

Factors Contributing to Increased Platelet Reactivity in People With Diabetes

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People with diabetes, particularly those with type 2 diabetes, exhibit increased platelet reactivity. Hyperglycemia contributes to greater platelet reactivity through direct effects and by promoting glycation of platelet proteins. Hypertriglyceridemia increases platelet reactivity. Both insulin resistance and insulin deficiency increase platelet reactivity. Insulin antagonizes activation of platelets. Thus, relative or absolute deficiency of insulin would be expected to increase platelet reactivity. Diabetes is associated with oxidative stress and inflammation. Resultant endothelial dysfunction promotes activation of platelets by decreasing production of nitric oxide (NO) that attenuates platelet reactivity. Oxidative stress accentuates this effect by attenuating activity of NO and promoting platelet activation. Inflammation and platelet activation are reciprocally related. Inflammation promotes platelet activation that, in turn, promotes inflammation. Accordingly, improved metabolic control achieved with regimens that improve insulin sensitivity and preserve pancreatic β -cell function is likely to decrease platelet reactivity and enhance effects of antiplatelet agents.

Platelets from subjects with diabetes exhibit increased reactivity (i.e., increased propensity to activate in response to a stimulus) (1). This review highlights factors that contribute to increased platelet reactivity. Type 2 diabetes is more prevalent than type 1 diabetes and is associated with a substantially increased risk of macrovascular complications. Accordingly, this review focuses on platelet reactivity in subjects with type 2 diabetes. Key aspects of type 2 diabetes are insulin resistance, metabolic abnormalities including hyperglycemia, and systemic abnormalities including oxidative stress and inflammation. The influence of each of

these abnormalities on platelet function is addressed.

Metabolic abnormalities and platelet function

Induction of hyperglycemia and hyperinsulinemia in healthy subjects without diabetes increases platelet reactivity (2). Consistent with this observation, improved glycemic control has been associated with decreased platelet reactivity (3). Hyperglycemia can increase platelet reactivity by inducing nonenzymatic glycation of proteins on the surface of the platelet. Such glycation decreases membrane fluidity and increases the propensity of platelets to activate (4). Osmotic effect of glucose is a second mechanism by which hyperglycemia can increase platelet reactivity (5). We found that brief exposure of platelets in vitro to hyperglycemia or a similar concentration of mannitol increased their reactivity. Activation of protein kinase C is a third mechanism by which hyperglycemia can increase platelet reactivity (6). Protein kinase C is an essential mediator of platelet activation.

People with diabetes exhibit increased expression of the surface glycoproteins Ib and IIb/IIIa (7). These glycoproteins mediate platelet adhesion and adherence. Thus, greater expression would be anticipated to increase the functional activity, if not the reactivity, of platelets in subjects with diabetes. Expression of these adhesion proteins correlates with hyperglycemia reflected by A1C. Hyperglycemia appears to promote platelet activity by increasing megakaryocyte production of glycoproteins.

Although hyperglycemia is the sine qua non of diabetes, abnormalities of lipid metabolism are uniformly observed. People with diabetes typically manifest hypertriglyceridemia. VLDL that is rich in

triglycerides increases platelet reactivity (8). This effect appears to be mediated, in part, by apolipoprotein E. Thus, both hyperglycemia and hypertriglyceridemia increase platelet reactivity in subjects with diabetes.

Insulin resistance, insulin deficiency, and platelet function

Most people who are destined to develop type 2 diabetes exhibit insulin resistance and consequent hyperinsulinemia for 1–2 decades before manifesting diabetes. During this interval, hyperinsulinemia compensates for insulin resistance and fasting hyperglycemia is not evident. Obesity can induce and exacerbate insulin resistance. Apoptosis of pancreatic β -cells leads to a relative and ultimately absolute deficiency of insulin. Progressive insulin deficiency is seen after type 2 diabetes becomes manifest. Both insulin resistance and insulin deficiency can alter platelet reactivity.

Insulin antagonizes the effect of platelet agonists such as collagen, ADP, epinephrine, and platelet-activating factor (9). This antagonism is mediated by activation of an inhibitory G protein by insulin receptor substrate (IRS)-1 (10). Insulin resistance reflects impaired insulin signaling, predominantly mediated by IRS. Thus, resistance by the platelet to the effects of insulin (relative insulin deficiency) or absolute deficiency of insulin attenuates insulin-mediated antagonism of platelet activation and thereby increases platelet reactivity.

