Patients with diabetes are at increased risk of acute myocardial infarction, heart failure, and end-stage renal disease (ESRD). Diabetes also predisposes to considerably worse outcomes when these complications develop, with increased mortality of patients with acute myocardial infarction and heart failure and more rapid progression toward ESRD in patients who manifest early evidence of renal insufficiency.

**Progressive Renal Insufficiency in Diabetes**

In the United States, diabetes is the leading cause of ESRD, which includes the need for kidney dialysis or transplantation. Unfortunately, the 5-year survival rate of ESRD patients with diabetes is only 20%, largely because of a very high incidence of cardiovascular disease (CVD). The reasons for this excess CVD are inadequately explored, but hypertension, dyslipidemia, and anemia probably play important roles. A major goal, therefore, should be early recognition of kidney damage so that measures can be undertaken to prevent progressive loss of renal function.

**Clinical Course of Diabetic Nephropathy**

The clinical course of nephropathy in both type 1 and type 2 diabetes is similar, consisting of an initial period of supranormal glomerular filtration rate lasting 10 or more years followed by ~5 years with microalbuminuria (Table) and then macroalbuminuria and loss of glomerular filtration rate. Microalbuminuria is found in both types of diabetes and identifies the patients destined to develop progressive kidney damage. Macroalbuminuria identifies patients with substantial histological damage and heralds a predictable, linear decline in glomerular filtration rate; the rate of loss of renal function varies widely among patients with diabetes who have nephropathy. For screening, yearly testing for albuminuria is required (at the onset of type 2 diabetes and after 7 years of type 1 diabetes). Regular evaluations of glucose control and monitoring of the rate of loss of renal function are indicated for each patient. For the older patient with type 2 diabetes, the possibility of coexisting kidney diseases should be evaluated. Numerous reports emphasize the prominent position microalbuminuria holds as an identifier of incipient renal insufficiency. It also predicts CVD. To reach the largest number of persons with diabetes (especially in the setting of primary care), the simple spot, early-morning-urine sample for determining the microalbumin-to-creatinine ratio should be encouraged as the first-line test.

In addition to serving as an identifying marker for the presence of kidney disease, it is possible that proteinuria plays a role in the pathogenesis of kidney damage. This is controversial, because the degree of proteinuria may simply reflect the severity of kidney damage. Regardless, successful treatment of hypertension reduces the degree of proteinuria and generally results in reduced kidney damage.

**Hypertension and Diabetic Nephropathy**

Hypertension is common in patients with diabetic nephropathy. Angiotensin-converting enzyme inhibitors (ACEIs) are widely recommended for controlling blood pressure in any hypertensive patient with kidney disease because proteinuria responds well to ACEIs even though blood pressure is not always controlled. In the Heart Outcomes Prevention Evaluation study, ACEIs also were found to have significant beneficial effects on CVD and the progression of kidney damage in patients with diabetes despite producing only a modest decrease in blood pressure. The therapeutic goal should be to achieve a blood pressure <130/85 mm Hg and to reduce proteinuria by restricting dietary salt and adding ACEIs or other blood-pressure lowering drugs. In one trial of type 2 diabetes patients with nephropathy, dihydroxyidine calcium channel antagonists (CCAs) were associated with excess mortality from CVD; these drugs are generally less effective in reducing proteinuria. The admonition against...
Urine Protein Measurements

<table>
<thead>
<tr>
<th>Urine Protein</th>
<th>Normal</th>
<th>Microalbuminuria</th>
<th>Macroalbuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-Hour collection, mg/d</td>
<td>&lt;30</td>
<td>30–299</td>
<td>≥300</td>
</tr>
<tr>
<td>Timed collection, µg/min</td>
<td>&lt;20</td>
<td>20–199</td>
<td>≥200</td>
</tr>
<tr>
<td>Spot collection, mg/g creatinine*</td>
<td>&lt;30</td>
<td>30–299</td>
<td>≥300</td>
</tr>
</tbody>
</table>

*Preferred method for screening and monitoring.

Complicating conditions that increase protein excretion include fever, heavy exercise, poor glucose control, heart failure, urinary tract infection, and vaginal fluid contaminant.

Complicating conditions that decrease protein excretion include use of nonsteroidal anti-inflammatory drugs (NSAIDs), malnutrition, and use of ACE inhibitors.

Owing to the variability in urinary albumin excretion, 2 of 3 specimens over a 3 to 6 month period need to be abnormal to classify a patient as having micro-/macro-albuminuria.

