Chapter

Controversies in Platelet Functions in Diabetes Mellitus Type 1

Gordon Ogweno and Edwin Murungi

Abstract

Individuals with diabetes mellitus (DM) are at high risk of thrombosis in which hyperactive platelets are implicated. The platelet hyperactivity has been linked to hyperglycemia. This hypothesis is supported by studies in type II diabetes mellitus showing increased sensitivity of platelets to stimulating agonists in the context of tissue resistance to high-circulating insulin. However, controversy still exists regarding the altered platelet functions in type 1 diabetes mellitus (T1DM) and the link to modifying factors such as blood glucose, hyperlipidemia, metabolic acidosis and insulin treatment. Moreover, increased insulin dosage or treatment appears to have antagonistic actions: diminished functions at low doses and enhanced activation at high doses, the switch being attributable to insulin-like growth factor. The physiological role of insulin in suppressing platelet activation is lost in T1DM, a scenario that favors increased platelet sensitivity to stimulating agonists. Furthermore, the response to antiplatelet agents and statins is sub-optimal in diabetics presenting clinical and research knowledge gap regarding the ideal antiplatelet treatment in DM in general and T1DM in particular. This chapter reviews the unique characteristics of platelet functions in T1DM highlighting the controversial areas linking unique behavior of platelets and the abnormal response to therapeutic interventions.

Keywords: type 1 diabetes mellitus, platelets, hyperactivity, thrombosis

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by high blood glucose levels. There are two major types: type 1DM (T1DM) or insulin-dependent DM (IDDM) due to insulin deficiency or absence; and type 2 DM (T2DM) or non-insulin-dependent DM (NIDDM) is due to insulin resistance.

Diabetes mellitus and impaired glucose tolerance are associated with cardiovascular risk [1, 2] and thrombosis [3] considered to be platelet in origin [4]. Data on platelet functions have largely been derived from T2DM, since it is the most prevalent. However, T1DM is unique in that platelets are exposed to hyperglycemia in the absence of insulin, while in T2DM they are exposed to both hyperglycemia and hyperinsulinemia. It is increasingly debatable the roles of these factors in alteration of platelet functions in T1DM owing to the acuteness and short duration of exposure. More so, the role of insulin on platelet functions is controversial [5] given the paucity of its receptors [6], and that the platelet glucose transporters are independent of it [6].

2. Platelet Indices and Morphology in T1DM

2.1 Platelet indices

Platelet indices such as platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P-LCR) are elevated in patients with IDM type 1 than non-diabetic controls [7] and are associated with cardiovascular complications [8]. These strongly correlate with duration of blood sugar control as assessed by extent of HbA1c [9] suggesting link with metabolic impairment. Notably, MPV size positively correlated with fasting blood glucose and HbA1C [10]. However, as to whether these changes are due to glucose and attendant osmotic effects or part of disease process remains largely unexplored.

2.2 Bone Marrow and megakaryocytes in T1DM

Changes in platelet indices in DM correlate with mekaryocyte DNA content or ploidy [11] reflecting direct influence on bone marrow function even prior to systemic circulation observations. The thrombopoiesis associated with T1DM releases an enormous amount of hyperactive platelets from the bone marrow into circulation [12]. Moreover, the newly released large but immature platelets from bone marrow have increased synthetic capacity for thromboxane and thrombospondin, have enhanced membrane surface expression of receptors such as GPIIbIIIa, CD61, and CD63, [13, 14], and have enhanced aggregation [14, 15]. In DM, the hyperglycemia acts through neutrophils to stimulate thrombopoietin (TPO) production in the liver and enhance megakaryocyte thrombopoiesis [16]. In T1DM, increased circulating TPO has been shown to be linked to elevated blood sugar levels and HbA1c HbA1C [17] providing evidence linking bone marrow megakaryopoiesis and metabolic state.

2.3 Platelet morphology and ultrastructure in T1DM

Peripheral blood smears of patients with diabetic complications show occasional giant platelets [8]. Biochemical examination has revealed altered membrane lipid composition, as well as Na +-K+ ATPase and Ca++-ATPase, which are sensitive to glucose concentrations compared with control from non-diabetic subjects [18].

