Pathobiology and cell interactions of platelets in diabetes

BERND STRATMANN, DIETHELM TSCHOEPE

Abstract

Diabetes is a well-recognised risk factor for athero-sclerotic cardiovascular disease and in fact most diabetic patients die from vascular complications. The Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) indicate a consistent relationship between hyperglycaemia and the incidence of chronic vascular complications in patients with diabetes. Platelets are essential for haemostasis, and abnormalities of platelet function may cause vascular disease in diabetes. Diabetic patients have hyperreactive platelets with exaggerated adhesion, aggregation and thrombin generation. In summary, the entire coagulation cascade is dysfunctional in diabetes.

This review provides a comprehensive overview of the physiological role of platelets in maintaining haemostasis and of the pathophysiological processes that contribute to platelet dysfunction in diabetes and associated cardiovascular diseases, with special emphasis on proteomic approaches and leukocyte-platelet cross-talk.


Key words: platelets, diabetes, endothelial dysfunction, thrombosis, vascular risk.

Introduction

Diabetes is accepted as an independent risk factor for cardiovascular events. The risk for coronary heart disease (CHD), stroke and peripheral arterial disease (PAD) is increased by a factor of two to four, as shown by the Multiple Risk Factor Intervention Trial (MRFIT). Diabetic patients are therefore grouped in the same risk group as those who have survived a stroke or a myocardial infarction. In addition to their increased risk for cardiovascular disease (CVD), patients with diabetes have a poorer prognosis than non-diabetic patients when they experience a major ischaemic vascular event. The prognosis for diabetic patients who undergo coronary revascularisation procedures is worse than that for non-diabetic subjects; patients with diabetes experience more postprocedural complications and have decreased infarct-free survival.

As a seminal component of the so-called metabolic syndrome, insulin resistance plays a significant role in the development of vascular dysfunction. An increase in the fasting insulin level predicts the development of hypertension in non-obese non-diabetic persons. Insulin resistance is associated with reduced nitric oxide-mediated vasodilatation and increased salt sensitivity. Insulin levels are directly correlated with plasminogen activator inhibitor-1 (PAI-1) and inversely correlated with tissue plasminogen activator (tPA). The fact that insulin induces PAI-1 activity both in vitro and in vivo supports the concept that hyperinsulinaemic states are pro-thrombotic. The metabolic syndrome is characterised by microalbuminuria, high triglycerides, low high-density lipoprotein (HDL) cholesterol, hypertension, left ventricular hypertrophy and increased platelet aggregation and coagulopathy. The pathophysiology of diabetic micro- and macroangiopathy may depend on whether the patient has type I or II disease but both types of diabetes are associated with a hypercoagulable state driven by platelet hyperreactivity. The majority of ischaemic coronary and cerebrovascular events are characterised by vessel occlusion caused by atherosclerotic plaque disruption, platelet aggregation and adhesion which result in intravascular thrombosis.

The role of platelets in haemostasis and diabetes

Platelets originate from the megakaryocytes in the bone marrow and circulate as discoid anuclear cells, having a life span of approximately 8–10 days. Besides thrombopoietin as a major hormonal regulator of platelet production, nitric oxide can also stimulate platelet production. Upon activation, platelets change from a discoid to a spherical shape with long, spiky pseudopods. Various physiological sub-
stances (thrombin, collagen, adenosine diphosphate [ADP], epinephrine, vasopressin, serotonin, platelet activating factor) are capable of activating platelets by binding to the membrane-located receptors, resulting in a well defined outside-in signalling. These intraplatelet events lead to integrin activation (inside-out’ signalling): the constitutive integrin \(\alpha_{IIb}\beta_{3}\) (glycoprotein \(\text{IIb/IIIa}\)) changes its steric conformation, exposing the high-affinity binding site for RGD (arginine-glycine-asparagine) containing ligands such as fibrinogen. This reaction results in cross-bridging of activated platelets by binding of the polyvalent ligand fibrinogen.\(^{29}\)

