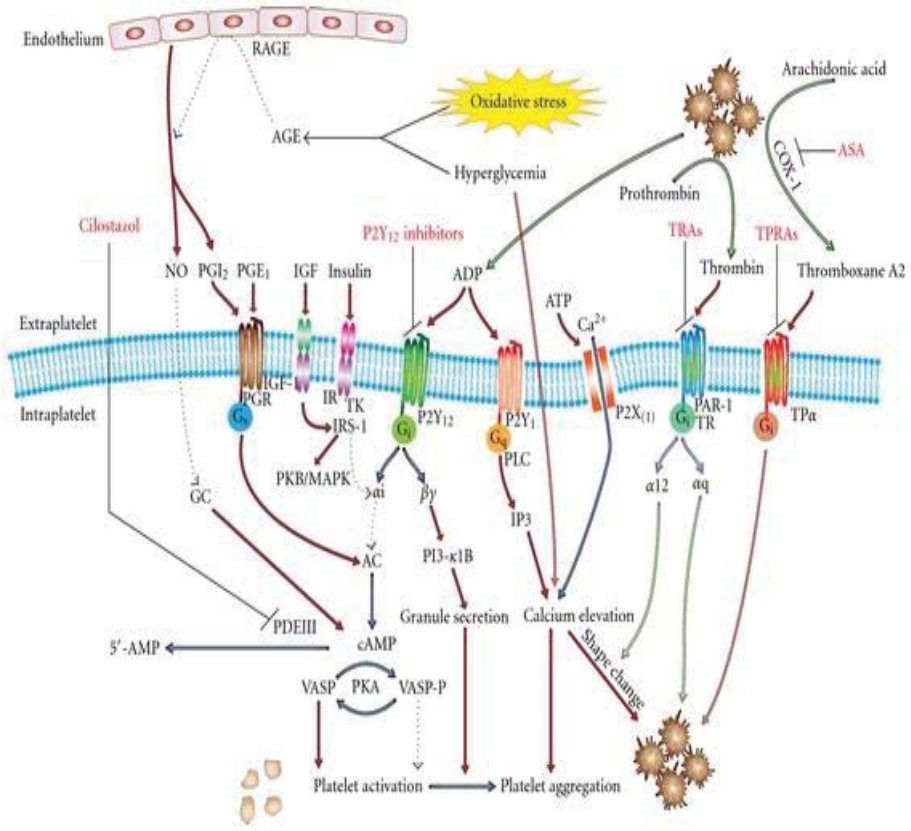

Figure 1: Molecular Pathways that lead to platelet hyperreactivity in DM patients and related possible therapeutic targets.

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