Ultra structural examinations show prominence of dense granules.

3. Platelet hemostatic functions in T1DM

Diabetes mellitus is a pro-thrombotic condition and platelets are implicated. This has been confirmed by number of laboratory methods such adhesion to immobilized surfaces, granule content secretion, aggregation, clot retraction, and membrane surface expression of activation biomarkers.

3.1 Platelet Adhesion in T1DM

In T1DM, there is evidence of increased platelets adherence to surfaces such as collagen and fibrinogen [19–21], and this corresponds to elevated plasma vWF Ag and activity [22] and low ADAMTS-13 Ag and activity [23]. These features are related to glycemic control [24] and only if vWF is present and elevated in plasma [25].

However, it is not yet established whether the increased adhesiveness are linked to aggregation and linked to or derived from ensuing endothelial injury.

3.2 Aggregation

In DM, platelets exhibit hyperactivity and increased sensitivity to agonists such as ADP, AA, collagen, and epinephrine [26], which augments successive increased secretion of and response to prostaglandins [21, 27]. Specifically, there is greater platelet reactivity in T1DM compared with T2DM and healthy controls as evaluated by light transmission aggregometry (LTA) and platelet function analyzer-100 (PFA-100) [28, 29]. Notably, aggregation curves are biphasic at low agonist concentrations showing greater augmentation of second wave [26] indicating increased secretion of and response to prostaglandins [27]. The mechanism for the biphasic wave response is due to altered ATP/ADP metabolism [30], nucleotide and thromboxane secretion [31], and calcium fluxes [32]. These are because, upon agonist stimulation, there is an initial phase characterized by glycogenolysis with minimal ATP synthesis causing translocation of alpha granule-containing glucose transporter 3 (Glut-3) to the surface, followed by a second phase of enhanced Glut-3 glucose entry, glycolysis, and ATP synthesis leading to both alpha and delta granule translocation and degranulation [33]. These processes are exaggerated in the presence of high vWF, cholesterol and poor glycemic control in T1DM [24].

In contrast, others have found no change in ADP-induced platelet aggregation in T1DM [34, 35]. The lack of consistency with other studies probably suggests loss of adhesive molecules into platelet microparticles [36] or modulation by factors extrinsic to the platelets such as magnesium ions [37], insulin [38], and acidosis [39].

3.3 Membrane surface receptor expression and platelet-leukocyte aggregates (PLA)

Evaluation of platelets from T1DM patients has shown increased membrane surface expression of activation markers such as P-selectin, platelet-leukocyte aggregates (PLA) (platelet-monocyte, platelet-granulocytes) [17, 40, 41]. Importantly, it has been demonstrated that first relatives of T1DM patients at risk of T1DM have increased expression of P-selectin, CD63, and thrombospondin compared with at-no-risk controls [42]. Given that these changes are also observed in megakayryocytes, and peripherally, there is ongoing debate whether the changes are predetermined and intrinsic to disease process or epigenetic secondary to the altered metabolic milieu, are yet to be resolved.

3.4 Secretion and other soluble markers of activation

Urinary excretion of thromboxane B2 (TXB2) was found higher in DM than in healthy controls [35]. This is in contrast to another study that found decreased levels of TXB2, β-Thromboglobulin (BTG) and platelet factor-4 (PF-4) in diabetic patients with uncontrolled blood sugar and high HbA1C [34].

3.5 Platelet microparticle

Platelet microparticles (PMPs) or membrane-covered vesicles that bleb or vesiculate off in response to oxidative stress are elevated in T1DM [43]. The elevated PMP in T1DM compared with T2DM [44] has not been explained. Nevertheless, the levels are predictive of vasculopathy [1].

4. Platelet: inflammation cross talk in T1DM

There is cross talk between inflammation and platelets in T1DM where leukocytes and platelets activate each other [45] and both leukocytes, especially monocytes, and platelets are hyperactivated [41, 46]. Whereas platelets release cytokines [47], and increased levels of these factors have been found in circulation in individuals with T1DM [40], a cause and effect relationship has been questioned [48]. What is known is that cytokines, especially IL-6 and IL-8, are platelet activators [49], but whether they are the cause of platelet hyperactivity in T1DM remains largely unknown.

