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DIABETIC CARDIOVASCULAR DISEASE: getting to the heart of the matter

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Abstract

Diabetes is a major risk factor for heart disease, and heart disease is responsible for substantial morbidity and mortality among people living with diabetes. The diabetic metabolic milieu predisposes to aggressive obstructive coronary artery disease that causes heart attacks, heart failure and death. Furthermore, diabetes can be associated with heart failure, independent of underlying coronary artery disease, hypertension or valve abnormalities. The pathogenesis of the vascular and myocardial complications of diabetes is, as yet, incompletely understood. Although a number of medical and surgical approaches can improve outcomes in diabetic patients with cardiovascular disease, much remains to be learned in order to optimize approaches to these critical complications.

Keywords

Diabetes; coronary artery disease; heart failure

INTRODUCTION

The cardiovascular complications of diabetes present a formidable challenge because of the high prevalence of diabetes and the adverse effects of cardiovascular disease on quality of life and survival. Recent statistics from the Centers for Disease Control estimate that heart disease is noted on more than two-thirds of diabetes-related death certificates among people 65 years or older [1]. Diabetes is a major risk factor for obstructive coronary artery disease (CAD), leading to myocardial infarction and heart failure. Diabetes is also associated with an increased risk of heart failure in the absence of valvular abnormalities, alcoholism, congenital anomalies, hypertension, or obstructive CAD. This disorder is known as diabetic cardiomyopathy. In this review, we discuss the epidemiology, pathogenesis and management of coronary artery and myocardial complications that affect diabetics, with an emphasis on data from human studies. Insights from in vitro and in vivo animal models will be discussed elsewhere in this issue.

Coronary Artery Disease

Epidemiology and course of disease—Diabetes is a major risk factor for the development of atherosclerosis leading to myocardial infarction, as well as to other manifestations of macrovascular disease, including stroke and limb ischemia. Analysis of Framingham Heart Study cohorts indicated that the magnitude of the increased risk of

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clinically apparent atherosclerosis and obstructive CAD was twofold to fourfold increased among diabetics with the greatest risk among women [2]. According to 2009 statistics from the Centers for Disease Control, 4.4 million diabetics in the United States have CAD, and nearly one quarter of diabetics over the age of 35 years self-report CAD, angina or myocardial infarction

(http://www.cdc.gov/diabetes/statistics/complications_national.htm#1). The Adult Treatment Panel III of the National Cholesterol Education Program considers diabetes mellitus as a factor that places individuals at highest risk for CAD [3].

When CAD occurs in diabetics, the course of disease is particularly aggressive and associated with worse outcomes than in non-diabetics. In diabetics, following an initial myocardial infarction, the risk of subsequent myocardial infarction, development of heart failure, and early and late death are higher than in non-diabetics [2, 4-6]. The risk of these complications is also greater for women than for men. The more aggressive course of CAD in diabetes has been appreciated for more than 30 years, and despite improvements in contemporary approaches to the management of type 1 and type 2 diabetes and advances in therapy for CAD, the increased risks conferred by diabetes persist today [7]. Independent of the extent of cardiac dysfunction, the prognosis for diabetics following acute myocardial infarction is worse in terms of post-infarction angina, heart failure and death [8, 9]. Diabetes confers this increased risk regardless of whether treatment is with thrombolytics, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery [10, 11]. The excess risk may relate in part to a greater proportion of diabetics with more extensive (e.g., multi-vessel) disease at the time of incident event [12]. Overall, among diabetes-related deaths of people aged 65 and older, 68% are noted to have heart disease [1].

