Inflammation and thrombosis in diabetes

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Summary
Patients with diabetes mellitus are at increased risk of cardiovascular morbidity and mortality. Atherothrombosis, defined as atherosclerotic lesion disruption with superimposed thrombus formation, is the most common cause of death among these patients. Following plaque rupture, adherence of platelets is followed by local activation of coagulation, the formation of a cross-linked fibrin clot and the development of an occlusive platelet rich fibrin mesh. Patients with diabetes exhibit a thrombotic risk clustering which is composed of hyper-reactive platelets, up regulation of pro-thrombotic markers and suppression of fibrinolysis. These changes are mainly mediated by the presence of insulin resistance and dysglycaemia and an increased inflammatory state which directly affects platelet function, coagulation factors and clot structure. This prothrombotic state is related to increased cardiovascular risk and may account for the reduced response to antithrombotic therapeutic approaches, underpinning the need for adequate anti-thrombotic therapy in patients with diabetes to reduce their cardiovascular mortality.

Keywords
Diabetes mellitus, inflammation, thrombosis, cardiovascular disease

Introduction
The prevalence of diabetes mellitus is rising with studies predicting more than 350 million people affected by 2030 (1). This population is at major risk for the development of cardiovascular disease (CVD) and consequent morbidity and mortality (2). Myocardial infarction and sudden cardiac death are the clinical manifestations of atherothrombosis, which is defined as atherosclerotic plaque rupture with superimposed thrombus formation (3). Several studies demonstrated that diabetic patients without prior cardiovascular disease have the same rate of myocardial infarction (MI) compared to non-diabetic subjects who had a previous event (4–6), highlighting the high risk of this population. The majority of diabetic patients have evidence of underlying insulin resistance (7), which in type 2 patients occurs prior to clinical presentation and is characterised by a reduction in sensitivity to the action of insulin preceding the development of beta cell failure and hyperglycaemia, the latter being dominant features of longstanding diabetes. Low grade inflammation is now widely accepted to be one link between insulin resistance, type 2 diabetes and CVD (8, 9). The origins of the heightened inflammatory activity are diverse, although abdominal obesity is thought to play a central role in this process (10, 11). The present review will focus on the effects of inflammation, insulin resistance and hyperglycaemia on thrombotic risk in diabetes patients.

Role of inflammation in atherothrombosis
Arteriosclerosis is recognised as a chronic inflammatory disorder which starts at an early age. Various changes, including insulin resistance, oxidative and shear stress lead to reduced endothelial function, promoting the migration of immune cells (macrophages and T-lymphocytes) into the vascular wall (12, 13). Later in atherogenesis, proliferation of smooth muscle cells (SMCs) and deposition of collagen increases, resulting in the development of an arteriosclerotic plaque which is protected by a fibrous cap comprised of collagen, elastin and proteoglycans derived from SMCs (3). Arteriosclerotic plaque may remain asymptomatic for many decades as the disease progresses. However, in susceptible individuals, inflammatory cells within the lesion expressing matrix-degrading metalloproteases (MMPs) and other proteases such as caphespin and trypstase/chymase result in enhanced matrix breakdown (14). These processes lead to thinning of the fibrous cap which may give rise to plaque rupture and superimposed thrombus formation, causing the acute complications of CVD, including unstable angina (UA) and MI.

