ELSEVIER

Cardiovascular complications in diabetes mellitus

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Diabetes is strongly associated with coronary, cerebral and peripheral arterial disease, as well as with microangiopathy. In those with diabetes, the extent of macrovascular disease increases and atherosclerotic plaques are more prone to rupture. Both hormonal abnormalities (insulin resistance that is typically present for many years before the onset of type 2 diabetes) and metabolic abnormalities contribute. Multi-targeted intensive therapy is imperative; however, unfortunately it is underutilized. Functional and structural derangements contribute to impaired arterial and ventricular compliance predisposing to congestive heart failure that is increasingly recognized to be a cause of morbidity and mortality in patients with diabetes.

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Introduction

As early as the 1930s, it was recognized by Himsworth [1] that two types of diabetes mellitus exist. One was shown to be attributable to an insufficiency of insulin (type 1); the other to resistance to the action of insulin (type 2). Nevertheless, until recently, thinking with regard to these two disparate types of diabetes has tended to consider them as one [2].

The type of diabetes associated prominently with coronary and other forms of heart disease is type 2 diabetes. This is characterized by a prolonged gestational interval in which insulin resistance is prominent and pancreatic β cells produce insulin in a compensatory fashion that is sufficient to maintain euglycemia. Work by Reaven and colleagues (reviewed in [2]) has demonstrated that accelerated coronary artery disease is associated not only with diabetes that follows but also with the insulin resistance itself.

Among the types of cardiovascular disease that are encountered in association with type 2 diabetes are epicardial coronary artery disease with manifestations that include sudden cardiac death and acute coronary syndromes comprising unstable angina pectoris and acute myocardial infarction; small vessel coronary artery disease; cerebrovascular disease; peripheral vascular disease; hypertension; and congestive heart failure.

This review focuses on the mechanisms that account for the accelerated and exacerbated coronary atherosclerosis associated with type 2 diabetes. It also concentrates on the increasingly recognized strong association between type 2 diabetes and congestive heart failure, particularly that with preserved systolic function (often referred to as diastolic heart failure).

Atherogenesis in diabetes

Atherosclerosis is typified by the progression of lesions from the earliest stage, the fatty streak, to later obstructive lesions that consist of diverse cells and matrix. The evolution of plaques is driven by growth factors and cytokines induced by stimuli such as oxidized low density lipoprotein. The conventional view that high grade occlusive stenotic coronary lesions represent the final step in a continuum that begins with fatty streaks and culminates in high grade stenosis, resulting in acute coronary syndromes, has been modified because thrombotic occlusion is frequently the result of rupture of minimally stenotic plaques. As many as two-thirds of the lesions responsible for acute coronary syndromes are minimally obstructive (lesions are less than 70% stenotic) before plaque rupture [3,4]. The disruption of 'vulnerable' plaques and the subsequent thrombosis can lead to intermittent, sudden plaque growth and can cause acute coronary syndromes. A vulnerable plaque is characterized by a large lipid core, a paucity of vascular smooth muscle cells, a thin fibrous cap and increased numbers of inflammatory cells (e.g. macrophages and lymphocytes), particularly in the shoulder regions [5].

Burke *et al.* [6••] found that hearts from patients with diabetes compared with age, gender and racially matched subjects exhibited greater atherosclerosis. The amount in distal vessels was particularly increased in hearts from patients with type 2 diabetes. The magnitude of necrotic core and the prevalence of macrophages in plaques were significantly greater in those with diabetes. These characteristics are consistent with the greater risk of plaque rupture that is demonstrated with histochemical studies in people with diabetes [7] and the two- to three-fold increased risk of myocardial infarction [8]. By using

carotid atherectomy samples, Sommeijer *et al*. found that type 2 diabetes is associated with augmented fibrosis and thrombosis [7].

In 13 105 subjects that have been followed prospectively for 20 years, type 2 diabetes was found to be associated with an increased risk of myocardial infarction and stroke that is independent of other established risk factors [8]. The increased risk of myocardial infarction and stroke is consistent with correlations between the concentration of glycohemoglobin in blood, and the size of the necrotic core and with macrophage content in plaques. This is independent of lipids, smoking and gender [6••]. The density of receptors for advanced glycation end products (AGEs) is increased in atheroma of people with diabetes, particularly associated with macrophages and within the necrotic core [6••].

Mechanisms of accelerated atherogenesis in diabetes

Results from the UK Prospective Diabetes Study [9] demonstrated a direct association between the concentration of glycohemoglobin in the blood and the risk of myocardial infarction and stroke. A role for glycation in the progression of atherosclerosis is supported by results shown in apolipoprotein E-deficient mice that are rendered hyperglycemic by streptozotocin and are treated with agents that break AGE cross-links or that inhibit the formation of AGEs. Both agents attenuated the sixfold increase in plaque area that was associated with streptozotocin-induced diabetes by 30–40% [10•]. AGEs appear to promote atherogenesis through the generation of reactive oxygen species, increased oxidation of low density lipoprotein, increased vascular permeability, increased endothelial cell expression of leukocyte adhesion molecules, and increased expression of procoagulant molecules [11].

