SEMINARS IN
NEPHROLOGY

Heart Disease in Diabetic Patients

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Cardiac artery disease and heart failure are major causes for morbidity and mortality in diabetes in general and in those with chronic kidney disease (CKD) in particular. Hypertension and dyslipidemia are more common in diabetes and the prevalence of coronary artery disease in diabetics is two-fold to four-fold higher than in nondiabetics. In those with CKD the incidence of cardiovascular complications is nearly two-fold higher than those without CKD. Recent studies suggest that the pathophysiology of cardiac disease is complex process involving both microvascular and macrovascular disease. In addition, myocardial lipotoxicity may be a novel contributing factor particularly in type 2 diabetics. Compelling evidence from cardiovascular outcomes trials indicates that treatment with drugs that block the renin-angiotensin system are cardioprotective in diabetics with microalbuminuria and early stages of kidney disease. Multiple risk factor intervention aimed at optimal blood pressure control (BP <130/<80 mmHG), lowering LDL cholesterol below 100 mg/dl, lowering triglyceride level to 150 mg/dl, A1C <6.5%, treatment with an ACE inhibitor or an angiotensin II receptor blocker, administration of once daily low-dose aspirin and smoking cessation together reduce cardiovascular morbidity and mortality in type 2 diabetics. Novel studies including diabetics with nephropathy aimed at improving outcomes in diabetics by treatment of anemia and optimal control of dyslipidemia are now underway. These and other clinical trials should provide important new insights into improving the quality of life in diabetics and ultimately preventing cardiac disease.
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Heart disease, including myocardial infarction, heart failure, and sudden death, is the leading cause of death in patients with diabetes mellitus. Moreover, diabetic patients with nephropathy are at higher risk for cardiac death than those without nephropathy.[1] The worldwide epidemic of diabetes has increased awareness of this disease sharply and its devastating consequences including end-stage renal disease. Diabetic retinopathy and proteinuria and manifestations of microvascular abnormalities occur early in the course of diabetes mellitus; in contrast, macrovascular complications such as myocardial infarction usually occur later. Nevertheless both microvascular and macrovascular disease affect the heart in the diabetes patient and contribute to cardiac morbidity and mortality. This article reviews current data on the epidemiology, pathophysiology, and clinical outcomes in patients with diabetes and heart disease.

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Heart Disease Is Common and Lethal in Types 1 and 2 Diabetes

The exact incidence and prevalence of heart disease among diabetic patients is not known. One explanation for the lack of precise estimates of heart disease frequency is that it is silent in many patients and likely begins in the early stages of type I and type 2 diabetes. Indeed, abnormalities in coronary artery vasodilation and left ventricular function occur in prediabetic patients or in those with diabetes and few risk factors (see later). Observational, population-based studies have shown relatively high incidence and prevalence of coronary heart disease among diabetic patients. For example, in type 1 diabetic patients followed-up in the Wisconsin epidemiologic study of diabetes mellitus, the 20-year age-adjusted cumulative incidences were 18.1% for angina and 14.8% for myocardial infarction. Of 273 deaths, 176 involved heart disease.[2] The rate of death after myocardial infarction in type 1 diabetic patients without proteinuria is 9-fold and with proteinuria is 40-fold higher compared with age-matched nondiabetic patients.[3] Type 2 diabetes is associated with a

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2-fold to 4-fold increase in the risk for coronary artery disease as compared with the nondiabetic population. Among nearly 4,000 Italian type 2 diabetic patients aged 50 years or older, coronary heart disease (CHD) prevalence was found to be 20%. In this population, age and duration of diabetes were significantly greater in those with CHD. Comparing patients with and without CHD, the prevalence of hypertension (52.9% versus 63.0%, $P < .001$), hypercholesterolemia (11.6% versus 14.1%, $P < .05$), and hyperlipidemia (17.8% versus 23.3%, $P < .001$) was significantly higher in the diabetic patients affected with CHD.[4] Also, community-based studies indicate that the relative risk for death in type 2 diabetic patients is increased 1.5 to 2 times that of nondiabetic patients, and the incidence of myocardial infarction (MI) or stroke risk is increased 2-fold to 3-fold. This marked increase in MI and cerebrovascular accident (CVA) is independent of other known risk factors for cardiovascular diseases.[5] In addition, observational studies indicate that the risk for first myocardial infarction in type 2 diabetic patients is equivalent to that of nondiabetic patients with a known history of MI. Based on these and other data, the National Cholesterol Education Program Guidelines designated diabetes as a high coronary risk equivalent.[6] In summary, diabetic patients are at increased risk for heart disease, mortality after MI is increased markedly among diabetic patients, and the presence of nephropathy further increases the mortality risk for a cardiac event. What is responsible for the increase in heart disease risk among diabetic patients?