Following plaque rupture, thrombosis is initiated when thrombotic components of the plaque are exposed to circulating blood. Platelet activation at the site of injury plays a major role in thrombus formation and proceeds in three stages: i) an initiation phase involving platelet adhesion, ii) an extension phase which includes activation, additional recruitment and aggregation of platelets, and iii) a perpetuation phase composed of platelet stimulation and stabilisation of clots (15). During the initiation phase platelets roll,
adhere, and spread on the collagen matrix to form an activated platelet monolayer. Adhesion is mediated by interaction between the glycoprotein (GP) Ib/V/IX receptor complex on the platelet surface with von Willebrand factor (vWF) and between the GP VI and GP Ia proteins with collagen at sites of vascular injury allowing the arrest and activation of platelets (16). Following adhesion and activation, local platelet activating factors, including adenosine diphosphate (ADP), thromboxane A₂ (TXA₂), serotonin, collagen and thrombin, are released. These factors help to recruit additional circulating platelets, and also contribute to several distinct manifestations of platelet activation, including, independent of the stimulus, the same series of actions: i) change of shape from discoid to a pseudopodial structure due to mobilisation of signalling molecules within the platelet, especially calcium, diacylglycerol (DAG), and inositol 1,4,5-trisphosphate (IP₃); ii) expression of pro-inflammatory molecules (e.g. P-selectin, soluble CD40 ligand and others); iii) secretory process of α-granules, dense bodies, and lysosomes; iv) disposal of arachidonic acid, which is rapidly converted to prostaglandins and lipoxygenase products; and v) conversion of the GPIIb/IIIa receptor into an active form, effectively allowing platelet aggregation (15, 17–19). The aggregation response is initiated when circulating platelets are exposed to agonists released by the plaque such as vWF and collagen. This triggers a signal promoting ion flux, protein kinase activation, cytoskeletal polymerisation, and arachidonic acid metabolism, resulting in conformational changes in the GP surface receptor IIb/IIIa (GPIIb/IIIa) to a ligand receptive state. Ligand receptive GPIIb/IIIa bind fibrinogen which bridges adjacent platelets and facilitates aggregation (3, 20). These processes are followed by local activation of coagulation which may involve both the extrinsic and intrinsic pathways. Activation of the extrinsic pathway includes binding of tissue factor (TF) and factor VIIa ([Fig. 1]) whilst activation of the intrinsic pathway encloses assembly of the intrinsic Xase complex consisting of activated factors VIIa and IXa. Both processes give an enzymatically active ‘tenase’ complex which activates factors IX and X, leading to thrombin generation, fibrinogen and FXIII activation and fibrin clot formation (21, 22). TF is expressed at high levels in macrophages and SMCs within arteriosclerotic lesions (23–25) and is thought to have a major role in determining thrombogenicity of human arteriosclerotic lesions. In contrast plasma proteins in the presence of a phospholipid surface classically provided by platelets are known as the source for the intrinsic Xase complex (26). However, in vitro work suggests that exposure of macrophages and SMCs to oxidised low-density lipoprotein (oxLDL) enhances their ability to support activity of the intrinsic pathway to increase plaque thrombogenicity (27). Together, these processes lead to the development of a platelet-rich thrombus which is stabilised via bridges formed by fibrinogen.

The common soil hypothesis, originally put forward by Stern, suggested that diabetes and CVD were essentially the same condition with common antecedents. Multiple factors such as insulin resistance, hyperglycaemia and oxidation products have been suggested to underpin this association, however in recent years low grade inflammation has emerged as a strong candidate involved in
Early changes include endothelial dysfunction with decreased nitric oxide (NO) production. NO is a key player in negative regulation of platelet activity and decreased levels result in hyper-reactivity of platelets (28). Furthermore, cytokines produced by inflammatory cells, such as macrophages and T-lymphocytes, induce TF expression in endothelial cells, macrophages and SMCs, thereby enhancing the pro-thrombotic properties of the arteriosclerotic plaque (29–31). The interaction between inflammation and coagulation is not limited to the site of vessel injury. Plasma levels of inflammatory markers are elevated in CVD (32) and correlate with incident diabetes (33–36). In obesity, which is associated with both diabetes and CVD, visceral adipose tissue is a major source for inflammatory activity. In overweight subjects adipose tissue contains activated T-lymphocytes (37) and macrophages (38, 39) which interact with adipocytes to produce inflammatory cytokines including interferon (IFN)-γ (40), monocyte chemotactic protein (MCP)-1, tumour necrosis factor (TNF)α, interleukin (IL)-6, and the fibrinolytic inhibitor plasminogen activator inhibitor (PAI)-1 (41). The expression of these cytokines contributes to increased production of fibrinogen to induce, together with elevated PAI-1 levels, a pro-thrombotic milieu (35, 42–50).

In the following, the interaction between inflammatory processes and their relation to coagulation in diabetes will be described in more detail.