Insulin resistance and associated hyperinsulinemia seen with obesity decades both before the onset of and during the early stages of type 2 diabetes are associated with accelerated development of cardiovascular disease [12,13]. One mechanism through which insulin resistance might promote formation of vulnerable plaques is by increasing the expression of plasminogen activator inhibitor type 1 (PAI-1) [14]. By using transgenic mice it has been found that overexpression of PAI-1 by vascular smooth muscle cells reduces their capacity to migrate through the extracellular matrix and to populate the neointima [15•]. Thus, the overexpression of PAI-1 might promote the formation of plaques that are particularly prone to rupture [14].

The effects of atherogenic factors are amplified in association with diabetes mellitus. For example, the risk associated with increased concentrations of C-reactive protein in the blood is greatest when in a state of hyperglycemia [16,17]. Signs of systemic inflammation accompany both the metabolic syndrome and insulin resistance [18]. Stringent control of hypertension is associated with a threefold decrease in the incidence of cardiovascular events in patients with diabetes and peripheral arterial disease (average blood pressure of 128/75 mmHg with stringent control compared with 137/81 mmHg with non-stringent control) [19]. The relative risk of myocardial infarction in middle-aged women with diabetes increases from 8.8 to 19 in association with the use of tobacco [20].

Diabetes mellitus is a pro-thrombotic state that not only increases the rate of progression of atherosclerosis but also increases thrombosis in response to plaque rupture [14]. The pro-thrombotic state is reflected by increased concentrations of soluble CD40 (a platelet released mediator of thrombosis and inflammation), P-selectin (reflecting platelet activation) and tissue factor (an initiator of the coagulation cascade) in the blood [21•]. Patients with diabetes mellitus have increased platelet reactivity. Thus, the propensity of platelets to become activated in response to a stimulus is increased in people with diabetes [22•]. The likelihood of no reflow and re-occlusion after percutaneous coronary intervention treatment of acute ST elevation myocardial infarction is increased in patients with hyperglycemia [23]. One mechanism that potentially contributes to this phenomenon is a direct effect of hyperglycemia on platelet reactivity [24]. The osmotic effect of hyperglycemia can directly increase platelet reactivity [24]. Another mechanism contributing is the reduced bioavailability of nitric oxide [25]. Insulin resistance and the associated hyperinsulinemia have been associated with increased concentrations of coagulation factors in the blood and the limitation of fibrinolysis, secondary to increased concentrations of PAI-1 [14,26]. Thus, both hormonal and metabolic abnormalities associated with diabetes contribute to a pro-thrombotic state.

Clinical implications of accelerated atherogenesis in diabetes

Stringent control of both the hormonal and the metabolic abnormalities of diabetes must be combined with aggressive control of coexisting cardiac risk factors to retard progression of atherosclerosis. Interventions that improve insulin sensitivity, including diet, exercise and the use of pharmacological agents such as thiazolidinediones and metformin, can delay the onset of type 2 diabetes in those at risk [27]. These are therefore useful in the treatment of type 2 diabetes. Results from the Steno-2 study demonstrated the value of a targeted, intensive, multifactorial intervention [28••] that includes modification and pharmacological therapy targeting hyperglycemia, hypertension, dyslipidemia, microalbuminuria and the procoagulant state. The risk of cardiovascular and microvascular events was reduced by ~50% by intensive treatment. Unfortunately, implementation of intensive therapy is uncommon

[29•]. Approximately 25% of patients with an acute coronary syndrome have a history of diabetes; yet, such subjects are unlikely to have been treated effectively before the acute event.

Heart failure in diabetes mellitus

Diabetic cardiomyopathy has been recognized for many decades. Early studies in experimental animals treated with streptozotocin or alloxan to induce insulin insufficiency demonstrated changes in calcium cycling and in myocardial contractility. We, and others, found that myocardial infarction of a given magnitude in patients with diabetes was associated with more severe congestive heart failure and that, despite the preserved systolic function, myocardial ultrasonic backscatter was altered in people with diabetes, which is indicative of structural alterations within the heart. It is now known that diabetes is a potent, independent risk factor for mortality in patients hospitalized with heart failure, and that the excess risk associated with diabetes is particularly prominent in women [30•].

Heart failure associated with diabetes can be manifested by diastolic dysfunction, systolic dysfunction or both, attributable to abnormal calcium cycling, impaired energetics and deposition of AGEs. The AGEs can alter ventricular compliance by the cross-linking of collagen, through receptor-mediated release of proinflammatory cytokines by macrophages or through non-receptor-mediated inactivation of nitric oxide and augmentation of oxidative stress. They have also been thought to increase renal sodium reabsorption, activate the sympathetic nervous system, alter peripheral arterial compliance, increase deposition of lipids within cardiomyocytes, induce small vessel coronary artery disease and incite oxidative damage to matrix proteins. As a consequence of impaired arterial compliance and endothelial function, myocardial oxygen demands are increased, predisposing to subendocardial ischemia that can exacerbate diastolic dysfunction.