Pathogenesis—The dyslipidemia associated with diabetes likely plays a key role both in the propensity for development of CAD and in its unusually aggressive course of disease. Post-prandial lipemia, hypertriglyceridemia, and low high-density lipoprotein (HDL) most likely relate to altered effects of insulin on hepatic lipoprotein synthesis and secretion, altered regulation of lipoprotein lipase and cholesterol ester transfer protein, and altered insulin effects on metabolism in skeletal muscle and adipose tissues [13]. In type 1 and type 2 diabetes, aggressive insulin therapy can ameliorate these lipid abnormalities [14]. However, in type 2 diabetes, these abnormalities are also accompanied by an increase in atherogenic small dense low-density lipoprotein (LDL) particles, which is not readily reversed with tight glycemic control [15]. The increase in small-dense LDL and decrease in HDL are each well established to be associated with incremental increase in risk for atherosclerosis [16, 17]. Triglycerides, as well, are associated with incremental risk, although for this lipid species, the epidemiological evidence is not as strong, likely related to well-appreciated within-person variability in clinical measures of triglycerides [18]. Beyond the risk conferred by these altered levels of lipids, oxidative damage to HDL-associated apolipoprotein A-1 and reduced HDL-associated paraoxonase-1 activity observed in the diabetic environment also contribute to impaired HDL function [19-21]. Overall, there is growing appreciation that alterations in HDL function may be more important than absolute HDL levels.

In diabetes, altered levels of metabolic substrates and their metabolic products can alter function of cells that are central to the pathogenesis of atherosclerosis. In the plasma of diabetics high levels of glucose and fatty acids and their metabolites bathe the coronary vessels and are associated with vascular dysfunction, possibly through generation of reactive oxygen species and/or inflammation [22]. Furthermore, these abnormal metabolites may promote endothelial cell injury, an inciting event in atherogenesis [23], or plaque erosion that can lead to an acute coronary syndrome. In developing lesions, altered levels of metabolites or impaired insulin signaling may promote lesion progression through untoward

effects on monocyte or foam cell function. Abnormal metabolites or the oxidative stress they induce may signal through pathways that initiate vascular calcification, a sine qua non of diabetic vascular disease that may further impair vascular function through diminished elasticity [24]. In addition, increased epicardial adipose tissue, which is very prevalent in obese and diabetic individuals, may accelerate atherosclerosis through local release of metabolites and adipocytokines [25-27].

Management—Despite advances in medical therapy of diabetes, diabetic patients with coronary disease fare poorly when compared to those without diabetes. This may reflect, in part, the observation that diabetics more frequently have silent ischemia related to autonomic dysfunction, such that they present later in the course of this chronic disease [28]. It also likely reflects the incomplete normalization of the absolute levels and the dynamic excursions of insulin, glucose and fatty acids despite aggressive diabetic management. Furthermore, while increased insulin levels and hyperglycemia generally predict adverse outcomes in diabetic patients [29], tight glycemic control, though seemingly logical, has been controversial with regard to decreasing macrovascular complications, such as CAD. Most recently, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found that independent of hypoglycemic events, type 2 diabetic subjects randomized to tight glycemic therapy had increased mortality, prompting early termination of the study [30, 31]. On the other hand, the lack of significant cardiovascular benefits in this trial must be weighed with the clear benefits of aggressive glycemic targets for decreasing microvascular disease, particularly in type 1 diabetes.

Controlling non-glycemic risk factors is also extremely important for treating CAD in the diabetic patient and is strongly recommended by both the American Diabetic Association and the American Heart Association [32]. Benefits have been noted with tobacco cessation and healthy lifestyle choices including exercise and weight reduction [33]. Multiple trials have shown decreased cardiovascular events in diabetic patients with aggressive lipid lowering using statin drugs [33-37]. Likewise, vigorous control of blood pressure decreases cardiovascular event rates. While most anti-hypertensive agents are effective in this regard, antagonism of the renin-angiotensin-aldosterone axis is particularly important in diabetic patients to decrease myocardial infarction and death, with data supporting the use of angiotensin converting enzyme inhibitors (ACE-I) from the Heart Outcomes Prevention Evaluation (HOPE) trial and the micro HOPE substudy, and the use of angiotensin receptor blockers (ARBs) from the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial [38, 39].

