Chapter 17
Mechanisms of Hypercoagulation and Aberrant Clot Lyses in Type 2 Diabetes

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Abstract Type 2 diabetes (T2D) has attained a pandemic status with more than half a billion cases expected by 2030; and many having cardiovascular complications, with main hallmark of these events, the presence of systemic (chronic) inflammation. Systemic inflammation is in turn characterized by a changed haematological system, including a pathologic coagulation system, endothelial dysfunction and ultimately vascular complications. This chapter discusses the pathogenesis of T2D, and how it is interlinked with cardiovascular disease and inflammation. Literature is reviewed that shows the inflammatory nature of the T2D, how this inflammatory profile and pathological inflammatory markers, affects the coagulation system, and how it plays a role in the impaired vascular function, which is a fundamental characteristic of T2D. As part of the pathogenesis we discuss the considerable literature showing that both hypercoagulability and hypofibrinolysis are present in a large number of inflammatory and vascular diseases, including T2D. We discuss novel methods to monitor and study manifestations of both hypercoagulation and hypofibrinolysis in T2D. We conclude by suggesting that the multifaceted nature of the condition suggests a patient-orientated approach is followed where both traditional and novel methods should be equally explored in the monitoring of T2D patients.

Keywords Type 2 diabetes • Hypercoagulation • Hypofibrinolysis • Inflammatory markers • Cardiovascular complications • Clot structure

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17.1 Introduction

Type 2 diabetes (T2D) have reached pandemic status with more than half a billion cases expected by 2030 [1]. Comorbidities of both obesity and T2D include cardiovascular disease, cancer and neuropsychiatric disorders [2]. Cardiovascular disease in particular, is one of the most common diabetes-associated complications, as well as a leading cause for death in these patients [3]. Important cardiovascular events include myocardial infarction and stroke [4] and the main hallmark of these events are the presence of systemic (chronic) inflammation. Systemic inflammation is in turn characterized by a changed haematological system, including a pathologic coagulation system [5–9], endothelial dysfunction [10] and ultimately vascular complications.

This chapter reviews and discusses literature that shows the inflammatory nature of the condition, how this inflammatory profile affects the coagulation system, including hyercoagulation and mechanisms of impaired clot lyses; and finally shows how these changes lead to the pathological and impaired vascular function, which is a fundamental characteristic of T2D (see Fig. 17.1).

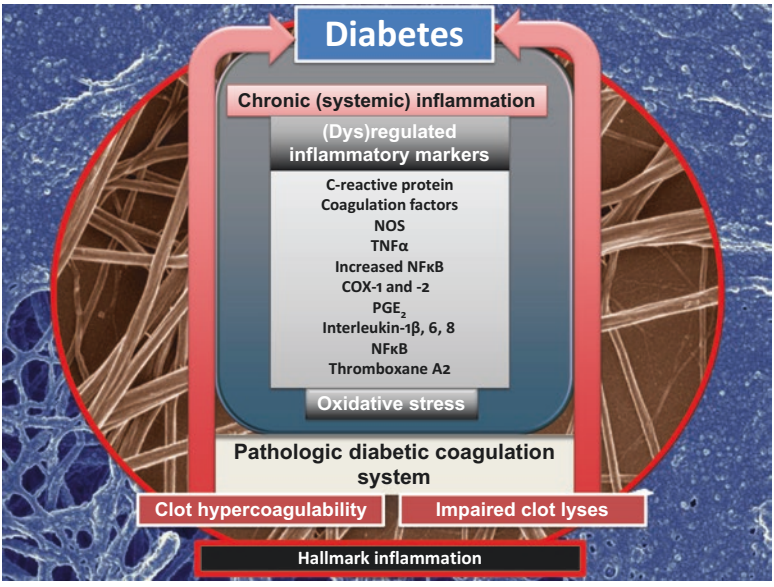

Fig. 17.1 The inflammatory nature of type 2 diabetes

17.2 Markers of Systemic Inflammation and Cardiovascular Disease (CVD)

As systemic (chronic) inflammation plays a fundamental role in many chronic conditions including T2D and CVD [11–15] and because CVD and vascular complications are a fundamental part of the ethiology of T2D, a quick review of the various dysregulated inflammatory markers in CVD follows. Dysregulated inflammatory markers like C-reactive protein (CRP), along with IL-2, IL-6, IL-8, TNF-α, NOS, PGE_2, the COX-family and thromboxane A_2 and NFκB, all belong to the cluster of general inflammation markers that are changed in systemic inflammation and CVD. In this chapter the focus will therefore be on the above-mentioned inflammatory markers, although there are others that also play important roles in inflammation.