Pathophysiology

A detailed review of the pathophysiology of ischemic heart disease and heart failure in diabetes has been published recently.[7-9] This section discusses some of the potential mechanisms. Diabetic patients have a strong propensity to develop premature diffuse atherosclerotic coronary disease, which underlies both MI and heart failure. Both structural and functional abnormalities of the microvasculature autonomic dysfunction contribute to the development of diabetic cardiomyopathy. In addition, macrovascular disease contributes to the pathophysiology of heart disease in diabetes. These processes account for the majority of cases of heart failure, coronary ischemic events, and sudden cardiac death in diabetic patients.

Diabetic Cardiomyopathy

The disease entity known as *diabetic cardiomyopathy* has been described extensively in young patients with diabetes in the absence of ischemic, hypertensive, or valvular heart disease. However, the pathogenesis of this disorder is understood incompletely. For example, it is not clear whether this term refers to both microvascular and macrovascular disease. The most convincing data to support the notion of a diabetic cardiomyopathy caused by microvascular disease is a 30% to 40% incidence of decreased radionuclide angiographic left ventricular ejection fraction response to dynamic exercise. Physiologic studies in normotensive normolipidemic diabetic patients suggest that exercise-induced increase in ejection fraction is impaired despite the absence of overt heart failure. Echocardiographic evidence for left ventricular dysfunction also has been shown in type 1 diabetic patients during exercise.[10] These findings imply that diabetic cardiomyopathy in young adult patients with diabetes is associated with high blood pressure or other risk factors such as overt ischemia.[11]

Role of Lipids

Lipotoxicity of myocardium has been postulated as a novel cause for cardiac dysfunction in diabetic patients with heart failure. According to this theory, deranged fatty acid metabolism is associated with insulin resistance and obesity resulting in abnormal partitioning of lipids within the cell and accumulation of abnormal amounts of triglyceride in cardiac tissue.[12] This may in turn lead to lipoapoptosis and sarcopenia, culminating in cardiomyopathy. Changes in the myocardium are amplified by hypertension and kidney disease. Experimental animal evidence supports the view that abnormal leptin physiology in obesity rats leads to excess accumulation of lipids in cardiac tissue. Tissue toxicity of lipid accumulation independent of vessel lumen lipid accumulation is the proposed pathogenic factor in this scheme.[13]

In type 2 diabetic patients without overt coronary artery disease, increased triglyceride and free fatty acid levels are associated with myocardial insulin resistance, endothelial dysfunction, and alteration of nitric oxide/cyclic guanosine monophosphate levels.[14] Carefully conducted studies using positron emission tomography scanning have shown that abnormal coronary vascular vasodilatory response is impaired in obese normotensive prediabetic patients.[15,16] Taken together, these studies suggest that endothelial dysfunction is an early sign of vascular disease in diabetes.

Role of Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system plays an important role in the pathophysiologic mechanisms behind diabetic heart disease. Both angiotensin II and aldosterone are associated with increased cardiac fibrosis and blockade of angiotensin-converting enzyme (ACE) inhibitor, the angiotensin II receptor and mineralocorticoid receptor can improve cardiac outcomes in diabetic patients with heart disease. These agents represent major critical therapeutic interventions in this population (see later).[7]

Importance of Hypertension

Hypertension frequently coexists with diabetes mellitus, occurring twice as frequently in diabetic as in nondiabetic persons. It accounts for up to 75% of added cardiovascular disease risk in people with diabetes, contributing significantly to the overall morbidity and mortality in this high-risk population. Patients with hypertension are 2 times more prone to have diabetes than are normotensive persons. Hypertension substantially increases the risk for CHD, stroke, retinopathy, and nephropathy. In patients

with type 2 diabetes, hypertension usually clusters with the other components of the metabolic syndrome such as microalbuminuria, central obesity, insulin resistance, dyslipidemia, hypercoagulation, increased inflammation, and left ventricular hypertrophy (LVH). In type 1 diabetes, hypertension often occurs subsequent to the development of diabetic nephropathy. Hypertension in diabetes is characterized by volume expansion, increased salt sensitivity, isolated systolic blood pressure (BP) increase, loss of the nocturnal dipping of BP and pulse, and increased propensity toward orthostatic hypotension and albuminuria.[17] Among the treatment strategies tested in hypertensive diabetic persons, low-density lipoprotein (LDL) cholesterol–lowering to less than 100 mg/dL and aggressive BP control to less than 130/80 mm Hg have proven effective in cardiovascular disease risk reduction. The combination of 2 or more drugs usually is necessary to achieve the target BP.[18]

