Cardiovascular disease and diabetes: the vulnerable patient

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Patients with diabetes exhibit an increased risk for cardiovascular complications, such as acute coronary syndromes, stroke, heart failure, or arrhythmias, as diabetes facilitates changes in the cardiovascular system of these patients. Atherosclerotic lesions have long been recognized as a cause for these events. However, recent findings support the idea that alterations in the circulating blood and the myocardium may be equally or even more important contributors to the development of life-threatening cardiovascular events in patients with diabetes. These alterations in the myocardium, vasculature, and blood characterize the vulnerable patient; the patient with diabetes at high risk for the development of cardiovascular complications in patients with diabetes. In this overview, we describe the changes that lead to vulnerability and summarize the current understanding of the pathophysiological mechanisms that contribute to the elevated risk for cardiovascular events in patients with diabetes.

KEYWORDS
Atherosclerosis; Cardiovascular events; Diabetes; Vulnerable patient

Introduction

Patients with diabetes exhibit an increased propensity for cardiovascular complications, such as acute coronary syndromes, stroke, heart failure, or arrhythmias. For decades, arteriosclerotic lesions, as well as alterations in vascular blood flow, have been recognized as the main causes for the development of these cardiovascular events, but recent data suggest that additional pathophysiological mechanisms are equally or perhaps even more important for the onset and the clinical course of such complications. Thus, our current understanding is driven by the recognition that these potentially life-threatening events are caused not only by vascular changes but also by alterations in the nature of the circulating blood and the myocardium. As such, these three components—vulnerable vessel, vulnerable blood, and vulnerable myocardium—characterize what is today referred to as the vulnerable patient, who is defined as a patient with a high risk for the development of cardiovascular complications (Figure 1). The present overview will elaborate on these changes and summarize our current understanding of the pathophysiological mechanisms that are contributing to the elevated risk of patients with diabetes developing cardiovascular events.

Vulnerable vessel

For decades, atherogenesis, which is characterized by remodelling of arteries and results in subendothelial accumulation of fatty compounds (plaques), was viewed as a progressive disease of the vessel wall, leading to the reduction in the lumen diameter to a point such that a few activated platelets would be sufficient to occlude the vessel and result in an acute myocardial infarction. Data from pathologists questioned that concept by suggesting that most myocardial infarctions are caused by low-grade stenoses. In addition, two types of atherosclerotic lesions (atherosclerotic plaques) were identified; namely, stable plaques, which lead to high-grade obstruction, and unstable plaques (also known as vulnerable plaques), which both result in increased vulnerability and a high incidence of thrombi. Thus, the understanding of atherogenesis has evolved and,
currently, the development of an atherosclerotic lesion is considered to be a multistage inflammatory process (Figure 2). The early stage is characterized by so-called endothelial dysfunction. Under the influence of specific risk factors, such as hyperglycaemia, as well as the direct interaction of adipose tissue-derived inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), the endothelium is activated. The resultant expression of adhesion molecules and the release of inflammatory mediators and chemokines facilitate the recruitment of inflammatory cells like monocytes and CD4-positive lymphocytes. These cells then enter the vessel wall and orchestrate the inflammatory response in the vessel wall through activation and interaction with molecules such as oxidized low-density lipoproteins (LDLs). Furthermore, the disturbance of endothelial function is associated with a reduction in the release of nitric oxide (NO), a mediator of protective effects (reduced vessel constriction, lower LDL levels, and reduced platelet aggregation) in the vessel wall. Interestingly, hyperglycaemia is associated with an imbalance between NO and peroxynitrite levels as well as a decrease in NO production. The impaired release of NO can be used clinically to assess endothelial dysfunction in patients. It has been shown that patients with impaired glucose tolerance and those with manifest diabetes present with impaired flow-mediated, endothelium-dependent vasodilation, suggesting the presence of endothelial dysfunction in these patients. In fact, endothelium-dependent vasodilation has been shown to predict future cardiovascular events, underscoring the importance of this early stage for further lesion development.