5. Modifiers of platelet function

Although platelet hyperactivity are vital to the pathophysiology of diabetes mellitus [42, 50–52], there are other factors in systemic circulation that modify disease progression. These factors include hyperglycemia and its control, insulin deficiency and therapy, acute metabolic acidosis, inflammatory markers that precede and coexist during disease states, and body calcium-magnesium fluxes levels.

5.1 Acute metabolic acidosis

Unlike in type 2 DM, acute metabolic diabetes keto-acidosis (DKA) characterized by lactic acidosis and ketonemia occurs in T1DM with a rate between 20 and 70% depending on the intensity of glucose control [53]. Subjects in DKA have increased blood levels of β-Thromboglobulin (β-TG), platelet factor-4 (PF-4), but their platelets are paradoxically less sensitive to aggregation agonists such as ADP and prostacyclin. The agonist sensitivity improves with glycemic control [54]. The initial depressed platelet function that improves with treatment is similar to previous findings by Janka [55] and Ileri et al [56].

Although ketones contribute to acidosis in DKA, only effects of lactic acid on platelets are well studied. Lactic acid dose dependently reduces platelet secondary wave aggregation *in vitro* [57–60]. The effect of pH changes is on impairing intracellular Ca++ store release [61, 62], thus interfering with cytoskeletal changes [63], facilitating platelet reactions [64]. In addition, the changes affect membrane surface expression of GP1b and P-selectin under anaerobic conditions [65] indicating metabolic effects. However, addition of lactic acid together with known platelet inhibitors such as aspirin is not additive but instead attenuates the effects [66, 67]. The paradoxical behavior can probably be accounted for by lactate being metabolized to produce ATP for platelet activation processes leaving protons to be buffered by other means.

5.2 Blood glucose and platelet functions in T1DM

Although platelet hyperactivity in T1DM has partly been ascribed to hyperglycemia, however, empirical evidence has been conflicting. Study results have ranged from no effects, decreased to increased platelet functions. The ambiguity may be attributed to confounders, depending on study designs, dose, and duration of exposure. Specifically, non-diabetic or healthy controls do not have the coexisting inflammatory biomarker seen in diabetics (T1DM from T2DM) who additionally have hyperlipidemia. Thus, in diabetics, duration of disease determines the level of non-enzymatic glycation. The route of glucose administration also matters. Oral intake

is accompanied by post-prandial secretion of gut and counter regulatory hormones while direct or parenteral administration bypasses the gut, with *in vitro* mixing with platelet-rich plasma excluding the leukocytes contribution.

Bridges and coworkers [19] first demonstrated the link between blood glucose and platelet function. They showed that either a postprandial oral glucose load or intravenous infusion increased platelet stickiness in both diabetics and nob-diabetics. The observation has since been confirmed by others mostly in T2DM [68–71]. Surprisingly, in one study of hyperglycemia platelet p-selectin expression was decreased during hyperglycemia compared with levels before oral intake [72]. These results are confounded other factors concurrently activating platelets such as post-prandial hyperglycemia on counter regulatory hormones [73] , procoagulant platelet microparticles [74], combined effect with insulin [75, 76], neutrophil-megakaryocyte thrombopoiesis [16], and hyperlipidemia [25, 77, 78].

In order to avoid the many confounders inherent in *in vivo* hyperglycaemia, *in vitro* studies designed to define the particular role of glucose have yielded mixed results. It has been shown that *in vitro* incubation of healthy PRP platelets with glucose upto 50 mmol has no effect on agonist-induced aggregation to ADP, AA or collagen, secretion of MDA or TXB2 [79] indicating no direct effects on platelets. Many *in vitro* studies involving short incubation periods with varying concentrations of glucose have shown no effects [80, 81]. However, studies have shown that glucose paradoxically increases platelet aggregation or surface P-selectin expression depending on the type of agonist [82–85].