CRP is a leading inflammatory biomarker for CVD [16–23] andis produced by the liver hepatocytesunder regulatory control from circulating cytokines, in particular IL-6 andtumour necrosis factor-α [19, 24]. Because it is increased in the presence of inflammation, it is used to screen for inflammation, particularly high-sensitivity C-reactive protein (hsCRP), adds prognostic information in CVD [19, 20, 25].

The interleukins are a cytokine group that is well-known to be upregulated in inflammation [26]. Interleukin 1 Receptor 1 (IL1R1) and its ligand, IL1β, are unregulated in CVD and infection [27]. IL-1β is also known to be present in autoimmune conditions and contributes to several chronic diseases, including atherosclerosis [28–30]. IL-6 regulates the immune response, haemopoiesis, the acute phase response, inflammation [31] and the central nervous system [31, 32]. Its expression is high and transiently unregulated in nearly all pathophysiological inflammatory conditions and also in autoimmune diseases [33, 34]. IL-8 is also a well-known circulating inflammatory cytokine [35, 36]. Macrophages and other cell types such as epithelial cells, airway smooth muscle cells and endothelial cells produce IL-8.

Tumour necrosis factor- α (TNF-α) is a cell signalling cytokine involved in inflammation and is one of the cytokines that make up the acute phase reaction, and its primary function is to regulate immune cells [37–40].TNF-α dysregulation plays an important role in the development of metabolic syndrome features, including dyslipidaemia and altered glucose tolerance, and is therefore is an important cytokine in the development and maintenance of systemic inflammation [39]. Vascular endothelial cells also respond to TNF-α by undergoing pro-inflammatory changes, which ultimately promote thrombosis [41, 42].

Another important marker of inflammation is the nitric oxide synthases (NOS) family. They are synthesized by many cell types involved in immunity and is also well known for its role in systemic inflammation and cardiovascular disease [43–46]. It is also crucial in maintaining cardiovascular homeostasis [45] and a modulator of vascular disease [47]. In CVD, endothelium damage induced by atherosclerosis leads to the reduction in bioactivity of endothelial NO synthase (eNOS) with subsequent impaired release of NO and ultimately leads to a cascade of oxidation-sensitive

mechanisms in the arterial wall [47, 48]. In a comprehensive review, Costa and coworkers discussed the 3 NOS isoforms, neuronal NOS (nNOS or NOS 1), endothelial NOS (eNOS or NOS 3), and an inducible NOS (iNOS or NOS 2). eNOS is considered the main isoform involved in the control of the vascular function, however, the role of nNOS in vascular homeostasis andcardiovascular disorders such as hypertension and atherosclerosis has recently come to light [43].

Prostaglandins (PGs) have two derivatives, namely prostacyclins and thromboxanes and are critical mediators of inflammation [49–54] Cyclooxygenases (COXs) are the biosynthetic enzymes of PGs.PGE_2 (which inhibits platelet activation and is also an effective vasodilator), and thromboxane (Tx)A2 (TXA_2); and is synthesized via three sequential enzymatic reactions: The first step being arachidonic acid (AA) release from membrane phospholipids by phospholipase A_2 ($cPLA_2$); then, AA is converted into the unstable endoperoxide intermediates PGG_2 and PGH_2 by cyclooxygenase-1 (COX-1) or COX-2 [55]. Markers like COX-1 and -2 and prostaglandin E_2 are all closely connected and also play a prominent role in inflammation and CVD [56]. As mentioned before, TXA_2 is also a product from COX [51, 57] and is a vasoconstrictor, and a potent hypertensive agent that also facilitates platelet aggregation. Both PGE_2 and TXA_2 are therefore key role-players in inflammation and CVD.