Other Management Strategies for Diabetic Nephropathy

What other strategies can be used to treat kidney disease in patients with diabetes? Similarities in the course of nephropathy in patients with both types of diabetes suggest that hyperglycemia is central to the pathogenesis of kidney damage. In fact, strict control of blood glucose (to hemoglobin A1c [Hb A1c] <7.0%) reduces the incidence of microalbuminuria and the progression from microalbuminuria to macroalbuminuria. There also are reports that the use of statin drugs to treat elevated low-density lipoprotein cholesterol not only acts to protect against CVD but also may slow the loss of renal function. Finally, a beneficial influence on the loss of renal function is achieved by restricting dietary protein. More than a century ago, it was reported that dietary protein restriction was an integral part of the management of chronic renal insufficiency; fortunately, this practice is nutritionally safe. Controlled trials of small numbers of patients and meta-analyses of large numbers of patients treated with low-protein diets (0.6 g of protein per kg of body weight per day) indicate that these diets can also slow the loss of renal function. Thus, not only should dietary education be a critical part of the management of any patient with diabetes to achieve glucose control and prevention of hyperlipidemia, but the need for a skilled and interested dietitian/nutritionist to provide education and counseling is augmented when nephropathy is present. The goal is to maintain glucose control and to prevent the accumulation of unexcreted waste products and other complications of renal insufficiency.

The practice of performing renal arteriograms and angioplasty for suspected renal artery stenosis in patients with diabetes who have coronary heart disease (CHD) should be discouraged; these patients are at high risk of developing acute renal damage from the angiography dye. In addition, renal arterial angioplasty is generally unsuccessful in maintaining renal arterial patency.

Conclusions and Recommendations for Diabetic Nephropathy

These considerations lead to guidelines for the therapy of patients with diabetic nephropathy. First, blood pressure should be strictly controlled. In addition to dietary salt restriction, initial therapy should include an ACEI (whether differences in the efficacy of ACEIs on tissue angiotensin converting enzyme are critical is unsettled). If blood pressure control is not achieved or there is a complication from ACEI use, β-blockers, diuretics, CCAs, or other drugs should be added (often these patients require several agents to achieve adequate blood pressure control). Treatment should also include strict control of blood glucose to Hb A1c <7.0%, as recommended after successful trials in controlling the progression of nephropathy in patients with both types of diabetes. In patients with diabetes who have LDL cholesterol levels above optimal (≥100 mg/dL), cholesterol-lowering drugs (eg, statins) should be considered. Patients who have progressive renal insufficiency despite these measures or who develop increasing macroalbuminuria should be referred to a nephrologist. Dietary protein should be limited in patients who have progressive renal insufficiency to reduce the accumulation of nitrogen-containing waste products and to take advantage of the antiproteinuric effects of dietary protein restriction and its beneficial influence on progression of renal insufficiency.

Diabetes and Left Ventricular Dysfunction

There are a number of unresolved issues concerning the relation between diabetes and left ventricular (LV) dysfunction that result in ongoing uncertainties regarding the management of the diabetic patient with heart failure. It is clear that diabetes predisposes to impaired LV systolic and diastolic function. However, it is often difficult, in practice or when interpreting trial data, to ascertain whether the impact of diabetes on LV function represents specific, direct metabolic effects on the myocardium or merely the effects of concomitant CHD or hypertension, which are common comorbid conditions in patients with diabetes.

Mechanisms Responsible for LV Dysfunction in Diabetics

The mechanisms by which diabetes predisposes to LV dysfunction and heart failure include (1) concomitant CHD, (2) concomitant hypertension, (3) LV hypertrophy, (4) disease of the coronary microvasculature, (5) endothelial dysfunction, (6) obesity, (7) autonomic dysfunction, and (8) metabolic abnormalities that contribute to the diabetic cardiomyopathy. Endothelial dysfunction is a characteristic of diabetes, and endothelium-derived substances may have profound effects on myocardial structure and function. For example, both endothelin and angiotensin II cause myocardial hypertrophy and increased interstitial connective tissue, and both may also contribute to myocardial apoptosis. Obesity, an integral component of the metabolic syndrome and type 2 diabetes, predisposes to the toxic effects of fatty acids on the myocardium and the additional detrimental effects of cytokines and angiotensin II released by adipose tissue. The possibility of a specific diabetic cardiomyopathy has been the subject of
debate for decades, but there are now substantive data indicating that diabetes impairs LV function through direct and indirect mechanisms. Several experimental models of diabetes have demonstrated altered myocyte gene expression, disorders of calcium ion homeostasis, and abnormal systolic and diastolic function in relation to elevations of blood glucose. It is also evident from natural history studies that the early cardiovascular manifestations of diabetes include increased LV mass and hyperdynamic LV function that may be related to a hyperadrenergic state. Such effects may also contribute to myocardial apoptosis and increased interstitial connective tissue deposition. Persons with diabetes and hypertension have greater LV mass and wall thickness than nondiabetic hypertensive patients. It is therefore not surprising that diabetes is one of the major factors, along with hypertension and CHD, associated with heart failure with normal systolic function, especially in older persons.