A number of multicenter trials have examined outcomes in diabetics with CAD following revascularization. Subgroup analysis from the Bypass Angioplasty Revascularization Investigation (BARI) study showed that coronary artery bypass grafting (CABG) in diabetics, who presented with acute coronary syndromes due to multivessel CAD, improved long-term survival better than PCI [40]. This survival benefit was most apparent among those receiving at least one arterial graft as opposed to those receiving only vein grafts. Subsequently, a number of studies have compared treatment modalities in diabetics with stable ischemic heart disease. The BARI 2D study showed that in diabetics with stable but more severe CAD (affecting all three coronary vessels), prompt revascularization by CABG compared to medical therapy conferred a reduction in major cardiovascular events. Initial results from the SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) trial also showed a benefit of CABG over drug-eluting stents in terms of decreased adverse cardiac events in CABG-treated patients and increased need for revascularization among those receiving drug eluting stents [41]. In diabetics with stable and less severe CAD, intensive medical therapy was as effective as PCI as a first-line therapy in BARI 2D [42]. Important additional data is expected to come from the ongoing Future

Revascularization Evaluation in patients with Diabetes Mellitus: Optimal Management of Multivessel disease (FREEDOM) study that will evaluate CABG versus PCI in a study design that incorporates the most advanced approaches to PCI and optimal medical management.

Heart Failure

Epidemiology and course of disease—Diabetes is a major risk factor for heart failure, with the relative impact of diabetes on the development of heart failure even greater than the impact of diabetes on the development CAD [2]. The Framingham Heart Study data suggest that proportion of all heart failure that is attributable to diabetes alone is ~12% in women and 6% in men [43]. The proportion of heart failure cases that is attributable to diabetes and its frequent co-morbidities – obesity and hypertension – is even greater. The prevalence of diabetes among all heart failure patients is estimated between 24% and 38% [44, 45]. Conversely, among patients with diabetes, it is estimated that the prevalence of heart failure is *more than 1 in 9* [46]. Furthermore, the risk of developing heart failure appears to be greater in women than men with diabetes: in the Framingham study, in which patients with diabetes (but without coronary disease) were followed for 20 years, the relative risk of developing heart failure was 3 for men but 8 for women [2]. Even after adjusting for age, blood pressure, smoking, cholesterol, and left ventricular hypertrophy, the relative risk was roughly doubled for men with diabetes but almost 4-fold for women with diabetes. Despite generally accepted treatment goals for glucose control, heart failure remains a significant cause of morbidity and mortality in diabetes [47-49].

As discussed above, CAD is a significant risk factor for the development of heart failure in diabetics who suffer a myocardial infarction, both during the initial hospitalization and after discharge from the hospital [9]. Data from the Studies of Left Ventricular Dysfunction (SOLVD) trial demonstrate that diabetes is a risk factor for progression of heart failure in patients with ischemic cardiomyopathy, although the data are less clear in non-ischemic diabetic patients with heart failure [50]. Other risk factors for the development of heart failure in diabetes include age, diabetes duration, and renal dysfunction. Each of these factors may contribute to the increased risk through exacerbation of CAD. However, heart failure in diabetes also occurs in the absence of underlying CAD and hypertension, an entity known as diabetic cardiomyopathy that is defined based on exclusion of other potential causes. On pathologic examination, diabetic cardiomyopathy is characterized by alterations in the intramural vasculature, myocyte hypertrophy, and interstitial fibrosis [51, 52]. Heart failure in diabetes, with or without underlying CAD, may present with overt symptoms of right or left heart failure, or it may be subclinical and picked up using non-invasive transthoracic echocardiography early, prior to the development of heart failure symptoms.

Diabetes is a risk factor for both diastolic and systolic cardiac dysfunction, both of which may be asymptomatic in early stages but can be detected using transthoracic echocardiography. While diastolic dysfunction is relatively rare (1%) in healthy, non-obese individuals [53], echocardiographic studies have demonstrated that from 40 to 75% of asymptomatic people with type 2 diabetes have diastolic dysfunction in the absence of other contributing factors [54, 55]. There is more controversy as to whether or not type 1 diabetes is a risk factor for the development of diastolic dysfunction. In one study of 87 type 1 diabetics with no known coronary disease and 87 matched controls, those with diabetes had lower early diastolic filling and an increase in atrial filling, longer isovolumic relaxation time, and longer mitral valve deceleration time, all suggesting impaired diastolic function [56]. In contrast, another study that evaluated diastolic function using more load-independent tissue Doppler measures, found that early diastolic relaxation was not different between diabetics and controls [57]. However, this study did demonstrate that type 1

diabetics had increased reliance on left atrial contribution to left ventricular filling. Furthermore, echocardiographic studies have demonstrated that despite overall normal ejection fraction, systolic abnormalities including lower mid-wall fractional shortening (FS) and peak systolic strain are present in up to 16% of asymptomatic patients [58-61].