NF-κB is a protein complex that is activated by pro-inflammatory cytokines such as interleukin 1 (IL-1) and TNFα [58] and the chronic activation or dysregulation of NF-κB signalling is the central to the pathogenesis of many diseases, including CVD [59, 60]. The activity of NF-κB in the canonical pathway results in upregulation of pro-inflammatory (TNFα, IL-6 and IL-8) and pro-thrombotic [MMPs and TF (tissue factor)] mediators, which are known to be pro-atherogenic [60].

Central to the dysregulation of the mentioned (and other) markers of inflammation is the resulting oxidative stress and ROS generation, which plays crucial roles in both inflammation and CVD [61–63]. In CVD there is an imbalance between the antioxidant defence mechanism and ROS production and this leads to oxidative stress [63–65]. Ultimately, oxidative stress, is a strong pro-thrombotic factor [66], and the hallmark of inflammation is a prothrombotic prevalence and this translates to hypercoagulation. Inflammation causes hypercoagulation (which is a prothrombotic state) because of an elevated expression of the above-mentioned markers, and also elevated expression of the prothrombotic molecules like plasminogen activator inhibitor-1, tissue factor (TF) and increased platelet activation [67–70]. TF is the main trigger of the coagulation cascade; by binding Factor VIIa it activates Factor IX and Factor X, thereby resulting in fibrin formation [71, 72]. Increased fibrinogen and pathological fibrin formation are key in the development of a hypercoagulable state during inflammation.

If we take a closer look at the pathology in T2D, we see that the primary cause of death in T2D patients, is CVD and it is 2–4× times higher in people with T2D compared with those who are non-diabetic [73]. It is thus noteworthy that patients with T2D have an increased risk of atherothrombotic events [74]. Also, T2D can be classified as an inflammatory condition, due to upregulation of different inflammatory markers [18].

17.3 Type 2 Diabetes and Its Relation with Cardiovascular Disease

The pathogenesis of T2D, and how it is interlinked with CVD and inflammation, is summarized below:

- There is an intimate relationship between inflammation and metabolism, including glucose, fat and cholesterol metabolism [75].
- T2D is known to be one common risk factors for CVD [63], and both obesity and T2D are associated with a state of chronic low-level inflammation [18, 76, 77] and cardiovascular complications [78, 79].
- Patients with CVD and T2D have increased circulating inflammatory markers [80] and a number of systematic reviews have shown the association between inflammatory markers, such as CRP, IL-1β, IL-6, TNF-α, IL-4, or IL-10, and cardio-metabolic diseases (e.g. T2D) [15, 81–86]. TNF-α e.g. has emerged as a key cytokine that influences intermediary metabolism [39].
- Oxidative stress plays an important role in T2D and it has a critical impact on the development and progression of vascular pathologies, including atherosclerosis and diabetic vasculopathy [64].
- Endothelial dysfunction is implicated in the pathogenesis of vascular disease seen in T2D [10]; and central to this dysfunction is microvascular complications which are related to oxidative stress, and inflammation, all factors traditionally associated with the pathogenesis of vascular damage seen in CVD [87].
- In T2D there is a decreased fibrinolysis, increased thrombin generation, and platelet hyperactivity.
- In T2D there is elevated levels of circulating TF and this is a biomarker for the severity of microvascular disease in these individuals [67, 72, 88].

17.4 Hypercoagulability and Hypofibrinolysis in Type 2 Diabetes

Recently, we have reviewed in great detail the considerable literature showing that both hypercoagulability and hypofibrinolysis are present in a large number of inflammatory and vascular diseases [89] (e.g. [90–123]). We have also shown that in T2D, fibrin structure is fundamentally changed, and that both erythrocytes and platelets are affected by oxidative stress and circulating up regulated inflammatory markers [6–9, 124–127]. Also see Table 17.1 for selected references for the co-occurrence of hypercoagulation and hypofibrinolysis in diabetes; adjusted from [89].