Diabetes and Onset of Heart Failure With Normal Systolic Function
It is a well-known clinical observation that heart failure symptoms can develop in patients with normal LV systolic function, and when this occurs, diabetes is often a contributing factor. The pathophysiology, management, and outcomes of persons with diabetes, heart failure, and preserved systolic function have not been specifically addressed. Management strategies are generally those recommended for LV systolic dysfunction, including use of β-blockers and ACEIs, although there is a paucity of data supporting such practice.

Diabetes and Onset of LV Systolic Dysfunction
Several longitudinal community-based studies have identified diabetes as a major risk factor for development of clinical heart failure. The Framingham Study, which involved 5209 patients followed up for 18 years, demonstrated nearly 2 decades ago that patients with diabetes have a higher likelihood of developing clinical heart failure. After adjustment for coronary artery disease and rheumatic heart disease, the relative risk of developing heart failure was 3.8 in diabetic men and 5.5 in diabetic women compared with nondiabetic patients. This effect also increased as a function of aging. The Framingham experience has been confirmed in several recent smaller series. In the Glasgow MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) cohort, the frequency of LV systolic dysfunction was highest in persons with diabetes (29% compared with 7.7% in persons without diabetes). In the New Haven cohort of the Established Population for Epidemiologic Studies of the Elderly, diabetes was the strongest predictor of development of heart failure in a multivariate analysis of 1749 subjects aged 65 years or older; diabetes more than doubled the risk of subsequent heart failure. Similarly, in the Cardiovascular Health Study, which involved 5888 subjects aged 65 years or greater, diabetes doubled the risk of developing heart failure in men over the course of 5.5 years and tripled the risk in women. Finally, recent data from the Kaiser Health System have demonstrated that diabetes control also significantly affects the likelihood of developing heart failure. In an analysis of >48 000 patients followed up for 2.2 years, the likelihood of onset of heart failure was directly related to levels of Hb A1c. In patients with Hb A1c <7%, the rate of heart failure was 4.2 per 1000 per year; in patients with Hb A1c >10%, this rate increased to 9.2 per 1000 per year. This effect was more pronounced in men than in women.

Diabetes Prevalence in Heart Failure Clinical Trials
Among 14 multicenter heart failure treatment trials or data registries that reported diabetes as a comorbidity of the study population, diabetes was present in 7974 of 32 649 patients, representing an overall prevalence of 24%. The prevalence of diabetes ranged from 14% to 28% in these studies. It is noteworthy that many of the heart failure multicenter trials published in the last 5 years did not report the prevalence of diabetes.

The leading cause of LV systolic dysfunction and congestive heart failure in developed countries in the current era is CHD, with a prevalence in the recent multicenter heart failure trials of >66%. Thus, ischemic heart disease often contributes to the manifestation of heart failure, and the progression of heart failure in many cases may be a reflection of progression of CHD. This indicates that the prevention and treatment of heart failure in many patients should include use of established primary and secondary prevention guidelines, including control of blood pressure, use of statins and aspirin, smoking cessation, and implementation of ACEI therapy in persons with diabetes and cardiovascular risk factors.

It is probable that the majority of persons with diabetes and heart failure in the multicenter heart failure trials are also those with CHD, with the expected worse prognosis of coronary disease patients with LV dysfunction. However, even among patients with CHD and LV dysfunction, those with diabetes have a higher mortality than those without diabetes, as reported in a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) database. No other multicenter trial or registry has described the diabetic populations concerning presence of underlying coronary artery disease, and no study (including the SOLVD database) has evaluated severity of CHD in the diabetic population relative to the nondiabetic population. In addition, no trial has described the diabetic patients with reference to hypertension and hypertension control.

Only a few trials have reported the outcome of patients with diabetes relative to the nondiabetic population. Even fewer report the results of the medical intervention separately in the patients with diabetes. The available data do uniformly demonstrate that persons with diabetes and heart failure represent a very-high-risk group with a substantially worse prognosis than those without diabetes. Data from the Survival and Ventricular Enlargement trial also demonstrate a significant increase in mortality in insulin-dependent patients compared with non–insulin-dependent patients (41% versus 26%, P < 0.001).