When platelets are activated they react by changing their morphology, aggregating, secreting various proteins and by liberating arachidonic acid that is rapidly converted to prostaglandins and lipoxygenase products. Constituents from a-granule stores like platelet factor-4 (PF-4)\(^{30}\) and b-thromboglobulin\(^{31-33}\) are released and cell surface activation markers like p-selectin,\(^{45-47}\) CD63 and CD40L\(^{56-57}\) are up-regulated. Activated platelets show increased adhesiveness and aggregation in response to collagen, thrombin and platelet activating factor. This may lead to increased microembolism in the capillaries and local progression of pre-existing vascular lesions.\(^{31-42}\) Abnormalities in platelet function may exacerbate the progression of atherosclerosis and the consequences of plaque rupture. The abnormal metabolic state that accompanies diabetes causes arterial dysfunction. Relevant abnormalities include chronic hyperglycaemia, dyslipidaemia and insulin resistance, which engender adverse metabolic events within the endothelial cell. Activation of these systems impairs endothelial function, augments vasconstriction, increases inflammation and promotes thrombosis; these are the characteristics of so-called endothelial dysfunction.

In diabetes the complex regulation of platelet activity is altered towards:

- increased reactivity and adhesion\(^{13,41,42}\)
- amplified agonist-receptor coupling\(^{43,44}\)
- increased capacity for prostaglandin generation\(^{45-47}\)
- decreased capacity for nitric oxide (NO-) generation\(^{48-50}\)
- enhanced generation of reactive oxygen species\(^{51,52}\)
- resistance to NO- and prostacyclin\(^{53,54}\)
- increased a-granule content with concomitantly increased release\(^{47}\)
- increased platelet volume\(^{58}\)
- increased numbers of glycoprotein receptors GPIb and GPIIb/IIIa\(^{59}\)
- increased membrane protein glycation\(^{60}\)
- altered membrane fluidity\(^{51,52}\)
- increased binding of adhesive RGD-protein ligands (e.g. fibrinogen)\(^{53,64}\)
- increased content and release of plasminogen activator inhibitor-1\(^{65,66}\)

Table 1 summarises the diabetes-related alterations in both intrinsic and extrinsic factors. Patients with diabetes frequently have hypercoagulable blood, as evidenced by increased plasmatic coagulators, depressed fibrinolysis, reduced endothelial thromboresistance and platelet hyper-reactivity.\(^{13,18,21}\) These alterations lead to a downshift of the coagulation threshold in the arterial circulation where occlusive thrombi induce hypoxic damage to parenchymal organs.\(^{47-50}\) On the other hand, occlusion of the capillaries by platelet or mixed platelet-leukocyte emboli may cause sustained occlusion of the functional microcirculation even without any acute clinical symptoms. Basement membrane thickening, microaneurysms and capillary occlusions have been reported and would serve as pathological substrate for the diabetic microangiopathy.\(^{57,71,72}\)