Because T2D is associated with both a hypofibrinolytic and hypercoagulable state, both these pathologies are of crucial importance in the overarching mechanism for increased cardiovascular risk in this population. This forms the basis of the pathology related to, and involved in atherothrombotic complications, which are the

Table 17.1 Selected references for the co-occurrence of hypercoagulation and hypofibrinolysis in type 2 diabetes

Type 2 Diabetes	Some references showing blood hypercoagulability	Some references showing reduced clot permeability or decreased susceptibility of clot to (fibrino) lysis
	[118, 150–156]	[128, 131, 132, 151, 154, 156–163]

Adapted from [89]

main cause of mortality in T2D. This inflammatory state in T2D presents itself as premature atherosclerosis, increased platelet reactivity and activation of coagulation factors, with associated hypofibrinolysis. Ultimately all of these pathologies together contribute to increased cardiovascular risk in this population [128].

Except for the pathological levels of inflammatory markers in T2D leading to ROS generation and oxidative stress that we discussed in the previous paragraphs, a number of factors have been implicated in impaired fibrin clot lyses are:

- Altered structure of the fibrin (ogen), including glycation and oxidation, resulting in a more compact clot with thinner fibres and increased branching that are more difficult to lyse [74, 129, 130].
- Increased incorporation of antifibrinolytic proteins (e.g. plasminogen inhibitor and complement C3 into the clot [131, 132] with both proteins having antifibrinolytic activities [74].
- Higher levels of plasminogen activator inhibitor-1 (PAI-1), which causes a pathological fibrinolytic process, because of a decreased plasmin generation [128]. PAI-1 has been found in blood from patients with T2D and in other conditions associated with insulin resistance [133–135]. IncreasedPAI-1 in blood is also associated with a tendency toward venous thrombosis and pulmonary embolism [135], and is associated with a decreased fibrinolytic activity or hypofibrinolysis [136]. This hypofibrinolysis are also related to insulin resistance [137]. Schneider and co-workers in 2004 already suggested that an increase in PAI-1 in vessel walls might predispose to acceleration of atherosclerosis and development of plaques with specific characteristics rendering them vulnerable to rupture [138]. Glycation of plasminogen in T2D also directly affects fibrinolysis by decreasing plasmin generation and reducing protein-specific activity [74].
- Elevated glucose levels result in increased plasminogen glycation, which affects protein clearance [139]. Tissue plasminogen activator (tPA) mediates plasminogen conversion to plasmin. Binding of tPA to fibrin typically increases the catalytic conversion of plasminogen to plasmin while simultaneously localizing plasmin generation to the site of thrombus formation, thus preventing systemic plasmin generation [74]. Therefore, hypofibrinolysis in T2D is also the result of glycation of plasminogen leads to both decreased plasmin generation and lower catalytic efficiency of plasmin activity [74].

All of the above, result in an inhibition of the fibrinolytic process and together with the known hypercoagulability contribute to the development of (specially ischemic) cardiovascular disease in T2D [74].

Two of the more novel methods to study clot structure in inflammatory conditions, including T2D, is thromboelastography (TEG) that shows both clot formation and clot

lyses, as well as scanning electron microscopy (SEM) that gives visual information regarding the structure of the actual clot. These two techniques are grouped under the general term, visco-elastic techniques, and together with inflammatory marker analysis, can give valuable information in an individualized patient-orientated approach, when treating individuals with T2D. For a background on the technique, see various publications of Vance Nielsen's group [140–146]. Table 17.2 shows the typical parameters that show clot formation and lyses with TEG, and Fig. 17.2 shows examples of healthy and aberrant T2D fibrin clot structures. In a typical healthy individual, we see a spaghetti-like fibrin network with elongated fibrin fibres (for additional examples of healthy fibrin fibres (see https://1drv.ms/f/s!AgoCOmY3bkKHgkFy7q1sVsxRv_2s) [147]. In T2D, plasma with added thrombin forms a clot with finer fibre structure and areas of thick matted areas [6, 9, 124, 126, 148, 149]. Such a pathologic finer fibrin structure might be the cause of the known hypofibrinolytic clot in T2D, where the denser clot areas, together with the netted areas may also lead to the characteristic a hypercoagulable state in T2D. We have also previously found that in T2D, the TEG results vary considerably, depending of the individual clot parameters. This condition is extremely complex, and therefore we have suggested a individualized approach, using not only traditional pathology tests, but also novel methods like SEM and TEG to monitor patient wellness [125].

