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Review

Platelets and diabetes mellitus

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ABSTRACT

Platelet activation plays a key role in atherothrombosis in type 2 diabetes mellitus (T2DM) and increased *in vivo* platelet activation with enhanced thromboxane (TX) biosynthesis has been reported in patients with impairment of glucose metabolism even in the earlier stages of disease and in the preclinical phases. In this regards, platelets appear as addresses and players carrying and transducing metabolic derangement into vascular injury. The present review critically addresses key pathophysiological aspects including (i) hyperglycemia, glycemic variability and insulin resistance as determinants and predictors of platelet activation, (ii) inflammatory mediators derived from platelets, such as soluble CD40 ligand, soluble CD36, Dickkopf-1 and probably soluble receptor for advanced glycation-end-products (sRAGE), which expand the functional repertoire of platelets from players of hemostasis and thrombosis to powerful amplifiers of inflammation by promoting the release of cytokines and chemokines, cell activation, and cell–cell interactions; (iii) molecular mechanisms underpinning the less-than-expected antithrombotic protection by aspirin (ASA), despite regular antiplatelet prophylaxis at the standard dosing regimen, and (iv) stratification of patients deserving different antiplatelet strategies, based on the metabolic phenotype. Taken together, these pathophysiological aspects may contribute to the development of promising mechanism-based therapeutic strategies to reduce the progression of atherothrombosis in diabetic subjects.

Contents

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Diabetes mellitus as a "CVD" equivalent

Cardiovascular disease (CVD) is the pivotal cause of morbidity and mortality in people with type 2 diabetes (T2DM). Diabetes mellitus is closely associated with both micro- and macrovascular complications. Accelerated atherosclerosis is the main underlying factor contributing to the high risk of atherothrombotic events [incident coronary heart disease (CHD) and ischemic stroke] in DM patients. Rates of diabetes-related complications have declined substantially in the past two decades in USA [1]. However, a large burden of disease persists, due to the continued increase in the prevalence of diabetes [1].

The concept of CVD risk equivalent originates from a study by Haffner et al. [2], in which a non-significant difference was found in the risk of death from CHD when diabetic subjects without prior myocardial infarction (MI) were compared with non-diabetic subjects with a history of MI. Several patients who present with symptomatic chronic heart disease have abnormal glucose homeostasis. The mortality from coronary artery disease (CAD) in men with T2DM has not changed significantly in the last years. Moreover, patients with diabetes mellitus have a poorer long-term prognosis after MI, with enhanced risk for heart failure and death. Changes in the structure of the myocardium (diabetic cardiomyopathy) lead to clinical diastolic dysfunction; thus, diabetes is an independent risk factor for heart failure [3]. Patients with diabetes and CVD have a worse prognosis. Mortality rates due to heart disease are two to four times higher among people with diabetes compared with those without diabetes after correction for traditional risk factors for CVD such as age, obesity, smoking, dyslipidemia, and hypertension [4]. Data from the UKPDS (UK Prospective Diabetes Study) regarding the adjusted rate of heart failure, demonstrate a rise from 2.3 events per 100 person-years in people with HbA_{1c} levels <6% to 11.9 events per 100 person-years in those presenting with HbA_{1c} levels >10% [5]. An increase in HbA_{1c} of 1% correlates to an increment of 8% in heart failure [5].

Thromboxane (TX)-dependent platelet activation in diabetes mellitus

Platelets from patients with diabetes synthesize more TX than normal platelets in response to a variety of agonists that induce deacylation of arachidonate from membrane phospholipids [6]. This increased TX production may be related to high concentrations of blood glucose or lipids, rather than being due to enhanced interaction between platelets and vessel wall [6]. Biochemical evidence of increased platelet activation *in vivo* can be obtained through non-invasive measurements of thromboxane metabolite excretion [7], that avoid artifactual platelet activation during and after blood sampling [8]. Enhanced platelet biosynthesis of TXA_2 has been associated with several cardiovascular risk factors, such as cigarette smoking [9], T2DM [10], type IIa hypercholesterolemia [11], and homozygous homocystinuria [12]. Patients with diabetes and peripheral arterial disease (PAD) had higher TX biosynthesis than age- and sex-matched control subjects [13]. Observation of enhanced platelet aggregation in DM was recognized already in 1965 [14]; since then many studies have demonstrated that platelet degranulation and synthesis of TX derivatives mediating further platelet activation are increased in DM [15], whereas platelet-mediated vasodilatation is impaired [16]. Furthermore, platelets from DM patients have a diminished sensitivity to natural anti-aggregating agents, such as prostacyclin (PGI_2) and nitric oxide (NO) [17]. Recent evidence suggests that reduced prostacyclin receptor expression in platelets, related to poor glycemic control, may contribute to platelet hyperreactivity in humans with type 2 diabetes [18].