Once inflammatory cells enter the vessel wall, monocytes differentiate to macrophages and foam cells, while T cells, which are mainly CD4-positive cells, transform towards Th1 cells, leading to the release of additional proinflammatory mediators, such as TNF-α, IL-2, and interferon-gamma (IFN-γ). At this stage, called fatty streak formation, vascular smooth muscle cells proliferate and migrate from the media into the developing lesion to further promote lesion development. Experimental data suggest that glucose increases smooth muscle cell proliferation and migration, the latter most likely through induction of osteopontin expression. Moreover, platelet hyperactivity that is associated with diabetes is thought to also contribute to lesion extension at this stage. In the next phase, advanced and potentially complicated lesions develop. Through apoptosis and cell death, as well as through an increase in proteolytic activity and lipid accumulation, the so-called necrotic lipid core of the plaque is formed. This necrotic core is

Figure 1 The vulnerable patient with diabetes. Vulnerable vessel, vulnerable blood, and vulnerable myocardium characterize the vulnerable patient—a patient with a high risk for the development of cardiovascular complications.
covered by a protective fibrous cap consisting of vascular smooth muscle cells and extracellular matrix—mostly collagen and elastin. Stable plaques can convert to unstable plaques, which are characterized by a large necrotic lipid core, infiltration of inflammatory cells, and a thin and vulnerable fibrous cap. Advanced plaques from patients with diabetes exhibit the characteristic features of vulnerable plaques by containing many macrophages and T cells, a large necrotic lipid core, pronounced neovascularization in the adventitia, and a high incidence of thrombi. Moreover, the advanced plaques of patients with diabetes demonstrate higher expression of procoagulatory molecules, such as tissue factor (TF), as well as high levels of matrix-degrading enzymes, such as matrix metalloproteinases. Therefore, plaques from patients with diabetes exhibit a high susceptibility for rupture and are more likely to induce thromboembolic events.

The understanding of plaque rupture as the main cause of acute myocardial infarctions has been furthered by post-mortem observations that have shown that culprit lesions from patients with acute myocardial infarctions demonstrate ruptured fibrous caps with subsequent activation of the coagulation cascade and formation of an occluding or non-occluding thrombus. Recent data employing novel techniques, such as intravascular ultrasound with virtual histology (IVUS-VH), confirmed these pathophysiological findings by showing that a longer duration of diabetes was associated with thin-cap fibroatheroma (TCFA), a plaque phenotype associated with the risk of rupture and coronary events, as defined by IVUS-VH. Moreover, TCFA was more common in the most diseased segments of patients with diabetes compared with those without diabetes.

Multivariate adjustment demonstrated the presence of diabetes as an independent predictor of TCFA defined by IVUS-VH, bolstering the concept that vulnerable plaques with subsequent plaque rupture are more common in patients with diabetes than in those without diabetes.

The concept of plaque rupture as the main and sole cause of an acute myocardial infarction has been challenged by data that suggest that additional ruptured plaques that are distinct from the culprit lesion can be found in patients with an acute coronary syndrome. These results suggest that plaque rupture alone may not be sufficient to cause acute coronary syndrome. This finding has shifted our understanding of the cause of coronary events from being due solely to vulnerable plaque to considering the role of the vulnerable patient, including vulnerable blood and vulnerable myocardium.

**Vulnerable blood**

Vulnerable blood describes components of the blood, such as inflammatory mediators, altered platelet function, hypercoagulability, and hypofibrinolysis, as well as microparticles (MPs) that may contribute to cardiovascular events (Figure 3).