Obese subjects who are insulin resistant exhibit increased activation of platelets. Platelet activation identified by the measurement of a thromboxane metabolite in urine and the concentration of CD40 ligand in blood was increased in obese compared with lean women. Decreased insulin resistance achieved by weight loss or treatment with pioglitazone (without weight loss) reduced the concentrations of these markers (11). Another study quantified the concentration of platelet-derived microparticles in blood; microparticles that are released during the activation of platelets were increased in obese subjects (12). Similar to results in the previous study, the concentration of microparticles was decreased

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after weight reduction (12). Thus, insulin resistance appears to increase the activation of platelets, consistent with increased platelet reactivity.

As mentioned previously, subjects with type 2 diabetes exhibit progressive deficiency of insulin as a consequence of pancreatic β -cell apoptosis. A consequence of pancreatic β -cell apoptosis is absolute deficiency of insulin. Accordingly, the relative deficiency of insulin imparted by insulin resistance is magnified by the superimposition of insulin deficiency. Platelet reactivity that is increased in obese subjects manifesting insulin resistance will be greater when type 2 diabetes is manifest and accompanied by absolute deficiency of insulin.

A recent study suggests that resistance to the effects of insulin is apparent in pathways independent of IRS in addition to those dependent on IRS (13). Consistent with this observation, platelets from subjects with insulin resistance show diminished sensitivity to the actions of NO and prostacyclin (14,15). NO and prostacyclin are produced by the intact endothelium and retard platelet activation by increasing intraplatelet concentrations of cyclic nucleotides, cyclic guanosine monophosphate, and cyclic adenosine monophosphate. Thus, resistance of the platelet to the effects of these agents promotes increased platelet reactivity. Accordingly, insulin resistance attenuates tonic antagonism of platelet activation and thereby increases platelet reactivity.

Oxidative stress, inflammation, and platelet function

Diabetes is associated with systemic inflammation and oxidative stress that may contribute to increased platelet reactivity. Superoxide has been shown to increase platelet reactivity (16). One mechanism by which superoxide may increase platelet reactivity is by enhancing intraplatelet release of calcium after activation (17). In addition, superoxide limits the biologic activity of NO (18). Attenuating the effect of NO would be anticipated to increase platelet reactivity. Oxidative stress impairs endothelial function and reduces production of NO (19). Impaired endothelial function also decreases the production of prostacyclin (20). Accordingly, oxidative stress that accompanies diabetes promotes greater platelet reactivity through direct effects on platelets and by inducing endothelial dysfunction. Endothelial dysfunction increases platelet reactivity be-

cause of decreased production and effect of NO and decreased production of prostacyclin.

Thrombosis that entails platelet activation is intimately intertwined with inflammation. People with diabetes exhibit increased markers of both platelet activation and inflammation (21). In particular, cross-talk between platelets and leukocytes amplifies leukocyte activation both by platelet activation and by platelet reactivity (22). For example, the release of platelet-activating factor by leukocytes primes platelets for activation and increases the extent to which they activate in response to other agonists (23).

An additional mechanism by which inflammation can increase platelet reactivity is by increasing expression of proteins that participate in the activation of platelets. For example, subjects with diabetes exhibit increased expression of Fc γ receptor type IIa (Fc γ RIIa) and associated increased platelet activation in response to collagen (24). Inflammation appears to increase expression of Fc γ RIIa, and attenuation of inflammation decreases expression of Fc γ RIIa (25). Thus, inflammation that accompanies diabetes contributes to increased platelet reactivity that, in turn, contributes to greater inflammation.

Summary

Diabetes is associated with increased platelet reactivity. Factors that contribute directly to greater platelet reactivity include metabolic abnormalities such as hyperglycemia and hyperlipidemia, both insulin resistance (relative insulin deficiency) and absolute insulin deficiency, as well as associated conditions such as oxidative stress, inflammation, and endothelial dysfunction. Although antiplatelet therapy is necessary to suppress increased platelet reactivity, control of hyperglycemia with regimens that decrease insulin resistance and prevent apoptosis of pancreatic β -cells should decrease platelet reactivity and enhance the efficacy of antiplatelet therapy by addressing root causes of increased reactivity.

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