Table 17.2 TEG parameters typically generated for whole blood and platelet poor plasma

Parmeters	Explanation
R value: reaction time measured in minutes	Time of latency from start of test to initial fibrin formation (amplitude of 2 mm); i.e. initiation time
K: kinetics measured in minutes	Time taken to achieve a certain level of clot strength (amplitude of 20 mm); i.e. amplification
A (Alpha): Angle (slope between the traces represented by R and K) Angle is measured in degrees	The angle measures the speed at which fibrin build up and cross linking takes place, hence assesses the rate of clot formation; i.e. thrombin burst
MA: Maximal Amplitude measured in mm	Maximum strength/stiffness of clot. Reflects the ultimate strength of the fibrin clot, i.e. overall stability of the clot
Maximum Rate of Thrombus Generation (MRTG) measured in $Dyn.cm^{-2}.s^{-1}$	The maximum velocity of clot growth observed or maximum rate of thrombus generation using G, where G is the elastic modulus strength of the thrombus in dynes per cm^{-2}
Time to Maximum Rate of Thrombus Generation (TMRTG) measured in minutes	The time interval observed before the maximum speed of the clot growth
Total Thrombus Generation (TTG) measured in $Dyn.cm^{-2}$	The clot strength: the amount of total resistance (to movement of the cup and pin) generated during clot formation. This is the total area under the velocity curve during clot growth, representing the amount of clot strength generated during clot growth
Lysis time (LY30)	% Percentage lysis obtained 30 min after MA

Adapted from [164]

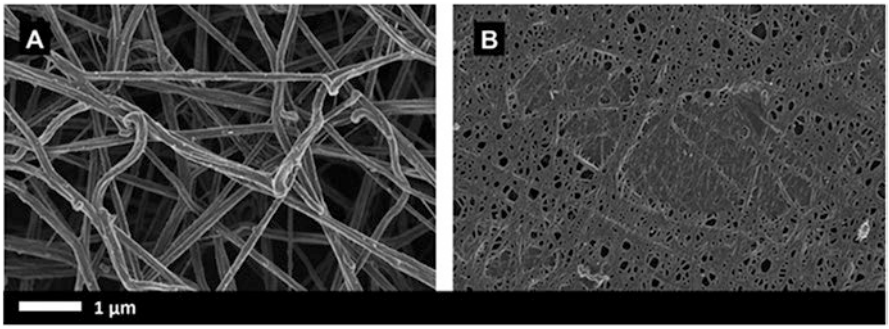

Fig. 17.2 (**a**) Fibrin clot from plasma of a healthy individual; (**b**) Fibrin clot from plasma of a patient with type 2 diabetes. Clots were created by adding thrombin to plasma

17.5 Conclusion

T2D is probably one of the most complex inflammatory conditions that clinicians need to treat, particularly due to the complex cardiovascular involvement. The mechanisms of both hypercoagulation and aberrant clot lyses in T2D are of great importance in the treatment of the condition. Furthermore, the multifaceted nature of the condition suggests that we follow a patient-orientated approach and educate clinicians to use e.g. TEG as an additional method for disease monitoring. Only by closely following each individual patient's progress with a variety of research and traditional laboratory pathology methods will we ensure the healthiness of this vulnerable population. The most important strategy is to manage systemic inflammation, and the resulting cardiovascular pathology; only then will we be able to reduce the T2D pandemic.

Ethical Approval Disclosure Ethical approval was granted at the University of Pretoria (UP) (Human Ethics Committee: Faculty of Health Sciences): E Pretorius. (EP was previously employed at UP).

Conflict of Interest The author has nothing to disclose.

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