## Platelet alterations

Activation and aggregation of platelets is one of the first steps following plaque rupture. In diabetes, platelet hyper-activation and hyper-aggregation plays a crucial role in thrombotic complications associated within this condition. In general, platelets are reported to respond more frequently to sub-threshold stimuli, becoming consumed more rapidly which results in an accelerated thrombopoiesis of fresh and hyper-reactive platelets in diabetes (51). This so called platelet dysfunction is related to several mechanisms including metabolic changes, oxidative stress and endothelial dysfunction (Table 1) (32).

### Table 1: Effects of altered glycaemic control on platelet function.

<table>
<thead>
<tr>
<th>Metabolic changes</th>
<th>Oxidative stress</th>
<th>Endothelial dysfunction</th>
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<tbody>
<tr>
<td>• Thromboxane synthesis ↑</td>
<td>• Platelet nitric oxide production ↑</td>
<td>• Nitric oxide production ↓</td>
</tr>
<tr>
<td>• Sensitivity to agonists ↑</td>
<td>• Intracellular Ca²⁺ concentration ↑</td>
<td>• Reactive oxygen species (ROS) ↑</td>
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<tr>
<td>• Activation of protein kinase C</td>
<td>• Platelet membrane sodium-potassium-ATP activity ↓</td>
<td>• Pro-inflammatory cytokines ↑</td>
</tr>
<tr>
<td>• Nitric oxide production ↓</td>
<td>• Activation of protein kinase C and nuclear factor-xB</td>
<td>• Platelet adhesion molecules ↑</td>
</tr>
<tr>
<td>• Superoxide formation ↑</td>
<td>• Formation of 8-iso-prostaglandin F₂α</td>
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<tr>
<td>• Non-enzymatic glycation of platelet membrane proteins</td>
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<tr>
<td>• Expression of p-selectin and glycoprotein receptors ↑</td>
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<tr>
<td>• Insulin sensitivity ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Reactive oxygen species (ROS) ↑</td>
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### Metabolic changes

Hyperglycaemia, a diagnostic characteristic of diabetes, plays a causal role in platelet hyper-reactivity. Increased thromboxane synthesis is related to platelet hyper-reactivity and is tightly regulated by glucose control (53). Acute, short-term hyperglycaemia also induces increased activation of platelets exposed to high shear stress conditions (54) and leads to increased sensitivity to agonists due to activation of protein kinase C (PKC), decreased production of platelet-derived NO, and increased formation of superoxide (55, 56). In addition, Ca²⁺ homeostasis is known to be impaired in diabetes with an increase in calcium mobilisation from intracellular storage pools, resulting in increased intracellular Ca²⁺ levels. This is thought to be due to a change in the activity and the direction of the Na⁺/Ca²⁺ exchanger (57). Furthermore, hyperglycaemia results in non-enzymatic glycosylation (glycation) of platelet membrane proteins which may cause changes in protein structure and conformation. This may lead to alterations of the membrane lipid dynamics causing enhanced surface expression of P-selectin and GP receptors, leaving platelets more susceptible to activators (55, 58).

Increased platelet sensitivity to aggregation agents can also be explained by an effect of non-enzymatically glycated low-density lipoproteins (glycLDL), which renders platelets more susceptible to oxidative stress. Moreover, glycLDL may cause platelet dysfunction by an increase in intracellular Ca²⁺ concentration and platelet NO production, as well as inhibition of the platelet membrane Na⁺/K⁺-adenosine triphosphatase activity. Whilst increased Ca²⁺ concentrations are consistent with the enhanced platelet sensitivity to aggregation agents, the higher NO production is thought to be a result of the higher Ca²⁺ levels as the form of NO present in normal human platelets is Ca²⁺-calmodulin dependent (59). Furthermore, other changes of the lipid profile can be found in patients with diabetes mellitus including elevated triglycerides, decreased high-density lipoprotein (HDL) and increased small dense LDL levels. All of these may affect platelet function by decreasing membrane fluidity or directly interacting with the intracellular system (55).

