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Review

Variability in the response to antiplatelet treatment in diabetes mellitus

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ABSTRACT

Atherothrombosis is a leading cause of death in patients with diabetes mellitus. Among factors contributing to the diabetic prothrombotic state, platelet activation plays a pivotal role. Numerous studies have investigated the benefits of antiplatelet therapy for primary and secondary cardiovascular prevention in diabetic patients. However, there are limited evidences that low-dose aspirin may be effective in this clinical setting. Several disease-specific factors have been identified as potential determinants of aspirin treatment failure. In this review, the main determinants of interindividual variability in response to antiplatelet agents are discussed, with particular emphasis on the pharmacokinetic and pharmacodynamic mechanisms of clinical efficacy and safety of antiplatelet drugs in patients with diabetes mellitus.

Contents

1. Diabetes and atherothrombosis

Diabetes mellitus (DM) represents a major cause of cardiovascular morbidity and mortality in western countries [1].

Macrovascular complications manifest themselves as accelerated atherosclerosis, clinically resulting in a 2- to 4-fold increase in coronary heart disease (CHD), in a 3-fold increase in the risk of cerebrovascular disease, and in a 2- to 4-fold increase in the incidence and severity of peripheral vascular disease [2]. Type 2 diabetes mellitus (T2DM) was accorded a CHD risk-equivalent: patients with DM but without previous myocardial infarction (MI) carry the same level of risk for subsequent acute coronary events as non-diabetic patients with previous MI [3,4]. Recent evidence suggests that increased use of effective prevention strategies, such as life-style modifications, antihypertensive and lipid-lowering drugs, may have significantly reduced (from 25% to 35%) major adverse event rate in diabetic patients [5]. Thus, the additional net benefit of other interventions (*e.g.* antiplatelet drugs) may be uncertain, especially for primary prevention. Nevertheless, diabetic vascular disease remains a growing health problem, especially in developing countries, where prevention strategies are lacking.

The abnormal metabolic state that accompanies diabetes is responsible for abnormalities in endothelial and platelet function, which may contribute to the cellular events that favor the atherosclerotic process and subsequently increase the risk of the adverse cardiovascular events.

Hyperglycemia is thought as a relevant risk factor for accelerated atherosclerosis and vascular disease [6], and may cause

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endothelial cell damage through at least three apparently unrelated pathways: advanced glycation end product (AGE) formation, activation of protein kinase C (PKC) pathway in the retina, kidney, heart and aorta, and sorbitol accumulation by way of the polyol pathway in this range of tissues [7]. These pathways are linked by an increased production of reactive oxygen species (ROS) [8]. Furthermore, hyperglycemia, through increased oxidative stress and receptor for advanced glycation end products (RAGE) activation, increases the activation of transcription factor-κB (NF-κB) both in endothelial [9] and vascular smooth muscle cells [10]. Activation of the NF-κB pathway causes a switch of the endothelial functions toward a pro-thrombotic condition. In fact, this transcription factor regulates the expression of genes encoding a number of mediators of atherogenesis such as leukocyte-cell adhesion molecules and chemoattractant proteins that recruit lymphocytes and monocytes into the vascular wall, as well as other proinflammatory mediators commonly found in atheroma. The enhanced expression of proinflammatory cytokines and other mediators, including adhesion molecules, suggests that inflammatory processes may contribute to endothelial dysfunction in DM.

Along with endothelial functional changes, an altered platelet metabolism and changes in intraplatelet signaling pathways may contribute to the pathogenesis of atherothrombotic complications of DM [11]. In fact, accumulation of activated platelets at sites of vascular lesions might result in high concentrations of platelet-derived substances, which in turn might support chemotaxis and recruitment of monocytes into the subendothelium at an early stage in atherogenesis [12].

It is still under debate whether enhanced platelet activation is merely a consequence of more prevalent atherosclerotic lesions (relevant to a risk of thrombosis complicating plaque rupture) or reflects the influence of the accompanying metabolic disturbances on platelet biochemistry and function [13]. The metabolic disorder rather than the attendant vascular disease may be responsible for persistent platelet activation in DM [13], as proven by the detection of enhanced thromboxane (TX) biosynthesis in type 1 diabetic children and adolescents at diagnosis, presumably driven by the underlying inflammatory burden [14], as well as in newly diagnosed type 2 diabetic subjects free of vascular disease [15], in relation to postprandial glycemic spikes. Consistently, acute, short-term hyperglycemia induces increased activation of platelets exposed to high shear stress conditions both *in vitro* and *in vivo* [16].

Chronic hyperglycemia had been demonstrated a causal factor for *in vivo* platelet activation in DM patients [13,17], and persistent enhanced TX biosynthesis in T2DM may be significantly reduced by tight metabolic control [18]. Moreover, the release of a platelet-derived inflammatory molecule, soluble CD40 ligand – in turn able to activate platelets – is largely TX-dependent, thus suggesting a potential mechanism of amplification of TX-dependent platelet activation [19].