The discordance in effects of glucose on platelets can be explained by the duration of exposure. While acute or short duration of exposure is associated with no or minimal effects, longer duration or chronic exposure stimulates thrombopoiesis in which reticulocytes increase adhesive receptors and are hyperactive to agonists [16]. The duration of glucose exposure correlates with HbA1c levels [86]. Contrary to popular belief, hyperactive platelets are evident even before observable metabolic features in individuals predisposed to T1DM with normal blood [41]. Early evidence of the influence of glucose on platelet functions via metabolic reactions was provided by Murer et al. [87] and Chaudhry et al. [88]. The two groups reported the presence of aggregation in media containing glucose or substitute substrates, the extent of which was related to glucose consumption and carbon dioxide production due to metabolism. In these experiments, addition of metabolic inhibitors inhibited aggregation. Moreover, alterations of membrane properties and energy requiring processes have been noted upon incubation of platelets with varying glucose concentrations [18] suggesting other mechanisms are at play.

Several preclinical animal studies have confirmed the dependency of platelet functions on glucose uptake and subsequent metabolism [33, 89]. Under resting conditions, the plasma membrane localized GLUT-1 glucose transporter facilitates glucose entry into platelets, activation glycolysis, and ATP production [90]. Upon stimulation with agonists such as thrombin, alpha granules containing both P-selectin and GLUT-3 translocate and fuse with plasma membrane to increase glucose uptake [91]. The resulting alpha granules degranulation, glucose influx, and increased ATP synthesis lead to P-selectin expression and aggregation [33, 92].

It appears that hyperglycemia in itself has little bearing on platelet activation unless accompanied by other changes. In a study of T1DM and T2DM, despite postprandial elevation of blood glucose in both types, however, markers of platelet activation were only increased in T2DM. Interestingly, insulin levels did not change in T1DM unlike in T2DM. Administration of insulin pre-meal was accompanied

by increase of postprandial platelet activation markers [74, 76, 93]. However, platelet-activating effects of insulin in T1DM are evident only when there is concurrent hypoglycemia [94]. At low extracellular glucose, insulin potentiates action of thrombin to increase glucose entry via Glut-3 with concomitant increase in surface expression of P-selectin and aggregation. Conversely, at high glucose concentrations, insulin becomes inhibitory through its action on protein kinase B (PKB) and hampers thrombin activation mechanisms leading to decreased platelet activation and aggregation [92].

5.3 Hypertriglyceridemia/hyperlipidemia

In T1DM, the frequency of occurrence of hyperlipidemia is variable [95–97], but when it occurs is associated with platelet hyper-activation [46] and aggregation [98]. The link between post-prandial lipids and platelet secretions [99] and aggregations has been known for a long time [100]. The case was made stronger by observations that treatments lowering the plasma lipids led to normalization of platelet aggregation [101] and glycoprotein expression [102]. Hyper lipidemia associated with uncontrolled T1DM thus becomes an added dimension in platelet hyperactivity together with roles of glucose and insulin.

5.4 Pharmacological treatments

5.4.1 Insulin treatment

Platelet hyperactivity, which largely occurs together with hyperglycemia and hyperinsulinemia, is well known in T2DM [103]. Notably, despite the absolute or relative deficiency of insulin in T1DM, platelet hyperactivity also occurs in T1DM. This phenomenon has elicited debate on the role of insulin in platelet functions. The data available on platelet functions in T1DM are usually at the beginning of insulin treatment or follow-up, which have reported mixed results: no change [86, 104, 105], reduced functions [38], or enhanced activity [24] . These discrepancies in study results can be accounted for by the differences in insulin dosages that produce hypoglycemia, duration of disease, individual peculiarities such as obesity, hyperlipidemia, and plasma calcium and magnesium balances.

Low dose or physiological levels of insulin inhibit platelet aggregation through several mechanisms [38, 106]. These include: decreasing intracellular cAMP levels [38], decreasing calcium mobilization [107] but increasing magnesium influx [108], nitric-oxide-mediated increase in cGMP [38], stimulation of prostacyclin synthesis [109]. Low-dose Insulin prevents second wave aggregation in diabetics, an effect augmented by calcium channel blockers [110]. It is therefore apparent that physiological levels of insulin suppress platelet function, effects that are reversed in its absence during diabetes mellitus type1.