Furthermore, platelets retain a functionally active insulin receptor (60). Insulin interacts with ADP- and thrombin-induced platelet functions through inference with the P2Y₁₂-mediated...
regulation of G_i. After receptor binding, insulin activates the insulin receptor substrate-1 (IRS-1) through tyrosine phosphorylation, which initiates association with G_\text{\alpha}-subunit. This results in inhibition of G_\text{\alpha}\_i activity and impaired suppression of cyclic adenosine monophosphate (cAMP), thus inhibiting P2Y_{12} signalling and thereby reducing platelet reactivity (61). However, in the presence of diabetes platelets lose their responsiveness to insulin leading to increased adhesion, aggregation, and pro-coagulant activity (62).

**Oxidative stress**

Oxidative stress represents another modulator of platelet activation. Studies demonstrated that hyperglycaemia induces an increase in glycation of LDL, which renders platelets more susceptible to oxidative stress by increasing platelet NO production, intracellular Ca^{2+} concentration, and inhibiting platelet membrane sodium-potassium-ATP activity (59, 63). Furthermore, chronic hyperglycaemia may induce reactive oxygen species (ROS) production directly via glucose metabolism and auto-oxidation and indirectly through the formation of advanced glycation end products (AGEs) and their receptor binding. ROS activates signalling molecules within endothelial cells including PKC and nuclear factor-κB leading to transcription of genes encoding pro-inflammatory and pro-thrombotic molecules (64). In addition, ROS leads to the formation of 8-iso-prostaglandin F_2\alpha, a non-enzymatic oxidation product of circulating LDL and arachidonic acid, which induces vasoconstriction and platelet hyper-reactivity (65–67).

**Endothelial dysfunction**

Endothelial dysfunction plays a crucial role in the development of atherothrombosis. Endothelial cells produce mediators of vasoconstriction (i.e. NO and prostacyclin) and vasoconstriction (i.e. angiotensin II and TXA) to regulate vascular tone and thrombotic processes. In diabetes, vasoconstrictive and pro-thrombotic effects dominate, and hyperglycaemia and insulin resistance play a crucial role by inhibiting NO production and increasing ROS production, leading to an increased expression of pro-inflammatory cytokines and platelet adhesion molecules (68). Apart from affecting platelet function these alterations may also alter coagulation and fibrinolysis to further contribute to an enhanced thrombotic milieu in diabetes.

**The fluid phase of coagulation**

A variety of studies have reported alterations in coagulation factors in relation to the metabolic milieu associated with insulin resistance and type 2 diabetes. Some, such as increased fibrinogen levels appear to be initiated by an inflammatory profile, whilst activation of coagulation proteins such as factor VII and XII is enhanced by the presence of triglyceride rich particles. Hyperglycaemia itself can also modify coagulation processes through post translational modifications of protein structure/function.

**Tissue factor**

TF is the key initiator of the coagulation cascade which binds to factor VIla leading to activation of factors IX and X resulting in thrombus formation (69). Both vascular and non-vascular cells are known to express TF including endothelial cells, SMCs, monocytes / macrophages, and platelets. Under physiological conditions endothelial cells express very little TF (70). However, after stimulation with cytokines including TNF\(\alpha\) (71), IL-1\(\beta\) (72), or mediators such as histamine (73), thrombin (74) or oxLDL (75), TF expression is increased. In contrast, SMCs constitutively express TF and in atherosclerosis SMCs and macrophages are known to express TF at high levels (23–25, 76, 77). Monocytes are the major source of vascular cells expressing TF (78). Similarly to endothelial cells, basal expression levels are low but upon stimulation expression increases significantly (79–82). However the role of platelets as a possible source for TF within the circulation is controversial. Butenas et al. were not able to detect TF activity on activated platelets (83), whilst in contrast other studies showed functionally active TF in platelets with exposure on the cell surface following activation (84–86).

In diabetes, TF levels are elevated (87) partly in relation to underlying low grade inflammation. In obesity, adipose tissue functions as a site of TF production due to the release of TF by adipocytes and resident inflammatory macrophages in the stromavascular fraction (88). Clamp studies demonstrated that hyperglycaemia results in elevated TF levels regardless of insulin concentration (89) and both AGEs and ROS are also able to increase TF level (70, 90). A recent study by Gerrits et al. demonstrated that insulin can inhibit TF synthesis in normal platelets whereas insulin inhibition is lost in platelets from patients with type 2 diabetes resulting in 1.6 fold higher TF expression (91).