Some of the functional changes in the diabetic heart are likely due to alterations in cardiac structure. There is an increase in left ventricular mass that is associated with both type 1 and type 2 diabetes [62, 63]. Among those with type 2 diabetes, there are some data suggesting that women may be more susceptible to developing left ventricular hypertrophy than men [63, 64]. Co-morbidities that frequently co-exist with diabetes, such as hypertension and obesity, obviously can contribute to an increase in LV mass. However, in several large epidemiologic studies, diabetes remained an independent predictor of LV mass even after adjustment for age, blood pressure, and body mass index [65, 66].

Early asymptomatic cardiac dysfunction in diabetics can progress to cause clinical symptoms of heart failure [56, 67-70]. Diabetics who present with heart failure symptoms may have heart failure with preserved ejection fraction (HFPEF), or they may have evidence of impaired ejection fraction (< 50%). Increased left ventricular end-diastolic pressure (as manifested by an increased E/E' ratio by echocardiography) and impaired left ventricular compliance (as manifested by diastolic wall strain) are associated with an increased risk for the development of heart failure in diabetic patients [71, 72]. There is also evidence that impairment of left ventricular compliance (another component of diastolic function) plays a crucial role in the transition of the diabetic patient from asymptomatic to symptomatic [72]. Systolic dysfunction in diabetes often occurs rather late in the process of heart failure development. Diabetics with acute heart failure present to the hospital with pulmonary edema more often than those without diabetes [73]. When they present with acute heart failure, diabetic patients are also more likely to have multiple co-morbidities including anemia, hypertension, peripheral vascular disease, and renal insufficiency.

Unfortunately, diabetes confers an increased risk of morbidity and mortality in patients with either systolic dysfunction or HFPEF [44, 74, 75]. Moreover, this increased risk has been demonstrated in studies performed in a wide range of settings including acute hospitalization, ambulatory care, and prospective clinical trials [74]. For example, in the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT) study, patients with diabetes had a twice the risk of heart failure hospitalization and death even after adjusting for other risk factors [76]. In this study, the increased risk conferred by the presence of diabetes was the same as that conferred by CAD. In the Beta-blocker Evaluation of Survival Trial (BEST), the poor prognosis associated with diabetes in patients with systolic heart failure was mostly limited to those patients with ischemic cardiomyopathy [77]. In a study of acute heart failure, in-hospital mortality in diabetic patients was predicted by: older age, systolic blood pressure <100mmHg, noncompliance, a history of hypertension, decreased ejection fraction, creatinine >1.5mg/dL, acute coronary syndrome, absence of medical therapy for heart failure and absence of PCI for CAD [73].

Pathogenesis—Exposure to high levels of metabolites has long been proposed to play a role in diabetes complications including heart failure. High glucose levels may exert deleterious effects through the functional consequences of changes in cardiomyocyte metabolism, alterations in the myocardial architecture and fibrosis, and/or damage to cardiac cells and tissue from adventitious glycosylation of proteins and damage to cellular macromolecules from oxidative stress [78, 79]. Consistent with this notion, worse glycemic control and higher fasting glucose levels are associated with increased incidence of heart failure [80, 81]. Altered presentation of glucose and other metabolic substrates may

contribute to heart failure through systemic and cardiac upregulation of the renin-angiotensin system, impaired cardiac mitochondrial respiration, and impaired calcium handling [82-84].