**Inflammation in atherothrombosis**

Several studies demonstrated that diabetic patients without prior cardiovascular disease have the same rate of myocardial infarction as non-diabetic patients who have had previous events, thereby highlighting the high risk of the diabetic population. The so-called...
The common soil hypothesis, originally put forward by Stern, suggested that diabetes and cardiovascular disease are created by a low-grade inflammatory milieu, which is causative for insulin resistance and vascular plaque formation. Inflammation can alter all processes that underlie the development of atherothrombosis in the vessel wall as described previously. However, the interaction between inflammation and coagulation is not limited to the site of vessel injury but can similarly be detected in the adipose tissue of obese patients. Visceral adipose tissue is a major source for inflammatory activity resulting from activated T-lymphocytes and macrophages, which, in conjunction with adipocytes, produce inflammatory cytokines, including TNF-α, IL-6, and plasminogen activator inhibitor (PAI)-1, a fibrinolytic inhibitor. These inflammatory stimuli induce the expression of fibrinogen which, together with elevated PAI-1 levels, forms a systemic prothrombotic milieu. The interaction between inflammation, platelet dysfunction, and hypercoagulability/hypofibrinolysis is discussed in more detail in the next section.

Altered platelet function

Activation and aggregation of platelets—critical initial steps following plaque rupture—are accelerated under diabetic conditions. Platelets respond more frequently to sub-threshold stimuli under hyperglycaemic conditions, which increase their turnover and result in an accelerated thrombopoiesis of fresh and hyper-reactive platelets in diabetes. This platelet dysfunction is related to several mechanisms, including metabolic changes, oxidative stress, and endothelial dysfunction. Hyperglycaemia induces thromboxane synthesis, which mimics the state of activated platelets exposed to high shear stress conditions. Furthermore, hyperglycaemia causes increased superoxide production, which decreases NO release and impairs calcium homeostasis as a consequence of oxidative stress. In addition, hyperglycaemia leads to non-enzymatic glycosylation of platelet membrane proteins, which may change protein structure and conformation, thereby altering platelet function. Insulin binding to its receptor reduces platelet reactivity by inhibiting P2Y12 signalling, whereas insulin resistance promotes platelet aggregation and procoagulant activity.

Hypercoagulability and hypofibrinolysis

A variety of studies report alterations of the coagulation system in patients with diabetes mellitus. TF is the key initiator of the coagulation cascade as it binds to factor VIIa, leading to the activation of factors IX and X and resulting in thrombus formation. TF levels are elevated under diabetic conditions as a consequence of the inflammatory milieu, hyperglycaemia, and oxidative stress. von Willebrand factor (vWF) is selectively expressed in platelets and endothelial cells and promotes the adhesion of thrombocytes to the vascular wall in zones of endothelial damage where it serves as a carrier protein for factor VIII. Both coagulation factors are up-regulated under inflammatory conditions, with elevated circulating levels that are associated with diabetes and
cardiovascular disease. In addition, elevated levels of fibrinogen further contribute to the pro-coagulatory milieu in patients with diabetes. Non-enzymatic glycation of fibrinogen under hyperglycaemic conditions leads to the formation of a tight and rigid fibrin network, which was previously shown to be associated with an increased risk for myocardial infarction. These changes impair the fibrinolytic function of plasmin on the clot surface and slow thrombus lysis. Furthermore, PAI-1, the inhibitor of fibrinolysis, is elevated in patients with diabetes mellitus and independently associated with cardiovascular risk. PAI-1 expression is induced by a variety of stimuli, including inflammatory cytokines, insulin, very low LDL, and free-fatty acids, all of which extensively present in diabetes mellitus. In addition, increased levels of tissue plasminogen activator (t-PA) have been observed in patients with diabetes. Given that t-PA activates plasminogen and is thus responsible for the fibrinolysis of fibrin clots, elevated t-PA levels could have a beneficial effect. However, several studies have demonstrated an association between elevated t-PA levels and cardiovascular disease.