**Factor VII**

TF binds and activates factor VII (FVII) resulting in activation of the coagulation cascade. More than 20 years ago the Northwick Park Heart study associated high levels of FVII coagulant activity with an increased risk for ischaemic heart disease (92). Since then studies have both confirmed (93) and contradicted this original finding (94–96). Elevated levels of FVII:ct have been associated with the metabolic syndrome in otherwise healthy individuals (97, 98). In first-degree relatives of patients with diabetes, who are known to have an elevated risk for the development of diabetes and CVD, FVII:ct levels are elevated and cluster with other risk factors.
associated with insulin resistance (99). However a study of diabetes patients and age and obesity matched controls demonstrated lower FVIIc and FVII antigen levels in diabetes compared to healthy controls, suggesting that increased FVIIc and FVII antigen levels are more related to body mass index and age than diabetes (100). A recent report by Karatela and Sainani could not confirm the association between FVII coagulant activity and obesity, but strengthens a positive correlation between FVIIc levels and plasma triglycerides, which are known to be elevated in insulin resistant diabetes (101–103).

Von Willebrand factor and factor VIII

vWF is selectively expressed in endothelial cells and platelets. It has two major functions: i) to promote platelet adhesion to the vascular wall following endothelial damage and ii) vWF serves as a carrier protein in the plasma for FVIII, stabilising it within the circulation and increasing the half life of FVIII. Low levels of vWF are associated with a platelet bleeding disorder, whilst FVIII is the protein deficient in classical haemophilia. Elevated levels of vWF and FVIII have been related to cardiovascular risk, although it is likely that this occurs in concert with other risk factors. Expression of vWF is regulated by a number of agonists including thrombin, complement components, histamine and numerous other mediators (104). Some of these agonists have an inflammatory component to their effect, linking elevated vWF to this aspect of the diabetes state. Many studies have demonstrated an association between elevated vWF and / or FVIII levels and CVD, but in most this association was lost after adjusting for common cardiovascular risk factors (95, 105, 106). However, elevated vWF and FVIII levels correlate with diabetes (107) and in such patients the association between vWF / FVIII levels and CVD persisted even after adjustment for traditional risk factors (108–110). Several cytokines, including TNFα and IL-6 are known to stimulate vWF expression from endothelial cells and CRP as a marker for low grade inflammation has been shown to be associated with elevated vWF levels, which could be one mechanism by which diabetes affects vWF levels (106, 111).

Factor XIII

Coagulation FXIII is a tetrameric pro-transglutaminase that consists of two A and B subunits and which, when activated by thrombin, has a crucial role in cross-linking a fibrin clot to provide a structure which has a rigid structure resistant to clot lysis. Under normal conditions FXIII-A is found only as a complex with the B subunit in plasma. The B subunit serves as a carrier protein for the A subunit and is found in excess in plasma, with 50% circulating as free molecules (128). Following activation by thrombin the A subunit is cleaved from the B subunit in a reaction facilitated by calcium and fibrin, releasing the active site of FXIII-A and catalysing cross-linking between the α and γ chain of fibrin, to stabilise clot structure. A role for FXIII in CVD was initially demonstrated by Kohler et al. and confirmed by others, showing that the FXIII-A Val34Leu polymorphism provides a protective effect from MI (128, 129). In diabetes, FXIII levels have been shown to be elevated, whereas FXIII cross-linking activity was not different compared to controls. Factor XIII B subunit levels correlated with features of the metabolic syndrome both in diabetes patients, their first degree relatives and healthy south Asian subjects (130, 131). The absence of an association between the FXIII A subunit and the insulin resistance syndrome may reflect the different site of synthesis with the A subunit, which is produced by haematopoietic cells and the B subunit by hepatocytes (113).
tissue of type 2 diabetic subjects (132), and we and others (133) have demonstrated C3 to be present in a fibrin clot and to have a role in thrombus formation in patients with MI. Our recent in vitro-experiments revealed that C3 binds to fibrin with tight affinity and prolongs clot lysis time in control subjects with further increases in the presence of diabetes (unpublished data, [134, 135]), directly interacting with fibrinolysis to influence the pro-thrombotic milieu.