Emerging experimental evidence suggests that lipotoxicity, caused by increased plasma free fatty acid and triglyceride levels in diabetes [85-87] also causes oxidative stress and contributes to risk of heart failure. Using positron emission tomography (PET) with ^{11}C -palmitate tracer injection, it has been shown that increased plasma free fatty acid concentrations in obesity and diabetes are associated with upregulation of myocardial fatty acid uptake, utilization and oxidation [88, 89]. This pattern of metabolism is associated with decreased efficiency (cardiac work per myocardial oxygen consumption) as quantified in PET and echocardiographic studies. This pattern is also associated with impaired diastolic function as quantified by echocardiography, and lower phosphocreatine/ATP ratios measured by magnetic resonance spectroscopy (MRS) [88, 90, 91]. Over time, increased fatty acid uptake in the human diabetic heart outpaces increases in fatty acid oxidation, similar to what has been reported for animal models, resulting in myocardial steatosis by ^1H -MRS and increased myocardial triglyceride stores on pathological analyses [92-94].

In animal model and in vitro systems, hyperglycemia and hyperlipidemia can cause oxidative stress through many mitochondrial and non-mitochondrial pathways. Thus, it is not surprising that in humans with diabetes, there is evidence of systemic oxidative stress as quantified by increased urinary 8-hydroxy-2'-deoxyguanosine, decreased ratio of reduced to oxidized red blood cell glutathione (GSH:GSSG), and increased plasma lipid hydroperoxides and malondialdehyde [95-98]. Although evidence for myocardial oxidative stress in diabetes has been well demonstrated in animal models of type 1 and type 2 disease, there have been relatively few reports of myocardial reactive-oxygen-species or oxidative-stress-mediated tissue damage in the human heart, likely related to the difficulties of obtaining appropriate tissue for analysis. Nonetheless, evidence for oxidative stress has been reported in atrial appendage tissue from diabetics undergoing CABG and in left ventricular tissue from carefully processed autopsy specimens [82, 83].

Intriguingly, in one study, insulin use and better glycemic control were risk factors for the development of heart failure [46]. The exact explanation as to how lower glucose levels and increased insulin treatment may confer increased risk, is not clear. However, insulin as an anabolic hormone, has been associated with left ventricular hypertrophy, a poor prognostic indicator [99-101]. Hypoglycemic episodes and/or decreased plasma glucose presentation to the heart for myocardial metabolism may also play a role in this increased risk.

Management—Given the presumed contributions of hyperglycemia to the pathogenesis of heart failure in diabetes, glycemic control for prevention of heart failure and its progression is an important goal. Nonetheless, in contrast to compelling clinical trial data in support of tight glycemic control to decrease microvascular complications [102, 103] and evidence of continued benefit in follow up after the end of such trials (i.e., legacy effect) [104], there are less data regarding glycemic control and specific outcomes in heart failure. In a cohort study that included both type 1 and type 2 diabetics, poor glycemic control, as evidenced by higher HbA1c, was associated with increased risk of heart failure [81]. In treatment of type 2 diabetics, the UKPDS demonstrated that for every 1% reduction in HbA1c, the risk of heart failure fell by 16% [105]. However, glycemic control alone is unlikely to be sufficient. Moreover, the ACCORD trial of intensive blood glucose lowering therapy in adults with type 2 diabetes, was terminated because of *increased* mortality in the intensive treatment group, unrelated to hypoglycemia, and it is possible that some of this mortality may have been related to heart failure [30, 31]. Considering the various approaches to glucose management, it is important to note that thiazolidinedione treatment is associated with fluid retention and is not recommended for patients with heart failure. Additionally, the “Black

Box” warning on rosiglitazone informs physicians of the potential increased risk for heart attack and the contraindication to use of the drug in patients with diabetes and cardiovascular disease. Metformin is also contraindicated for patients with heart failure because of the risk of lactic acidosis.