Moreover, hyperglycemia-induced oxidative stress may enhance peroxidation of arachidonic acid to form biologically active F2-isoprostanes [20]. Among them, 8-iso-prostaglandin (PG) $F_{2\alpha}$ is a nonenzymatic oxidation product of circulating LDL and arachidonic acid, widely recognized as a reliable marker of lipid peroxidation both *in vitro* and *in vivo* [13,20]. 8-iso-$PGF_{2\alpha}$ is a weak agonist of platelet TX receptor (TP) but may amplify activation by low concentrations of other agonists [20]. This may be relevant to settings where platelet activation and enhanced lipid peroxidation coincide, such as in DM. 8-iso-$PGF_{2\alpha}$ generation correlates with the rate of TXA_2 biosynthesis [13] in T2DM patients, and improvement of metabolic control is accompanied by significant reduction in both 8-iso-$PGF_{2\alpha}$ and 11-dehydro-TXB_2 (a stable enzymatic metabolite of TXB_2) levels. Thus, changes in the rate of arachidonate peroxidation to form biologically active iso-eicosanoids, such as 8-iso-$PGF_{2\alpha}$, may represent an important biochemical link between altered glycemic control, oxidant stress and platelet activation in T2DM [10,13,20].

This point of view is strengthened by the finding that platelets represent a site of insulin resistance. In fact, an insulin receptor is expressed on platelet [21]. Under physiological conditions, insulin receptor signaling results in increased intraplatelet cyclic nucleosides, thus reducing sensitivity to several agonists, such as thrombin, arachidonate, and ADP [22]. In insulin resistant states, altered insulin signaling may be responsible for increased intraplatelet Ca^{2+}, enhanced platelet reactivity, and decreased sensitivity to endogenous antiplatelet molecules, including NO and PGI_2 [23]. Consistently, in subjects with visceral obesity (a determinant for T2DM development), insulin resistance is accompanied by enhanced TX-dependent platelet activation, mediated, at least in part, through enhanced lipid peroxidation [24–26]. Oxidative stress-induced activation of stress-sensitive signaling pathways in platelets might therefore represent a common biochemical basis for the pro-thrombotic state characteristic of T2DM, visceral obesity and metabolic syndrome [20].

2. Secondary prevention

Since diabetic patients present persistent TX-dependent platelet activation [18], low-dose aspirin represents the antiplatelet drug of choice for a secondary prevention strategy in subjects who had a previous cardiovascular event [27]. Aspirin has long been regarded as a first choice in the management of atherothrombotic disease and is widely used in diabetic patients, being regarded as cost effective [28]. Aspirin irreversibly acetylates the hydroxyl group of a serine residue at position 529 of the cyclooxygenase (COX)-1 enzyme, thereby blocking platelet formation of TXA_2 [29].

Although in high risk patients the benefit of aspirin in secondary prevention is well-established, in diabetic patients data are generally extrapolated from subgroup analysis from clinical trials enrolling both diabetic and non diabetic subjects. Based on this evidence, diabetic subjects had a risk reduction after antiplatelet therapy that were comparable to non-diabetic individuals and it was estimated that 38 ± 12 vascular events per 1000 diabetic patients would be prevented if they were treated with aspirin as a secondary prevention strategy [30]. The Antithrombotic Trialists' (ATT) Collaboration meta-analysis [31] confirmed these results, showing that antiplatelet therapy was associated with about one-quarter reduction in serious vascular events.

On the basis of these evidences and as endorsed in current British, European and American guidelines [32,33] aspirin (75–162 mg/day) is clearly recommended as antiplatelet agent for a secondary prevention strategy in diabetics with a history of cardiovascular disease. The level of evidence for aspirin recommendation is high (level A) [27].

Since DM is associated with an approximately 20% higher risk of recurrent ischemic events in patients with acute coronary syndrome (ACS) and is a strong predictor of stent thrombosis [34–36], the American Heart Association recommends dual antiplatelet therapy with aspirin and clopidogrel as the antiplatelet treatment of choice for DM patients with ACS [37–39]. However, a lower response to clopidogrel has repeatedly been shown in DM patients compared with non-DM patients in both the immediate and maintenance phases of therapy [40–42]. Among patients with DM, those who require insulin therapy have the highest degree of platelet reactivity while on dual antiplatelet therapy [43].

Novel and more potent P2Y12 receptor inhibitors represent attractive treatment alternatives in high-risk patients such as those with DM. In DM patients with ACS, prasugrel significantly reduced major adverse cardiovascular events (cardiovascular death, nonfatal MI, or nonfatal stroke) as compared to clopidogrel and the