The SOLVD Treatment and Prevention Trials and the Trandolapril Cardiac Evaluation (TRACE) trial reported the effects of ACEI therapy on outcome of persons with diabetes and heart failure. In the 3 trials, mortality and heart failure
hospitalization rates were higher in patients with diabetes than in persons without diabetes. In the SOLVD Treatment Trial, enalapril provided no significant mortality reduction in patients with diabetes, whereas there was a significant reduction in mortality in such patients receiving enalapril in the SOLVD Prevention Trial and in those receiving trandolapril in the TRACE trial.

Only one of the trials investigating β-blocker therapy in heart failure examined the effect of such therapy in patients with diabetes. MERIT-HF (Metoprolol Controlled-Release Randomised Intervention Trial in Heart Failure) demonstrated that patients with diabetes had higher mortality than heart failure patients without diabetes. However, a subset analysis failed to demonstrate a significant survival benefit in patients with diabetes after β-blocker therapy with metoprolol. Whether this represents the effects of a β₁-selective agent and whether greater efficacy may be achieved in patients with diabetes with use of a nonselective β-blocker with α₁-blocking properties, such as carvedilol, will be determined only by future trials or analysis of existing trial data.

Myocardial Revascularization
There are very limited data regarding the impact of myocardial revascularization on survival and quality of life in patients with diabetes, CHD, and LV dysfunction. A retrospective analysis of data from the SOLVD Treatment and Prevention Trials has demonstrated a significant improvement in survival in such patients with myocardial revascularization plus medical therapy compared with the results of medical therapy alone. Revascularization also resulted in an improvement in symptoms and reduction in hospitalization for heart failure.

Conclusions and Recommendations
Diabetes is a major risk factor for the development of heart failure, both systolic and diastolic. Moreover, in patients with heart failure, diabetes represents a major risk factor for cardiac complications and death. The use of ACE inhibition and β-blockade is strongly recommended for all persons with diabetes and LV systolic dysfunction unless contraindicated, because these are the only agents proven to improve the natural history of heart failure. ACEI use in patients with diabetes is well founded, but the efficacy of β-blockade is less certain and requires further investigation.

The use of primary and secondary heart failure prevention measures should be advised in patients with diabetes in accordance with standard guidelines. Future research is needed to define the prevalence and prognostic importance of diabetes in heart failure populations in relation to the comorbidities of hypertension and CHD, to determine the efficacy of heart failure interventions in this population, and to determine whether aggressive control of diabetes influences outcome of patients with heart failure. Future prospective clinical heart failure intervention trial design should include planned analysis and prospective randomization of patients with diabetes. The longitudinal course of LV mass and function in relation to markers of diabetes disease severity needs to be examined to determine risk factors for development of heart failure. Finally, the role of prospective screen-

Acute Myocardial Infarction
In-hospital and long-term mortality rates after acute myocardial infarction (AMI) are twice as high among individuals with diabetes as among those without diabetes. Approximately 30% of hospitalized patients with AMI will have diabetes, compared with a diabetes prevalence of 6% to 8% in the general population. Diabetes is also a major risk factor for adverse outcomes in patients with unstable angina.

There are numerous factors responsible for this increased risk. Thrombolytic trials have demonstrated improved outcomes with reduction in the time to presentation and to institution of treatment. Persons with diabetes, particularly in the setting of autonomic neuropathy, have impaired angina recognition and may not consider shortness of breath, nausea, vomiting, unexplained fatigue or diaphoresis, or disturbances of glycemic control as symptoms of cardiac ischemia. Atypical symptoms could also prevent recognition of AMI by caregivers and be a cause of treatment delay. Too often, AMI is the first clinical expression of CHD in the patient with diabetes, who may have experienced prior, unheeded symptoms of cardiac ischemia. Furthermore, one should not assume that the absence of angina in the post–myocardial infarction (MI) patient is a reliable index of CHD stability. Surveillance with noninvasive testing may be of benefit in some persons with diabetes.