Nontraditional Risk Factors

Numerous nontraditional risk factors have been linked to the development of cardiac and cardiovascular disease in diabetic patients with microalbuminuria as a principle factor.[19] In addition, prothrombotic factors, inflammatory cytokines, and markers of oxidative stress have been associated with heart disease in diabetic patients. These factors are thought to indicate a state of chronic inflammation, which is an important pathogenetic factor for atherosclerosis. Longitudinal follow-up evaluation of participants in the atherosclerosis risk in communities study showed that levels of albumin, fibrinogen, and von Willebrand factor; factor VIII activity; and leukocyte count are predictors of CHD among patients with diabetes.[20]

Anemia is an emerging risk factor for cardiovascular disease and is common in patients with diabetes and nephropathy. Anemia has been implicated in the development of heart failure and may play a role in coronary artery disease events including CHD in diabetic patients.[21-23] Recent studies indicated that LVH is common in chronic kidney disease (CKD) patients even in early stages of the disease. In prospective studies, worsening anemia is an independent predictor of new-onset LVH and carries the same relative risk as increasing systolic blood pressure.[24,25] Importantly, anemia and hemoglobin were shown to confer a similar risk increase for LVH. Specifically, for each 0.5-g/dL decrease in hemoglobin level there was a 32% increase in risk for LVH, whereas for every 15-mm Hg increase in systolic blood pressure there was a 36% increase in risk for LVH during the 12-month follow-up interval. In addition, retrospective analyses indicate that left ventricular mass regression is associated with increased survival on dialysis, but this has not been shown in a prospective study.[26-28] However, clinical trials designed to assess directly the effect of correction of anemia on cardiovascular outcomes in patients with diabetes have not yet been conducted.

Outcomes in Diabetic Patients With Heart Disease

Improving outcomes in diabetic patients with and without kidney disease means finding ways to reduce onset and progression of atherosclerosis and CHD. The high rates of cardiac death undoubtedly are related strongly to atherosclerotic complications including heart failure, MI, and sudden death. Several clinical trials have shown that interventions designed to reduce atherosclerosis progression and block the renin-angiotensin-aldosterone system improve outcomes in this patient population.

Lipid-Lowering Trials

There are no long-term lipid-lowering trials examining the efficacy of this intervention in diabetic patients with kidney disease. However, several trials have documented that decreasing LDL cholesterol with long-term administration of statin drugs is effective in both primary and secondary prevention of CHD among type 2 diabetic patients.[8,29-32] In general, these studies show a 20% to 30% reduction in relative risk for coronary artery disease events including death. In the Collaborative Atorvastatin in Diabetes Study, type 2 diabetic patients with an LDL-cholesterol concentration of 4.14 mmol/L or less, a fasting triglyceride level of 6.78 mmol/L or less, and at least 1 other factor were randomized to 10-mg daily atorvastatin or placebo. This trial was terminated 2 years earlier than expected because of the dramatic finding that after a median duration of follow-up evaluation (3.9 years), there was a 36% reduction in risk for acute CHD in those randomized to atorvastatin. The investigators concluded that no justification was available for having a particular threshold level of LDL-cholesterol as the sole arbiter of which patients with type 2 diabetes should receive statins.[7,8] Taken together with the results of the reversal of atherosclerosis with aggressive lipid (REVERSAL) and pravastatin and atorvastatin evaluation and infection therapy-thronbolysis in Myocardial infraction 22 (PROVE-IT) trials published this year, the National Cholesterol Education Program revised its guidelines to include an LDL goal for the highest risk patients of less than 70 mg/dL. This is an unprecedented recommendation and has major implications for health care policy and health care economics. Greater adoption of therapeutic strategies that include aggressive lipid lowering has the potential to result in dramatic improvement in survival among diabetic patients with heart disease.