Plasminogen activator inhibitor

PAI-1 belongs to the serine protease inhibitor (serpin) superfamily. It is a single chain GP which can be secreted from a variety of cells including hepatocytes, vascular endothelial cells, SMCs, adipocytes and platelets (136). It is responsible for the regulation of the fibrinolytic system by rapid formation of inactive complexes with its target serine proteases, tissue-type (t-PA) and urokinase-type (u-PA) plasminogen activators to prevent plasmin generation and thereby fibrin(ogen)olysis (137, 138). Various studies have shown that PAI-1 levels are elevated in CVD (139, 141). In diabetes PAI-1 levels are increased and independently associated with cardiovascular risk (48, 142, 143). Furthermore, various studies demonstrated an association of PAI-1 with features of the metabolic syndrome, including body mass index, blood pressure, plasma triglycerides and insulin levels in both healthy individuals and patients with diabetes (48, 144, 145). The liver is thought to be the major source for PAI-expression. PAI-1 is an acute phase reactant and cytokines can alter plasma levels by induction of expression in the liver (146). Similarly, insulin, very-low density lipoproteins and free fatty acids stimulate PAI-1 expression (147). In addition to the liver, adipocytes are known to express PAI-1 and levels are elevated in obesity (148). Macrophages play an important role in this process as they can produce PAI-1 themselves (149) and macrophage cytokines such as TNFα stimulate PAI-1 production in adipose tissue (150). Furthermore, studies of human adipocytes and adipose tissue explants have reported that insulin induces PAI-1 production in adipocytes (151). However, a single stimulus in vivo may be insufficient to result in increased PAI-1 concentrations but several stimuli as present in diabetic state are required (152, 153).

Tissue plasminogen activator

T-PA is a single chain active serine protease and is synthesised by endothelial cells. Under physiological conditions t-PA activates plasminogen at a very slow rate. After formation of a fibrin clot both t-PA and plasminogen bind to fibrin resulting in a 1,000-fold enhanced catalytic activity of t-PA (154). Clinical studies have found an association of t-PA with components of the metabolic syndrome (155, 156) and levels were higher in subjects with glucose intolerance compared to healthy individuals (157). Similarly, other clinical studies demonstrated an elevation of t-PA levels in diabetes patients (158, 159). Given that t-PA is responsible for fibrinolysis of fibrin clots one would expect a beneficial effect of elevated plasma levels. However, several studies demonstrated an association between elevated t-PA levels and CVD (160–163). PAI-1 and t-PA levels have found to be strongly associated, with both forming complexes within circulation (164), and elevated t-PA levels may reflect raised PAI-1 levels in insulin resistance and diabetes.