**Vulnerable myocardium**

Platelet-derived MPs, the first species identified, carry both phospholipids and TF (considered to be the main initiators of blood coagulation) on their outer membrane. TF has also been identified as a component of MPs from monocytes/macrophages, leucocytes, and endothelial cells. In addition, it has been demonstrated that MPs can also harbour and transport microRNA, a class of small non-coding RNA that binds to messenger RNA, to act as endogenous post-translational gene regulators and thereby influence protein expression of the target cells. Interestingly, elevated circulating levels of various MPs are found in patients with diabetes mellitus. Analyses of MPs from patients with diabetes revealed elevated numbers of TF-bearing MPs compared with healthy controls. More specifically, patients with diabetes exhibited higher percentages of TF-positive MPs from T-helper cells, granulocytes, and platelets; these correlated with parameters of the metabolic syndrome, suggesting a role for MPs in the genesis of the prothrombotic profile in diabetes.

MPs are vesicles that are released from various cell types, including platelets, endothelial cells, and leucocytes, following activation or apoptosis. MPs vary in size (0.2–1 μm) and, depending on their origin, in membrane composition of phospholipids and proteins. Once they are released into the circulation, they bind and fuse with their target cells through receptor–ligand interaction and act as biological vectors, which modulate inflammatory and coagulation reactions.
different components of the vulnerable myocardium are relatively unexplored, but some markers that characterize myocardial vulnerability have been defined. Current thinking suggests that there are markers associated with atherosclerosis-derived ischaemia, such as electrocardiogram abnormalities, perfusion and viability disorders, as well as wall-motion abnormalities. These markers can be distinguished from those independent of atherosclerosis-derived ischaemia, such as sympathetic hyperactivity, left ventricular hypertrophy, or other electrophysiological disorders. In patients with diabetes, these components appear to be of crucial importance in the context of cardiac events.

Chronic heart failure affects one in five patients with diabetes, leading to greater than four times the risk observed in the general population. 

This increased risk can be at least partially attributed to a clustering of cardiovascular risk factors, including obesity and hypertension, leading to coronary artery disease and subsequent ischaemic cardiomyopathy. In addition, a significant subset of patients with diabetes acquires pathophysio logically distinct impairment of cardiac function (i.e. diabetic cardiomyopathy) during the course of the disease. The pathophysiology of this alteration in myocardial function is not completely understood, but it can be attributed to metabolic derangements of the cardiomyocytes, which are similarly found in lean type I and obese type II diabetic individuals. 

Diabetes induces a variety of functional, structural, and metabolic abnormalities of the heart that cause cardiac hypertrophy, myocardial stiffness, and impaired diastolic function, which ultimately result in global heart failure. The incidence of heart failure is associated with the effectiveness of glucose control, suggesting that hyperglycaemia is either a disease-driving risk factor or a surrogate marker for insulin resistance. 

Insulin resistance of the cardiomyocyte causes a shift in energetic substrate utilization from glucose to fatty acid oxidation. This metabolic shift impairs the energetic flexibility of the cardiomyocyte and increases its oxygen demand. Fatty acid oxidation thereby requires more oxygen to produce an equivalent amount of adenosine triphosphate (ATP) as reached by glucose oxidation. The oxygen demand of the diabetic heart is further increased by mitochondrial uncoupling reactions, which contribute to an inefficient energy production. Consequently, the hearts of patients with diabetes rely more heavily on sufficient oxygen supply when compared with those of patients without diabetes, and they are more vulnerable to ischaemia, resulting in larger myocardial infarct sizes when challenged with comparable ischaemic stimuli compared with patients without diabetes. This is endangered in the presence of microvascular disease, which often coincides in patients with diabetes. Diabetic microangiopathy is the consequence of endothelial dysfunction and deposition of advanced glycation end product (AGE), leading to impaired vascular capacity to increase blood flow under extensive tissue demand, which also gets further reduced under hypoglycaemic conditions. 

Endothelial dysfunction is attributable to decreased endothelial NO release as a consequence of oxidative stress.