Blood Pressure Lowering

The United Kingdom Prospective Diabetes Study clearly showed that aggressive blood pressure lowering in hypertensive, type 2 diabetic patients results in a 40% reduction in stroke and a 35% reduction in overall mortality.[33] Aggressive versus nonaggressive blood pressure control amounted to a 10 mm Hg lower systolic and a 5 mm Hg lower diastolic blood pressure. Similarly, the Hypertension Optimum Trial, which randomized hypertensive type 2 diabetic patients to 1

of 3 diastolic blood pressure groups (<90, <85, and <80 mm Hg) showed a 50% reduction in mortality related to MI in those randomized to the lowest versus the highest diastolic BP goal. Moreover, the average difference in diastolic blood pressure between these 2 groups was 4.1 mm Hg. Thus, relatively small differences in blood pressure were associated with relatively large improvements in outcome. Moreover, ad hoc analysis of the entire cohort of the United Kingdom Prospective Diabetes Study showed that lower blood pressure in general was associated with a decreased risk for MI.[34]

Blockade of the Renin-Angiotensin-Aldosterone System

The exact mechanisms whereby drugs that interrupt the renin-angiotensin-aldosterone system (RAAS) provide cardiac protection in diabetic patients are not completely known. Decreasing blood pressure, inhibiting thrombosis, reducing inflammation and fibrosis, decreasing albuminuria, cardiac remodeling, and inhibition of atherosclerosis all are potential protective mechanisms afforded by blocking the RAAS. The Heart Outcomes Protection Study showed that ramipril reduced MI and sudden death by 25% among type 2 diabetic patients.[35] Similar findings were observed in hypertensive type 2 diabetic patients with LVH who were treated with losartan as compared with atenolol in the Losartan Intervention For Endpoints trial.[36] In this trial, losartan was associated with a 25% reduction in risk for composite outcome of sudden cardiac death and nonfatal stroke and MI in type 2 diabetic patients with similar blood pressure control. Multiple risk factor intervention in microalbuminuric type 2 diabetic patients including use of an ACE inhibitor or angiotensin II receptor antagonist was associated with a 53% reduction in cardiovascular events including MI, coronary revascularization, and sudden death.[37] In type 2 diabetic patients with nephropathy, losartan treatment was associated not only with a 28% reduction in risk for end-stage renal disease, but also with a 32% reduction in risk for new-onset heart failure.[38]

Trials in CKD

As noted earlier, there are no large-scale published studies whose primary purpose was to examine the effects of interventions on cardiac disease outcomes in patients with diabetes and CKD. Among the studies cited earlier, some participants had evidence of CKD and the benefit of blood pressure and lipid lowering (as well as blockade of the RAAS) was observed. Currently, there are several ongoing trials designed specifically to examine cardiovascular outcomes in patients with CKD and 2 studies are focused on diabetic patients with CKD in particular. The Die Deutsche Diabetes Dialyze study is a long-term, prospective, double-blind, randomized, placebo-controlled trial comparing 20 mg atorvastatin once daily to placebo in approximately 1,200 diabetic patients on maintenance hemodialysis.[39] The primary outcome is a composite of cardiovascular events including coronary artery disease and heart failure events. This study has been completed and the results will be available soon. The Study of Heart Protection in Renal Patients trial is a large-scale, double-blind, randomized trial comparing aggressive versus less-aggressive lipid lowering on cardiovascular outcomes including coronary events and heart failure among 9,000 patients with CKD, including those on hemodialysis.[40] The Trial to Reduce Cardiovascular Events with Aranesp Therapy is a multicenter, international, double-blind, placebo-controlled trial designed to determine whether treatment of anemia in type 2 diabetic patients with nephropathy and anemia can improve survival and reduce cardiovascular morbidity and mortality. This trial will enroll 4,000 patients who will be followed-up for a minimum of 2 years. This is the first, large-scale, clinical trial in CKD patients designed to determine whether anemia treatment can improve cardiovascular outcomes in a high-risk population.[41]

Management

Current recommendations for improving outcomes in patients with diabetic nephropathy include decreasing blood pressure, tight glycemic control, blockade of RAAS, lipid lowering, smoking cessation, treatment of anemia, and aspirin administration.