---

### Table 1. Platelet intrinsic and extrinsic factors altered in diabetes (adapted from Yazbek et al.\(^{135}\))

| Factor                                      | Change
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycoprotein IIb/IIIa expression and activation</td>
<td>↑</td>
</tr>
<tr>
<td>Soluble and platelet-bound p-selectin(^{60,55})</td>
<td>↑</td>
</tr>
<tr>
<td>Thrombospondin(^{60})</td>
<td>↑</td>
</tr>
<tr>
<td>CD 36(^{56})</td>
<td>↑</td>
</tr>
<tr>
<td>CD 63(^{56})</td>
<td>↑</td>
</tr>
<tr>
<td>Glycoprotein IIb-IX expression(^{59,137})</td>
<td>↑</td>
</tr>
<tr>
<td>Thromboxane A(_2) activity(^{67})</td>
<td>↑</td>
</tr>
<tr>
<td>b-thromboglobulin(^{31,33})</td>
<td>↑</td>
</tr>
<tr>
<td>Platelet factor(^{40,43,44})</td>
<td>↑</td>
</tr>
<tr>
<td>Coagulation factors and cytokines</td>
<td></td>
</tr>
<tr>
<td>Thrombin generation(^{67})</td>
<td>↑</td>
</tr>
<tr>
<td>Fibrinogen(^{67})</td>
<td>↑</td>
</tr>
<tr>
<td>Prothrombin factors 1 and 2(^{40})</td>
<td>↑</td>
</tr>
<tr>
<td>Thrombin-antithrombin complex(^{46})</td>
<td>↑</td>
</tr>
<tr>
<td>Factors VII, VIII, XI and XII(^{46})</td>
<td>↑</td>
</tr>
<tr>
<td>Kallikrein(^{67})</td>
<td>↑</td>
</tr>
<tr>
<td>Protein C(^{46})</td>
<td>↑</td>
</tr>
<tr>
<td>Fibrinolytic factors</td>
<td></td>
</tr>
<tr>
<td>Tissue plasminogen activator activity(^{40})</td>
<td>↑</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-1 levels(^{40,43,44})</td>
<td>↑</td>
</tr>
<tr>
<td>Endothelial factors</td>
<td></td>
</tr>
<tr>
<td>Von Willebrand factor antigen(^{13,37,141})</td>
<td>↑</td>
</tr>
<tr>
<td>Von Willebrand factor activity(^{28,137,141})</td>
<td>↑</td>
</tr>
<tr>
<td>Vascular cell adhesion molecule-1, intercellular adhesion molecule-1(^{32})</td>
<td>↑</td>
</tr>
<tr>
<td>Tissue factor(^{42})</td>
<td>↑</td>
</tr>
<tr>
<td>Transforming growth factor-(b)^(^{42})</td>
<td>↑</td>
</tr>
<tr>
<td>Type IV collagen(^{42})</td>
<td>↑</td>
</tr>
<tr>
<td>Fibrinectin(^{42})</td>
<td>↑</td>
</tr>
<tr>
<td>NO synthase activity(^{48-50})</td>
<td>↓</td>
</tr>
<tr>
<td>(\text{O}_2^-), \text{ONOO}^-) production(^{51,52})</td>
<td>↓</td>
</tr>
<tr>
<td>Prostacyclin synthesis(^{53,54})</td>
<td>↓</td>
</tr>
<tr>
<td>Prostacyclin sensitivity(^{53,54})</td>
<td>↓</td>
</tr>
<tr>
<td>Receptor for advanced glycation end products expression(^{65,42})</td>
<td>↓</td>
</tr>
<tr>
<td>Other factors</td>
<td></td>
</tr>
<tr>
<td>Plasma histamine(^{43})</td>
<td>↑</td>
</tr>
<tr>
<td>Plasma serotonin(^{43})</td>
<td>↑</td>
</tr>
<tr>
<td>Tumour necrosis factor-(a)^(^{48})</td>
<td>↑</td>
</tr>
</tbody>
</table>

---
The clinical significance of platelet hyperactivity in diabetes may be derived from the Platelet Aggregation as a Risk Factor in Diabetics (PARD) study, showing that the incidence of macrovascular end points in male diabetic patients was strongly related to the degree of spontaneous platelet aggregation at study entry.85,87