Strategies to reduce thrombotic risk in diabetes

In summary, patients with diabetes feature an increased prothrombotic risk related to complex interactions between the fluid (complement, coagulation/fibrinolysis) and cellular (macrophage, platelet) phases of inflammatory and thrombotic processes. These interactions promote all phases of vascular damage from early endothelial dysfunction through to plaque formation, rupture and occlusive thrombus formation. The specific changes in thrombus formation generates a platelet-rich clot which is more compact, resistant to lysis and associated with increased cardiovascular risk (Fig. 2) (119, 120). Current guidelines for primary prevention of CVD in people with diabetes mellitus by the American Heart and Diabetes association (165) recommend, beside general lifestyle modifications, the therapy of overall cardiovascular risk factors, which include management of high blood pressure and elevated lipids. In addition glycaemic control is important and the HbA1c goal in general is <7% with an individual goal as close to normal (<6%) as possible without causing significant hypoglycaemia (165). However, lowering of HbA1c has only a modest effect on cardiovascular risk reduction in diabetes patients (166). Therefore, to prevent CVD oral anti-diabetic agents (OADs) should ideally lower blood glucose and address the cardiovascular risk cluster; an aspect of management which is reviewed comprehensively elsewhere (167). Briefly, some of the OADs exhibit favourable effects on the pro-thrombotic profile. As demonstrated by the UK prospective Diabetes Study (UKPDS), metformin reduced the risk of ischaemic heart disease compared to other hypoglycaemic agents (168). This may be explained as metformin affects the coagulation system by inhibiting platelet aggregation and reducing levels of fibrinogen, factor VII and PAI-1. Furthermore, clots formed in the presence of metformin lyse more quickly suggesting a direct effect on clot structure (169, 170). Relatively little is known about the role of sulphonylureas on the thrombotic profile. However, studies demonstrated that they exert anti-platelet activity (171, 172) and reduce PAI-1 levels (173). Thiazolidinediones show similar effects on both platelets and PAI-1 levels (174–176). Furthermore, clinical studies demonstrated that glitazones can delay progression of atherothrombotic lesions (177), although outcome studies have been disappointing. In the PROactive trial, pioglitazone failed to reach the primary end point (all-cause mortality, non-fatal silent and non-silent MI, stroke, acute coronary syndrome, cardiac revascularisation, major leg amputation or leg re-vascularisation) but...
Figure 2: Components of the pro-thrombotic risk cluster in diabetes mellitus. The presence of these alterations leads to the development of a compact and dense clot structure which is more difficult to lyse and associated with an increased cardiovascular risk. FVII:c: factor VII; vWF: von Willebrand factor; FVIII: factor VIII, FXIII: factor XIII, PAI-1: plasminogen activator inhibitor-1; t-PA: tissue-plasminogen activator.
telet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) showed, that subjects with diabetes tended to have a greater reduction in ischaemic events (HR 0.70) without an observed increase in major bleeding rates and therefore a greater net benefit with prasugrel compared to clopidogrel (194). In contrast, the PLATElet inhibition and patient outcome (PLATO) trial demonstrated, that ticagrelor, when compared to clopidogrel, reduced ischaemic events in acute coronary syndrome patients irrespective of diabetes status and glycaemic control, without an increase in major bleeding (195).

In addition to the anti-atherothrombotic properties of these agents some also exert an impact on underlying low grade inflammation. In general, life style intervention, particularly weight loss results in a decrease in inflammatory proteins (196, 197), thereby improving insulin resistance and the pro-thrombotic milieu. Thiazolidinediones, peroxisome proliferator-activated receptor-γ (PPARY) agonists, which primarily act on adipocytes but also on macrophages (198), are well known to decrease inflammatory molecules including CRP, TNFα and IL-6 independent of improvements of insulin sensitivity (32, 199). Similarly, metformin has favourable effects on some inflammatory markers such as CRP. However, this effect is not as pronounced as CRP reduction following weight reduction or treatment with PPARγ agonists (200). Statins, which are used to reduce the overall cardiovascular risk in these patients, are recognised to exert anti-inflammatory properties, characterised by a reduction of high sensitivity-CRP and a decrease of inflammatory cells within the arteriosclerotic plaque (201). The anti-inflammatory properties of thiazolidinediones, metformin and statins are side effects of their primary mode of action. In contrast, high dose aspirin directly inhibits inflammation and the glucose lowering effects of salicylates, described more than a century ago, are thought to be due to this mode of action (202–204).

Conclusion and future directions

Patients with diabetes are at increased risk of morbidity and mortality from CVD. Athero-thrombosis is a complex disease promoted by inflammatory thrombotic interactions which increase risk of occlusive arterial disease. In insulin resistant type 2 diabetes and in long standing type 1 diabetes, the fluid and cellular phases of inflammation and thrombosis formation are up regulated leading to further increased risk of arterial disease. The importance of thrombosis formation in the pathogenesis of, and outcome from, acute coronary syndromes emphasises the need for further understanding of the mechanisms underpinning the effects of the metabolic milieu associated with the presence of diabetes. There is an urgent need for clinical studies of carefully phenotyped patients with diabetes to establish the optimum anti-thrombotic regimes for the management of acute coronary syndromes and for the primary and secondary prevention of CVD in this population.

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Conflict of interest

None declared.

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