Left ventricular mass increases in proportion to the severity of impairment of glucose tolerance, particularly in women [31]. An elevated concentration of fasting glucose is a risk factor for congestive heart failure with or without concomitant coronary artery disease [32]. The presence of diabetes is a powerful predictor that heart failure and death will occur in long-term survivors of acute myocardial infarction [33]. Patients with ST segment elevation acute myocardial infarction who are diabetic exhibit increased long-term mortality as a concequence of heart failure, whether or not they have been treated with revascularization procedures [34•]. Diabetes profoundly increases the development of heart failure following acute coronary syndromes [35]. In patients that are hospitalized for heart failure with preserved systolic function, conditions such as hypertension, diabetes and obesity are common [36]. Systolic hypertension (also known as wide pulse pressure hypertension) reflects increased central arterial stiffness [37]. The strong association between diastolic heart failure and systolic hypertension appears to mirror deleterious cardiac responses to back reflected central arterial pressure waves with consequent increases in left ventricular chamber stiffness.

Because coronary artery disease has such a prominent association with type 2 diabetes, it is somewhat surprising that factors other than coronary flow limitation, particularly congestive heart failure, are prominent determinants of risk for death and recurrent myocardial infarction in patients with unstable coronary artery disease [38•]. Thus, despite the use of bare metal and drug-eluting stents in diabetic patients undergoing revascularization procedures, mortality in the subsequent three years is 63% greater in those with diabetes than controls that are not diabetic [39]. Even after adjustments for differences in baseline characteristics, the hazard ratio remains elevated at 1.462 [39].

Therapeutic considerations relevant to the increased prevalence of heart failure

The use of infusions of glucose, insulin and potassium for the treatment of acute myocardial infarction was initially explored more than half a century ago and has since been supported by electrocardiographic, infarct size and hemodynamic assessments. Stringent glycemic control enhances survival in patients with diabetes who sustain an acute coronary syndrome [40]. In addition to the metabolic benefit that has been postulated, the potentially direct protective effects of insulin in the setting of acute myocardial infarction have been recognized [41]. In patients with diabetes that are undergoing coronary artery bypass graft surgery, perioperative outcomes are improved by the implementation of stringent glycemic control [42].

One target for amelioration of heart failure has been to disrupt the cross-linking of collagen attributable to the deposition of AGEs. Aminoquanidine treatment, known to prevent accumulation of collagen-associated AGEs, obviated the otherwise increased myocardial stiffness in diabetic rats [43]. In studies of experimental animals and in one clinical study, the potential utility of agents that can break cross-links has been demonstrated [44].

The use of both angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers are cornerstones for the treatment of congestive heart failure and the induction of favorable remodeling after acute myocardial infarction. Antagonism of another element of the rennin-angiotensin system (RAS), aldosterone, has been the focus of considerable attention [45]. Weber *et al.* [46] have demonstrated diminution of myocardial fibrosis by aldosterone antagonism. Pitt *et al.* [47] have shown that

this has a striking clinical benefit in patients with congestive heart failure. Both angiotensin II and aldosterone have been implicated in augmenting myocardial fibrosis, perhaps by increasing concentrations of PAI-1 in the heart, with consequent diminution of the dissolution of fibrin — a known scaffold for the deposition of fibrous tissue. Increased expression of PAI-1 in cardiomyocytes contributes to cardiac fibrosis after myocardial infarction [48]. Inhibition of angiotensin-converting enzyme attenuates impaired fibrinolysis and reduces cardiac perivascular fibrosis in genetically obese diabetic mice [49].

The advent of insulin-sensitizing agents has been widely embraced; however, one class of these, the thiazolidinediones, has been associated with weight gain and peripheral edema. Dose-related peripheral edema occurs in as many as 18% of patients when thiazolidinediones are used in combination with insulin; however, diuretics are not particularly helpful. Mechanisms implicated are direct sodium-retaining effects on the distal tubule of the kidney, arterial vasodilatation, increased sympathetic activity and altered endothelial permeability. Thiazolidinediones do not adversely affect cardiac structure or function. In fact, beneficial effects on left ventricular function have been reported in studies of experimental animals [50]. It is certainly the case that in the presence of congestive heart failure augmented plasma volume induced by thiazolidinediones might be deleterious. Nevertheless, even symptomatic congestive heart failure is not an absolute contraindication to the use of thiazolidinediones [51].

Conclusions

Insulin resistance and type 2 diabetes are strongly associated with accelerated atherogenesis, the evolution of plaques particularly prone to rupture, a pro-thrombotic anti-fibrinolytic and systemic inflammatory state, functional and structural derangements impairing arterial and left ventricular compliance, and intensification of deleterious effects of atherogenic stimuli. Multi-targeted intensive therapy is effective and essential. Unfortunately, it is not yet implemented widely in clinical practice.

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