Activated platelets: a proteomic approach

With its numerous effects on platelet function, diabetes predisposes to atherosclerosis and thrombosis, including increased primary and secondary platelet aggregation, platelet activation with release of contents of a-granules and enhanced surface expression and activation of glycoprotein IIb/IIIa complex.88-90 Besides the mitogenic factors PDGF (platelet-derived growth factor), TGF-b (transforming growth factor-b), VEGF (vascular endothelial growth factor), bFGF (basic fibroblast growth factor), PDEGF (platelet-derived epidermal growth factor) and IGF-1 (insulin-like growth factor-1), a-granules contain PF-4 (platelet factor-4), PAI-1 (plasminogen activator inhibitor-1), b-thromboglobulin, fibrinogen, fibrinectine, thrombospondin and vWF (von Willebrand factor), which are increased in measurable amounts upon activation.76 In diabetic patients platelets show a hypersensitivity to collagen and the elevated expression of platelet Fc-receptor correlates with the increased collagen-induced aggregation.77,80 Glycoprotein VI has been identified as the major platelet collagen receptor.81,82

Recently, Copping and co-workers characterised the proteins released from activated platelets in a proteomics-based assay and identified more than 300 proteins which were released by platelets upon activation with thixbin.83 Of these proteins many had not been previously attributed to platelets, including secretogranin III (potential monocyte chemoattractant precursor), cyclophilin A (vascular smooth muscle cell growth factor) and calumenine (inhibitor of the vitamin K epoxide reductase-warfarin interaction). It was also confirmed that these proteins were localised in platelets and released upon activation.

Secretogranin III stimulates monocyte adhesion to the vessel wall and their transendothelial migration.91 Cyclophilin A acts as an autocrine stimulus for extracellular signal-repressed kinase (ERK1/2) and vascular smooth muscle proliferation and is secreted by vascular smooth muscle cells in response to oxidative stress.92 Copping et al. propose that cyclophilin A released from activated platelets may stimulate the migration and proliferation of smooth muscle cells, a process becoming implicated in the development of atherosclerosis.93 Since PDGF is also a mitogen for fibroblasts and smooth muscle cells, stimulating angiogenesis and collagen production, there could be an accelerating effect if both growth factors are up-regulated. Calumenin inhibits the activity of vitamin K epoxide reductase, which converts vitamin K to its hydroquinone form, a cofactor for the enzyme g-carboxylyase, thus inhibiting g-carboxylation.94 Because morphogenetic protein (MGP) function requires g-carboxylation in the aortic vessel wall, the authors speculate that warfarin treatment and calumenin deposition in atherosclerotic plaques may promote vascular calcification by blocking vitamin K-dependent g-carboxylation and hence MGP activity.83,87

Therefore it is likely that platelet adhesion contributes to the development of atherosclerosis through proteins which are released from platelets upon activation.

Activated platelets: a genomic approach

As platelets are not supplied with all elements of the transcriptional apparatus, constitutive proteins have to be synthesised in megakaryocytes and packed into platelet precursors, which are afterwards shed into the peripheral circulation.95-97 Glycoprotein GPIIb and GPIb/IIIa act as specific receptors for cytoadhesive proteins. The measured amount of glycoproteins in activated platelets exceeds the expected increase with larger platelet volume.98 Thus, there seems to be a change in the level of expression and/or synthesis. As the surface glycoproteins are megakaryocytic lineage markers, it is assumed that the change takes place at the level of megakaryocytic thrombopoiesis. Insulin influences the size and maturation status of megakaryocytes in culture, indicating a possible influence of insulin on the endomitotic cycle of megakaryocytes.99 A study in adult genetically related Brattleboro (BB) rats, a model for immunogenic type I-like diabetes mellitus, resulted in significant qualitative and quantitative changes in platelets and megakaryocytes when simultaneous DNA and lineage-specific alpha b3 (CD41, GPIIb/IIIa) staining patterns were analysed.100

These results can be explained by an enhanced recruitment of progenitor cells along with consumption of the mature higher-ploidy megakaryocytes in recent-onset diabetes. Enhanced megakaryocyte maturation together with the release of a high number of larger platelets then reflects a superimposed insulin effect, which could be mediated by various interleukins.94-97

The finding that circulating peripheral platelets are already in an activated state in newly diagnosed patients, and even in prediabetic, immunologically affected, patients suggests a chronic condition of ongoing platelet consumption.100 The reaction of the bone marrow may be an increased release of platelets considering that the peripheral platelet count does not appear severely affected in human studies; this suggests increased turnover.100

In summary, the observations in spontaneously diabetic BB rats and available human data suggest that there is a primary alteration in the level of bone marrow (megakaryocytic) stem cells which appears in a thrombopoetin-dependent manner. The interplay of the differential biological mediators upon the process of stem cell differentiation, clonal expansion, megakaryocyte maturation and the process of platelet formation in the diabetic state remains to be elucidated.