The studies that showed increased platelet hyperactivity concurrent with hyperinsulinemia induced hypoglycemia [94], with attendant increase in counter-regulatory hormones such as adrenaline [111, 112] and increase in vWF-platelet adhesiveness [24], results which were similar to findings in T2DM [113].

Experimental *in vitro*, insulin has antagonistic effects on PRP activation in healthy humans. While at low levels, it decreases platelet aggregation to ADP, at supraphysiological levels, aggregation to ADP is increased [114]. *In vitro,* in healthy controls, supraphysiological insulin enhances ADP-induced whole blood platelet expression of

P-selectin as well as fibrinogen binding, in addition to PRP aggregation. These effects are independent of extracellular calcium and glucose [115]. Insulin, both at physiological and supranormal levels, enhances platelet P-selectin, fibrinogen binding, and platelet-leukocyte aggregates in whole blood [115, 116]. Insulin at low doses decreases platelet aggregation, while at high doses enhances platelet aggregation due to the paradoxical changes in intraplatelet cGMP levels [114].

Whereas low-dose insulin decreases platelet aggregation, high dose increases platelet aggregation in vitro [115, 117]. These effects are mediated by paradoxical changes in intraplatelet cGMP levels [116] and co-operativity with insulin-like growth factor on platelets [118]. Indeed platelets pose few insulin receptors and responses are weak but potentiated by IGF-1 [118] in the presence of extracellular calcium [119]. This is because insulin and IGF-1 circulate together and share a lot of similarities in both structure and receptors [120, 121]. Thus, at high insulin concentrations, the effects of IGF-1 predominate, thus explaining the increased platelet aggregation and response to agonists in patients on hyperinsulinemia.

In healthy, non-diabetic non-obese subjects, insulin decreases platelet adherence to collagen surfaces, decreases agonist-induced (ADP, collagen, AA, and TRAP) platelet aggregation but increases intracellular cGMP. These responses are abolished or blunted in obese individuals [122].

5.4.2 Anti-platelet treatments

Aspirin suppressed platelet functions TXA secretion, LTA, and PFA although there are no observable differences between healthy and DM individuals [35]. In case of stable (>1 month) dual 100 mg aspirin and 75 mg clopidogrel, insulin-treated DM has elevated platelet reactivity as assessed by LTA and PFA compared with NIDM and non-diabetic controls [29]. The refractory effect of antiplatelets in the presence of insulin has been reported [123]. Aspirin has been shown to attenuate maximum aggregation in newly diagnosed T1DM via its effects on ADP, epinephrine, and thrombin. The effects are most marked in reducing the secondary [26] indicating propensity for secretory phase. The refractory state to anti-platelets responses of platelets to agonists in the presence of high glucose is dependent on the signaling pathways tested. For example, hyperglycemia blocks the NO-cGMP-protein kinase pathway but spares the thromboxane secretion [124].

5.4.3 Statins

In patients with hyperlipidemia type II, statins reduced ADP-induced platelet aggregation regardless of the type of drug. However, there was no change with collagen or ristocetin agonist. In addition, the changes were not observed in fibrinogen levels, spontaneous aggregation, and adhesion [125]. The effect of lipid lowering agents in attenuating platelet functions appears to be related to changes in fibrinogen levels [126], suggesting modulation through inflammatory mediators.

5.5 Inflammation

Inflammation is common to both T1DM and T2DM. However, in T1DM inflammation is upstream involving cellular interactions that release cytokines and fibrinogen [127]. The cytokines and fibrinogen have been found to influence platelet activation independent of hyperglycemia [123, 128]. Since fibrinogen is an acute phase protein

associated with acute inflammatory conditions, its correlation with platelet functions points to the role of inflammation in the modulation platelet response after stimulation.

6. Mechanisms of altered platelet functions in T1DM

6.1 Oxidative stress

Owing to the absence or deficiency of insulin in T1DM glucose undergoes autooxidation with accumulation of reactive oxygen species [129]. The consequence is peroxidation of membrane lipids and proteins [130] promoting platelet aggregation [131].

However, it is still controversial whether oxidative stress is a consequence of metabolic complications in T1DM or the cause of the disease [47].