Factors specific to diabetes may not only increase the risk of MI but also adversely affect its outcome. Autonomic nervous system (ANS) dysfunction results in sympathovagal imbalance and may lower the threshold for life-threatening arrhythmia and increase the risk of hemodynamic instability. Up to 50% of individuals with type 2 diabetes (with disease duration >10 years) have ANS dysfunction manifested as impaired heart rate variability. Fibrinogen levels may be elevated in patients with diabetes, particularly in the setting of proteinuria or poor glycemic control. Elevated levels of plasminogen activator inhibitor-1 indicate impaired fibrinolysis, and diabetic platelets are more aggregable than nondiabetic platelets. Such diabetes-related alterations may increase the risk of thrombosis at the site of plaque disruption and possibly increase the risk of reinfarction after thrombolytic therapy. The diabetic ventricle is more prone to maladaptive remodeling, which increases the risk of heart failure and cardiogenic shock. The status of the noninfarct zone, an important determinant of the remodeling process, may be affected by silent infarction, ANS-related diastolic or systolic dysfunction, diabetic or hypertensive cardiomyopathy, impaired microvascular perfusion, and more extensive epicardial CHD.

AMI patients with diabetes are distinguished by a higher prevalence of comorbidities, including dyslipidemia, hypertension, renal insufficiency, and peripheral and cerebral vascular disease. There is a higher rate of previous MI, an excess risk of heart failure before and at presentation, and more extensive epicardial CHD. Patients with diabetes present at a younger age; women are affected as often as men.
In almost all respects, the management of AMI is similar for patients with and without diabetes. Specific contraindications to the use of proven therapies must be recognized. For example, hyperkalemia and renal insufficiency may preclude the use of ACEIs. Targets for treatment include reestablishment of coronary flow and myocardial perfusion, plaque stabilization, prevention of recurrent ischemia, limitation of LV remodeling, arrhythmia suppression, and initiation of a lifelong program of secondary prevention.

Reperfusion Therapy
Persons with diabetes derive the same or greater relative survival benefit from fibrinolytic therapy as those without diabetes. Previous concerns about the hemorrhagic risk associated with diabetic retinopathy have not been substantiated. Similarly, acute success rates with primary percutaneous coronary intervention are comparable in the presence or absence of diabetes, although restenosis and long-term mortality rates remain higher in patients with diabetes.

Antiplatelet Therapy
Platelet aggregability is increased in patients with either type 1 or type 2 diabetes. Aspirin is the mainstay of antithrombotic therapy for all patients with acute coronary syndromes and should be provided as first-line therapy. The glycoprotein IIb/IIIa inhibitors improve outcomes for high-risk patients with unstable angina and non–ST-segment elevation, especially those undergoing percutaneous coronary intervention. In 2 large-scale clinical trials, the IIb/IIIa antagonists were shown to benefit both patients with and those without diabetes. They may also favorably affect rates of restenosis after percutaneous coronary intervention.

Antithrombin Therapy
Intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin should be provided as clinically indicated, regardless of diabetic status.

β-Adrenoreceptor Antagonists
Trials performed in the prereperfusion era established conclusively that β-blockers confer early and late survival benefit in patients with diabetes that exceeds that seen among persons without diabetes. Relative concerns regarding alterations in lipid profiles/glycemic control and the masking of symptoms of hypoglycemia do not pertain in this setting. The standard contraindications related to pump function, atrioventricular conduction, and active bronchospasm should apply.

Angiotensin Converting Enzyme Inhibitors
ACEIs may be more effective in diabetic patients than in persons without diabetes after AMI. Post hoc analyses in 2 large trials demonstrated striking benefits in survival, function, and the incidence of heart failure, which were substantially greater for patients with diabetes. ACEIs should be given early to all diabetic AMI patients unless contraindications are present.

Glycemic Control
Substantial evidence points to the admission glucose level as an independent predictor of early and late mortality after MI in patients with and without diabetes. The DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) study suggests that strict glycemic control for 3 months can significantly improve survival at 1 and 3 years after MI.

Post-MI Management
AMI should prompt a meticulous search for CHD risk factors, including diabetes. For patients with newly recognized diabetes, this provides an opportunity for prompt referral to a diabetes management team, in addition to a program of cardiac rehabilitation.

Future Research Directions
The comprehensive investigation of diabetes and its management can only be achieved through the performance of randomized clinical trials that (1) recruit patients with established diabetes, (2) stratify by diabetes status at the time of randomization, and (3) are powered according to anticipated event rates. In most instances, the small increase in sample size required to achieve these important objectives will provide vital information that will enable the clinical application of the study findings. In view of the near-linear relationship between fasting glucose and CHD mortality, further investigation of patients with impaired fasting glucose or impaired glucose tolerance is warranted. The potential risk/benefit of new diabetic therapies in the AMI setting must also be assessed. The scientific community is encouraged to consider investigations directed at metabolic abnormalities existing in myocardial and vascular cells as potential targets for new therapies, as well as the modulation of hemostatic and inflammatory processes that influence plaque vulnerability and thrombogenesis.

References


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