Functional changes in platelet proteins may rely on single nucleotide polymorphisms within the megakaryocytic genetic code. The thrombosis-associated PI-A1/PI-A2 single nucleotide polymorphism of the fibrinogen receptor integrin GPIIb/IIIa has been investigated as a candidate of such an assumption. The relative frequency of the PI-A2 allele has been found to be increased in patients with diabetes but, in contrast to the non-diabetic population, this
increase appeared independent from clinical atheroscler-
sis.\textsuperscript{109} This finding supports the hypothesis of a primary risk condition operating by megakaryocyte lineage stem cells and fits with the so-called common soil hypothesis of type 2 diabetes. Consistent with the concept of genetic precondi-
tioning, a polymorphism of the platelet collagen receptor
GPLa/IIa was described to be associated with the develop-
ment of diabetic retinopathy.\textsuperscript{105}

As collagen is an important mediator of platelet activation,
the corresponding receptors have been studied extensively.
The binding of collagen to glycoprotein (GP) VI induces
platelet activation through a pathway that involves phos-
phorylation of the FcRg-chain followed by the binding of Syk and the
phosphorylation-dependent activation of PLCg2.\textsuperscript{77-94}

The platelet integrin \(\alpha_{b} \beta_{1}\) is activated by the binding of
von Willebrand Factor (vWF) to the GPIb complex and may stimu-
late activation of \(\alpha_{b} \beta_{1}\). Three VNTR-polymor-
phisms are relevant to the expression and function of the
GPIb\_a-subunit located within the mucin-like macrogly-
copeptide region of GPIb\_a.\textsuperscript{102,103} Another dimorphism
(Met ⇔ Thr\textsubscript{145}) located within the region of the ligand-
bounding, leucin-rich motifs (LRM) is the basis of the HPA-2
platelet alloantigen system and is in linkage disequilibrium
with the VNTR-polymorphism.\textsuperscript{104,105} Preliminary results
show that the Met\textsubscript{145}-allele seems to be associated with
the risk for coronary artery disease or stroke in young
persons. A C ⇔ T substitution upstream of the start codon
influences an adjacent Kozak sequence and thus the rate
of protein biosynthesis. The −5C allele (f=15% in the western
population) increases the mean level of GPIb\_a on the
platelet plasma membrane due to the enhancement of
mRNA translation.\textsuperscript{106,107} An association of the −5C allele
with the severity of negative outcomes after acute myocar-
dial infarction in younger patients (≤ 62 years) was seen in
recent studies.\textsuperscript{108} A synergistic effect of the −5C and the
Met\textsubscript{145} polymorphisms were detected, resulting in an
increased risk for stroke in young individuals.\textsuperscript{109}

The relative level of \(\alpha_{b} \beta_{1}\) correlates to three \(\alpha_{b}\) alleles.
Allele 1 (807T/1638A/2531C, f=39%) is associated with
increased levels of \(\alpha_{b} \beta_{1}\) whereas allele 2 (807C/1638G/
2531C, f=53%) and allele 3 (807C/1638A/2531C, f=8%) are
each associated with decreased levels of this recep-
tor.\textsuperscript{100,101} Individuals who are homozygous for allele 1
express on average four-fold the amount of \(\alpha_{b} \beta_{1}\) receptor
compared to persons who are homozygous for allele 2. A
strong association between allele 1 and non-fatal myocar-
dial infarction was found among patients below 62 years
and an even stronger correlation was detected in younger
persons (<49 years) in the same study.\textsuperscript{112} A significant asso-
ciation was found in younger patients with stroke\textsuperscript{113}
and in patients with diabetic retinopathy.\textsuperscript{114} In a cohort of
Dutch women, individuals with 807TT genotype and at
least two markers of compromised endothelial function
(smoking, diabetes or microalbuminuria) have a signifi-
cantly increased relative risk of cardiovascular mortality.\textsuperscript{115}