6.2 Hyperglycemia

Persistent hyperglycemia leads to formation of non-enzymatic glycation of proteins, so-called advanced glycation end products (AGEs). Accumulation of these products facilitates cytoskeletal reorganization causing externalization of membrane phosphatidyleserine (PS) [132] , altered membrane fluidity [133], and increased expression of glycoproteins GPIb, IIbIIIa [134], P-selectin, and PLA [135].

Hyperglycemia induces secretion of TPO that potentiates agonist-induced activation of mature platelets. Levels positively correlate with blood glucose and level of control HbA1C [17].

6.3 Signal transduction mechanisms

Collagen at low dose selectively promotes granule secretions through GPVI receptors, a finding not found with high doses or thrombin [136].

DM platelets have upregulated protein C Kinase promoting aggregation [137], downregulation of cAMP, and subsequent increased expression of P2y12

6.4 Ca++signaling

Calcium fluxes are essential for platelet functions, and abnormalities in regulation contributed by prolonged exposure (24 hours) to high glucose are associated with platelet hyperactivity [138].

In T1DM, there is coexistence of insulin deficiency/absence and hypomagnesaemia [139]. Hypomagnesaemia is associated with oxidative stress [140] and increases in platelet baseline intracellular Ca++. The consequence of un-opposed intracellular calcium leads to signal transduction sequences that eventually promote membrane glycoprotein expression, adhesion, secretion, and aggregation [141, 142].

6.5 Lipids

DM subjects have hypertriglyceridaemia, apo E, and HDL receptors that modify cation transporters and nitric oxide synthase involved in platelet aggregation and activation [143–145].

6.6 Prostacyclin

Endothelium of individuals with diabetes mellitus is deficient in prostacyclin thought to contribute to enhanced platelet hyperactivity. However, in vitro testing found platelets from DM were less sensitive to PGI2 than normal controls [146].

6.7 Immune mechanisms

Inflammatory markers such as TNFα, cytokines, and immune complexes are abundant in diabetes, and these are thought to play a role in platelet activation. Cytokines contribute to platelet activation [147–149], and these are amplified by the presence of glucose and ADP [150].

6.8 Platelet-Neutrophil interaction

Animal studies have provided evidence for indirect platelet activation in DM that in the presence of hyperglycemia, neutrophils are stimulated to release S-100 calcium-binding proteins A8/A9 that lead to production of TPO from the liver. The released TPO consequently acts on bone marrow megakaryocytes to release reticulocytes [16]. Reticulocytes have high surface expression of GPIIbIIIa, P-selectin, and release cytokines [16]. The expressed P-selectin interacts with SGL-P on neutrophils to release neutrophil extracellular traps (NETs).

6.9 Thrombopiesis

DM and hyperglycemia are associated with release of large, immature platelets [12]. This indicates that the platelet hyperactivity in diabetic subjects is partly central from bone marrow, thus explaining lack of sensitivity to antiplatelet agents [151].

7. Clinical significance of platelet functions

Microangiopathy is common in T1DM and is associated with hyperactive platelets expressing agonist stimulated P-selectina and platelet-leucocyte aggregates [41]. A number of clinical trials have reported decreased efficacy of anti-platelets in DM subjects [152]. The reasons are multifactorial, but can be summarized as lack of effect in leukocyte-platelet interactions, chronic effects of hyperglycemia especially oxidative stress, insulin resistance, and inability of megakaryocytes to respond.

8. Conclusion

T1DM is associated with platelet hypersensitivity to stimulating agonists. Hyperglycemia, in a dose and duration-dependent manner, provides the substrates for energy generation that powers alpha granule translocation to the membrane surface. Enhanced expression of P-selectin and GPIIbIIIa contributes to increased platelet aggregation evident in T1DM. Platelet hyperactivity in T1DM represents a reversal of the attenuating effects of low dose or physiological insulin. This is augmented by the attendant hyperlipidemia. However, the paradoxical hyperactivity in the presence of hyperinsulinemia is due to counter-regulatory hormones and

potentiation by insulin-like growth factor. Overall, platelet activation in T1DM occurs through multiple signal transduction pathways not targeted by currently available antiplatelet agents. These pathways offer avenues for the development of novel antiplatelet remedies with improved therapeutic efficacy.

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