Although there has been an expanding pool of literature on the enhanced platelet sensitivity to a variety of aggregating agents *in vitro* in T2DM [19], it is not clear whether these abnormalities are intrinsic to the platelet or are a consequence of circulating factors that affect platelet function, as it has been demonstrated for insulin immunocomplexes [20]. Platelets derived from the bone marrow of diabetic animals show dysregulated endoplasmic reticulum stress proteins, GRP78 and protein disulfide isomerase, that contribute to increased thrombosis by promoting tissue factor activation [21].

Intra-platelet glucose concentration mirrors the extracellular concentration, since glucose entry into the platelet does not depend on insulin [16]. Chronic hyperglycemia has been clearly identified as a causal factor for *in vivo* platelet activation and platelet hyper-reactivity in DM patients [10,20]. In this setting we demonstrated enhanced TX biosynthesis and provided evidence for its platelet origin [8]. Moreover, tight metabolic control led to a significant reduction of urinary TX metabolites [8]. Furthermore, we demonstrated that the metabolic disorder rather than the attendant vascular disease appears to be responsible for persistent platelet activation in this setting [13]. Acute hyperglycemia induces increased activation of platelets exposed to high shear stress conditions as reflected by a sharp increase in the urinary excretion of 11-dehydro-TxB_2 [22]. Moreover, increased levels of von Willebrand factor (vWF) in the circulation correlate with the increase in platelet activation [22], suggesting that acute, short-term hyperglycemia in T2DM may precipitate vascular occlusions by facilitating platelet activation [22].

Oxidative stress

DM is associated with oxidative stress, in particular with overproduction of reactive oxygen species (ROS), as well as with reduced platelet antioxidant levels. Hyperglycemia may induce ROS production directly *via* glucose metabolism and auto-oxidation and indirectly through the formation of AGE and their receptor binding. ROS, in turn, may activate other signaling molecules, such as PKC and NF-κB, leading to transcription of redox-sensitive genes [23].

In poorly controlled diabetes, plasma has less antioxidant capacity, and contains increased lipid hydroperoxides and F_2-isoprostanes, such as 8-iso-prostaglandin (PG) $F_{2\alpha}$ [22], only partially reversible with improved glycemic control. 8-iso-$PGF_{2\alpha}$ is a nonenzymatic oxidation product of arachidonic acid in circulating LDL and is a reliable marker of lipid peroxidation both *in vitro* and *in vivo* [24]. F_2-isoprostanes formation *in vivo* seems to reflect primarily, if not exclusively, a nonenzymatic process of lipid peroxidation. Enhanced urinary excretion of 8-iso-$PGF_{2\alpha}$ has been described in association with cardiac reperfusion injury and with cardiovascular risk factors, including cigarette smoking, diabetes mellitus, and hypercholesterolemia [25]. Besides providing a likely noninvasive index of lipid peroxidation in these settings, measurements of specific F_2-isoprostanes in urine may provide a sensitive biochemical end point for dose-finding studies of natural and synthetic inhibitors of lipid peroxidation. Thus, isoprostanes are emerging as a new class of biologically active products of arachidonic acid metabolism of potential relevance to human vascular disease [10]. Although the biological effects of 8-iso-$PGF_{2\alpha}$ *in vitro* suggest that isoeicosanoids may modulate the functional consequences of lipid peroxidation, evidence that this is likely *in vivo* remains inadequate at this time. 8-iso-$PGF_{2\alpha}$ induces vasoconstriction and may modify aspects of platelet function such as adhesive reactions and activation by low concentrations of other agonists [10]. The hypothesis that increased oxidative stress in T2DM may induce increased generation of 8-iso-$PGF_{2\alpha}$ and that this compound could, in turn, contribute to platelet activation is supported