Genetic polymorphisms concerning the transcriptional
regulation of the \(\alpha_{b}\)-gene are single base substitutions with-
in the proximal 5’-regulatory region: C-52T and C-
92G.\textsuperscript{114,117} They contribute to the regulation of integrin \(\alpha_{b} \beta_{1}\)
expression on megakaryocytes and blood platelets and
therefore modulate collagen-related platelet function \textit{in vivo}. The density of platelet \(\alpha_{b} \beta_{1}\) has not been found to be
a risk factor for venous thrombosis. This is a typical finding
for most platelet glycoprotein dimorphisms.

**Leukocyte-platelet cross-talk in diabetes**

Pathophysiological processes such as inflammation or
thrombosis show multicellular activation involving
endothelial cells, leukocytes and platelets. The complex
interactions between these cells – the cross-talk – is influ-
enced by several mediators. Platelets may influence leuko-
cyte activation, chemotaxis and phagocytosis.\textsuperscript{108}

Platelet-derived adenosine nucleotides and platelet-
derived growth factor (PDGF) may induce leukocyte
degranulation. Adherent platelets,\textsuperscript{117} platelet-derived
microparticles,\textsuperscript{120} and platelet-release substances, such as
PDGF, platelet factor 4 and thromboxane A2 (TXA2)
may inhibit neutrophil superoxide production. Leukocyte
chemotaxis, adhesion and superoxide generation are
inhibited by p-selectin and NO released from
platelets.\textsuperscript{122,123} In summary, platelets and platelet-derived
products influence leukocyte function in several ways.

Leukocytes may influence platelet adhesion directly or
through leukocyte-released superoxide. Platelet aggrega-
tion and secretion are induced by superoxide, platelet activat-
ing factor, metalloproteases like cathepsin G, and neu-
rophil elastase. Platelets and leukocytes may form platelet-
leukocyte aggregates or conjugates (PLAs), mainly via
platelet-expressed p-selectin and its receptors p-selectin
glycoprotein ligand-1 (PSGL-1) and CD15, as well as via
fibrinogen bridging between glycoprotein (GP) IIb/IIIa and
CD11b/CD18.\textsuperscript{124}

Li and co-workers were able to demonstrate platelet-
leukocyte cross-talk in a whole blood assay.\textsuperscript{114} Leukocytes
activated with N-formyl-methionyl-leucyl-phenylalanine
(MLP) induced platelet activation with increased expres-
sion of platelet p-selectin. The effects may be related to the
generation of PAF, 5-lipoxygenase production and super-
oxide. Collagen-induced activation of platelets led to a sig-
nificant leukocyte activation which was monitored by the
expression of CD11b on leukocytes. During platelet-leuko-
cyte cross-talk, p-selectin and GPIIb/IIIa take part in cellu-
lar signalling.\textsuperscript{124}