Reactive oxygen species are formed by the mitochondria in response to increased metabolic flux and fatty acid oxidation, in addition to AGE formation. Furthermore, AGEs are created by non-enzymatic glycosylation of structural and functional proteins under hyperglycaemic conditions, which directly alters protein integrity and activates inflammatory pathways via binding to the pattern recognition AGE receptor. 

Oxidative stress is directly linked with cardiomyocyte death and cellular apoptosis. This causes remodelling reactions with deposition of extracellular and intracellular matrix proteins and interstitial fibrosis. The resulting ventricular stiffness and cardiac hypertrophy impairs diastolic relaxation as detected by abnormal mitral valve inflow patterns as an early sign of diabetic cardiomyopathy. Ventricular relaxation further depends on a rapid diastolic cycling of cytosolic calcium to the endoplasmic reticulum. This process is impaired in the diabetic myocardium owing to decreased expression of relevant calcium transporters, including sarcoplasmic endoplasmic reticulum calcium ATPase (SERCA2), impaired cellular energy homeostasis, and functional abnormalities of contractile microfilaments. 

The consecutive diabetic calcium overload prolongs cardiac repolarization and the QT interval. This makes the heart vulnerable to early repolarization events as potential triggers for ventricular tachycardia. Accordingly, patients with diabetes display prolonged QT intervals, which independently predict sudden cardiac death and mortality. A variety of conditions coincide with diabetes mellitus that can contribute to rhythm instability and QT prolongation, including cardiac hypertrophy, myocardial infarction, and hypoglycaemia. Hypoglycaemia causes sympathoadrenergic activation, electrolyte disturbance, and pro-coagulatory, inflammatory reactions, which have been associated with increased clinical events. 

Moreover, impairment of the myocardial autonomic nervous regulation further increases the vulnerability of the heart. This is part of diabetic polyneuropathy, which is similarly dependent on hyperglycaemia-induced oxidative stress, AGE formation, and microangiopathy. As diabetic neuropathy primarily affects long nerve fibres, the vagus nerve, which is the longest autonomic nerve of the body, is affected early. This causes parasympathetic myocardial denervation with an accelerated sympathetic tone, leading to sinus tachycardia and impaired heart rate variability as well as inefficient energy demand. The clinical relevance of disturbance of the autonomic nerve system becomes apparent by a two- to three-fold increase in risk for sudden cardiac death in the presence of cardiac autonomic neuropathy. Damage of sensoric nerve fibres can detach the heart from pain perception and lead to silent myocardial ischaemia and infarction with consequential inappropriate therapeutic actions in a state of unawareness.

The vulnerable myocardium is, therefore, characterized by an altered metabolic state in conjunction with neural and vascular impairment, which increases its susceptibility to external stressors, including ischaemia, hypoglycaemia, and electrolyte imbalance. This leads
to increased risk and worse outcomes for clinical events, including myocardial infarction and rhythm disorders, which all contribute to the impaired prognosis of the diabetic population.125

Summary

The recognition that cardiovascular risk in patients with diabetes is determined not only by the vulnerable vessel but also by components of the vulnerable blood and the vulnerable myocardium has major implications for future research and therapeutic developments. To achieve a more precise and accurate risk stratification in patients with diabetes in the future, novel risk markers should be identified, taking into account all three components of the vulnerable patient. As previously suggested, the ideal way to screen and assess a patient’s vulnerability should include an inexpensive, relatively non-invasive, widely available, and readily applicable method in an asymptomatic population that is capable of adding predictive value to the established risk factors.94 Given the increasing healthcare burden of diabetes, both small trials and analyses from large cohort studies should focus on the development of screening tools to identify high-risk individuals. Moreover, therapeutic strategies to reduce cardiovascular risk in patients with diabetes should consider new treatment options for all three components of the vulnerable patient, paving the way for a more integrated approach to preventing cardiovascular events in this high-risk population.

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