Blood Pressure Lowering

First and foremost in improving outcomes in patients with diabetic nephropathy is to treat blood pressure to goal of less than 130/less than 80 mm Hg. This should include nonpharmacologic and pharmacologic therapies. Weight loss, physical exercise, modest alcohol intake, dietary sodium intake of 2 g/d are important for controlling blood pressure. For pharmacologic therapy, use an ACE inhibitor or an angiotensin-receptor antagonist combined with a diuretic. Most diabetic patients with nephropathy are hypertensive and require multidrug therapy to achieve the BP goal of less than 130 mm Hg. In most patients, either calcium channel blocker (CCB) or a β-blocker can be used but both also can be administered. Nondihydropyridine CCBs have a higher likelihood of reducing proteinuria but either class is acceptable as an add-on drug.[42,43] Finally, adding on an angiotensin-receptor blocker or a mineralocorticoid antagonist such as spironolactone or eplerenone may be helpful particularly if the patient has heart failure or is post-MI.[44,45] However, combining these agents must be performed with extreme caution because of the risk for significant hyperkalemia, particularly in elderly patients.[46]

Block the RAAS

Blocking the RAAS with an ACE inhibitor or angiotensin-receptor blocker is recommended by the American Diabetes Association and the National Kidney Foundation. This maneuver is designed to decrease blood pressure and to reduce proteinuria and to block many downstream pathways responsible for renal disease progression as well as for cardiovascular protection.

Improve Glycemic Control

Decreasing the A1c to a level less than 7% is associated with improved microvascular outcomes[47-49] and is the recommended goal by the American Diabetes Association.[50] It should be noted that the Diabetes Control and Complications Trial (DCCT) data suggested that an A1c level of 7% represents a mean plasma glucose of about 170 mg/dL. Tighter glycemic control to 6.5% was used in the Gaede et al[37] study (see earlier) and is recommended by some diabetologists. This is attainable with appropriate diet, weight loss, and a combination of insulin with noninsulin therapies such as thiazolidinediones. Metformin can be used, but this agent is contraindicated if serum creatinine is >1.4 mg/dL.

Decreasing LDL Cholesterol With a Statin

Decreasing LDL cholesterol starting with a statin is the best approach for this patient's dyslipidemia. Targeting an LDL cholesterol of less than 70 mg/dL in this patient is consistent with new Adult Treatment Panel III (ATPIII) guidelines.[51] Statins, in addition to decreasing cholesterol, have other effects such as anti-inflammatory and antioxidative properties that may be beneficial. Cardiovascular protection, although not proven in advanced renal disease, is prudent in a patient at very high risk such as a diabetic patient with a history of prior MI. This drug class is well tolerated by diabetic patients with nephropathy, and there is a very small risk for myositis or rhabdomyolysis in patients even with doses of 20 to 40 mg per day. Additional lipid-lowering agents such as ezetimibe, niacin, or cholestyramine can be added on to statins. However, both niacin and cholestyramine carry a significant risk for untoward side effects.

Treatment of Anemia

Before treating anemia with erythropoietin and iron, the National Kidney Foundation and European best practice guidelines recommend an initial work-up that includes history, physical examination, stool guaiac, complete blood count with red blood cell indices, and iron studies (serum iron, TIBC, ferritin). Additional testing for vitamin deficiencies and hemolytic or other causes of anemia also should be undertaken based on the findings and results of the recommended work-up. Blood erythropoietin levels are not recommended for the diagnosis or management of anemia attributed to CKD.

Treatment of anemia with erythropoietin and iron is recommended by the National Kidney Foundation for CKD patients with a hemoglobin level of less than 11.0 g/dL according to current guidelines. The rationale for this is based on observational data in end-stage renal disease patients and quality-of-life studies and in short-term regression of LVH. However, it should be noted that there are no outcome studies proving benefit of treatment of anemia for reducing cardiovascular events or slowing progression of kidney disease.

Use Aspirin

A daily dose of aspirin (81-325 mg) as an endothelial protective agent may help to reduce the risk for recurrent coronary event and stroke. This is a prudent and cost-effective maneuver and the American Diabetes Association recommends aspirin for cardiovascular protection for all adult diabetic patients with macrovascular disease.

Smoking Cessation

Smoking, in addition to its linkage to macrovascular disease, has been shown to accelerate a decrease in kidney function in some studies.[52-55] All patients who smoke should be provided with every opportunity and aids to stop.

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