The complex pathological process of diabetic angio-
pathy involves atherosclerosis, inflammation and thrombo-
osis, with platelet and leukocyte dysfunction playing a
central role. In diabetic microangiopathy, increased
platelet and leukocyte activation and heterotypic aggrega-
tion are present.\textsuperscript{2,125-128} Leukocytes from diabetic subjects
exhibit enhanced adhesion molecule expression\textsuperscript{103}
and increased aggregability. They are associated with impaired
cell deformability,\textsuperscript{129} decreased chemotaxis\textsuperscript{128} and altered
superoxide anion production.\textsuperscript{131}
Platelets and leukocytes are known to interact and modulate each others’ function. Platelet-leukocyte cross-talk involves both heterotypic cell-cell contact and soluble mediators released from platelets and leukocytes which may prime both platelets and leukocytes and thus enhance platelet and leukocyte reactivity.\(^{12}\) Hu and co-workers evaluated platelet-leukocyte cross-talk and its contribution to platelet and leukocyte dysfunction and microangiopathy in type 1 diabetes mellitus patients.\(^{13}\) Whereas basal single platelet p-selectin and leukocyte CD11b expression levels were similar in diabetic patients and healthy subjects, circulating platelet-leukocyte aggregates and the amount of plasma elastase were elevated in diabetic patients. Upon treatment with the thromboxane A\(_2\)-analogue U46619, a remarkable increase of platelet p-selectin expression and platelet-leukocyte aggregation was detectable. The leukocyte-specific agonist N-formylmethionyl-leucyl-phenylalanine (fMLP) induced more marked CD11b expression in patients with diabetes mellitus with microangiopathy. Platelet-leukocyte cross-talk induced by U46619 showed no difference between patients and healthy subjects. FMLP evoked marked leukocyte activation, which subsequently caused mild platelet p-selectin expression. This leukocyte-platelet cross-talk was more pronounced in patients than in healthy subjects. Enhanced leukocyte-platelet cross-talk was correlated to platelet hyperactivity among diabetes mellitus patients with microangiopathy only.

Hu et al. found that patients with diabetes mellitus had elevated plasma levels of elastase, which can in turn induce platelet activation. Also, other soluble mediators of platelet-leukocyte cross-talk such as platelet activating factor (PAF) and the superoxide anion are enhanced in type 1 diabetes and could therefore act together.\(^{12}\) Platelet-leukocyte monocyte aggregation was observed in diabetics with microangiopathy, which may facilitate tissue factor transfer between monocytes and platelets,\(^{13,14}\) resulting in increased thrombin generation. The fact that basal p-selectin levels did not differ significantly but platelet-leukocyte aggregates were distinguishable in healthy subjects and patients lead to the concept that platelet-leukocyte aggregates may be a more sensitive marker of platelet activation in vivo. Hu et al. suppose that leukocyte-platelet cross-talk may also prime platelets to be more sensitive to activation, which was demonstrated in the in vitro activation with U46619 in the case of patients with microangiopathy.\(^{12}\)

Type 1 diabetes is associated with platelet and leukocyte hyperactivity, enhanced platelet-leukocyte aggregation and enhanced leukocyte-platelet cross-talk, especially in patients with microangiopathy. The enhancement of leukocyte-platelet cross-talk may contribute to diabetic platelet hyperreactivity and to the microvascular complications in type 1 diabetes mellitus.

**Conclusion**

In diabetes a vicious cycle is set up in which vascular disease may lead to platelet damage, and altered platelet function may contribute to vascular disease. The loss of sensitivity to the normal restraints generated by the vascular endothelium is the major defect in platelet function. Platelet-leukocyte cross-talk plays a pivotal role in platelet activity and is a very sensitive analysis tool. Inflammation not only leads to activation of coagulation, but also coagulation affects inflammatory activity. As the alterations in platelet activation are partly dependent on the metabolic status of the patient, various treatment modalities for diabetes mellitus affect platelet function differently. With analysis of the platelet proteome it may become possible to recognise the proteins involved. This could lead to new therapeutic intervention concepts in dealing with diabetes.

---

**References**


21. Banga JD, Sjøa JJ. Diabetes mellitus, vascular disease and thrombo-


77. Poole A, Gibbins JM, Turner M et al. The Fc receptor gamma-chain and the tyrosine kinase Syk are essential for activation of mouse platelets by collagen. EMBO J 1997;16:2334-41.