In general, treatment for systolic heart failure patients with diabetes is similar to that of heart failure patients without diabetes. Although an extensive review of all data on the treatment of heart failure is beyond the purview of this article, we will discuss some special considerations of heart failure treatment in the diabetic patient. Blockade of the renin-angiotensin-aldosterone axis is a mainstay of treatment for all patients with heart failure – including those with diabetes. In large, randomized clinical trials, angiotensin converting enzyme inhibitor (ACE-I) therapy clearly decreases mortality and heart failure readmission. The risk-reduction conferred by ACE-I therapy is almost identical in patients with diabetes as it is in those without diabetes [74, 106]. ACE-I therapy may also help prevent progression from asymptomatic to symptomatic heart failure in diabetes, and is thus indicated in diabetics even without frank heart failure for prevention [107]. ACE-I therapy has obvious benefits for patients with diabetes and renal disease, and can be used even in patients with significant renal dysfunction, provided there is close follow-up [108]. However, this class of medications should generally be avoided in patients with type 4 renal tubular acidosis (hyporeninemic hypoaldosteronism), a tendency towards hyperkalemia, hypotension, bilateral renal artery stenosis, a history of angioedema, concurrent nephrotoxic therapy, pregnancy, or other contraindication to ACE-I therapy.

Blockade of the renin-angiotensin system with ARBs also decreases the development of symptomatic heart failure in patients with diabetes [109, 110]. These drugs are generally better tolerated than ACE-I. Treatment with an ARB is generally recommended in patients who cannot tolerate ACE-I therapy for issues such as ACE-I-induced cough [74]. However, as with ACE-I therapy, ARBs are generally not appropriate for patients who have a tendency to hyperkalemia or who have type 4 renal tubular acidosis.

Aldosterone antagonism is effective in improving survival in patients with severe heart failure and in those with heart failure after a myocardial infarction [111, 112]. Subgroup analysis in the Eplerenone Post-Acute Myocardial Infarction and Heart Failure Efficacy and Survival Study (EPHESUS) demonstrated that patients with diabetes had the same survival benefit as non-diabetics [112]. However, there has been no specific evaluation of the efficacy of eplerenone in patients with diabetes and diabetic cardiomyopathy. In the absence of contraindications, aldosterone antagonism is a reasonable approach for heart failure in diabetics (providing that patients do not have a tendency to hyperkalemia or significant renal dysfunction or other contraindications), but additional studies will be required to achieve the level of proof of efficacy that exists for ACE-I or beta-blocker therapy.

Neurohormonal blockade with beta-adrenergic blockers is also a mainstay of therapy for systolic dysfunction. Although initially counterintuitive as a therapy for a heart with impaired contractility, beta-blockers have proven to be one of the most effective medical treatments for decreasing mortality in heart failure [113]. Subgroup analyses of major clinical trials of patients with heart failure show that the survival benefits gained from beta-blocker therapy apply equally to those with diabetes as to those without it [113]. The improved survival in diabetic patients on beta-blocker therapy is due to both a decreased incidence of sudden death and decreased pump failure [114]. Although there have been concerns raised that patients with diabetes may not mount an appropriate response to hypoglycemia under beta-blockade, in most patients the benefits of this therapy outweigh this risk.

While it was once considered a contraindication, diabetes currently it is not an absolute contraindication to heart transplantation, and transplant may be the treatment of choice in some patients with advanced heart failure [115]. Diabetics have similar survival as non-diabetics at one and five years post-transplant, and there is no difference in the incidence of acute rejection, transplant arteriopathy, or renal dysfunction post-transplant between diabetics and non-diabetics [116]. Although diabetes was thought to carry an increased risk of post-transplant infection, most studies have not born this out [117].

The treatment of diabetes-related HFPEF is less well defined, since no medical treatments have been shown to decrease mortality in patients with HFPEF [44]. Current guidelines recommend treatment of underlying contributing factors (e.g., hypertension) as an initial approach [118]. Diuretics are useful for control of edema in these patients, and other treatments used for heart failure with systolic dysfunction (e.g., beta-blocker, ACE-I) may be helpful for symptom relief [118].

CONCLUSIONS

Individuals with type 1 and type 2 diabetes carry an increased risk of vascular and myocardial disease. These complications contribute significantly to morbidity and mortality among those living with diabetes. While a number of therapeutic approaches have improved outcomes in both CAD and heart failure in diabetes, more remains to be understood regarding the links between the altered metabolic state in diabetes and the cardiovascular pathology with which it is associated. Such new knowledge will enable development of more effective therapies that are specifically aimed at the underlying causes of the cardiovascular complications in diabetics.

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