Microvascular and Macrovascular Complications of Diabetes

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Diabetes is a group of chronic diseases characterized by hyperglycemia. Modern medical care uses a vast array of lifestyle and pharmaceutical interventions aimed at preventing and controlling hyperglycemia. In addition to ensuring the adequate delivery of glucose to the tissues of the body, treatment of diabetes attempts to decrease the likelihood that the tissues of the body are harmed by hyperglycemia.

The importance of protecting the body from hyperglycemia cannot be overstated; the direct and indirect effects on the human vascular tree are the major source of morbidity and mortality in both type 1 and type 2 diabetes. Generally, the injurious effects of hyperglycemia are separated into macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy). It is important for physicians to understand the relationship between diabetes and vascular disease because the prevalence of diabetes continues to increase in the United States, and the clinical armamentarium for primary and secondary prevention of these complications is also expanding.

Microvascular Complications of Diabetes

Diabetic retinopathy

Diabetic retinopathy may be the most common microvascular complication of diabetes. It is responsible for ~ 10,000 new cases of blindness every year in the United States alone.[1] The risk of developing diabetic retinopathy or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia. Development of diabetic retinopathy in patients with type 2 diabetes was found to be related to both severity of hyperglycemia and presence of hypertension in the U.K. Prospective Diabetes Study (UKPDS), and most patients with type 1 diabetes develop evidence of retinopathy within 20 years of diagnosis.[2,3] Retinopathy may begin to develop as early as 7 years before the diagnosis of diabetes in patients with type 2 diabetes.[1] There are several proposed pathological mechanisms by which diabetes may lead to development of retinopathy.

Aldose reductase may participate in the development of diabetes complications. Aldose reductase is the initial enzyme in the intracellular polyol pathway. This pathway involves the conversion of glucose into glucose alcohol (sorbitol). High glucose levels increase the flux of sugar molecules through the polyol pathway, which causes sorbitol accumulation in cells. Osmotic stress from sorbitol accumulation has been postulated as an underlying mechanism in the development of diabetic microvascular complications, including diabetic retinopathy. In animal models, sugar alcohol accumulation has been linked to microaneurysm formation, thickening of basement membranes, and loss of pericytes. Treatment studies with aldose reductase inhibitors, however, have been disappointing.[1,4,5]

Cells are also thought to be injured by glycoproteins. High glucose concentrations can promote the nonenzymatic formation of advanced glycosylated end products (AGEs). In animal models, these substances have also been associated with formation of microaneurysms and pericyte loss. Evaluations of AGE inhibitors are underway.[1]

Oxidative stress may also play an important role in cellular injury from hyperglycemia. High glucose levels can stimulate free radical production and reactive oxygen species formation. Animal studies have suggested that treatment with antioxidants, such as vitamin E, may attenuate some vascular dysfunction associated with diabetes, but treatment with antioxidants has not yet been shown to alter the development or progression of retinopathy or other microvascular complications of diabetes.[1,6]

Growth factors, including vascular endothelial growth factor (VEGF), growth hormone, and transforming growth factor β, have also been postulated to play important roles in the development of diabetic retinopathy. VEGF production is increased in diabetic retinopathy, possibly in response to hypoxia. In animal models, suppressing VEGF production is associated with less progression of retinopathy.[1,3,7]

Diabetic retinopathy is generally classified as either background or proliferative. It is important to have a general understanding of the features of each to interpret eye examination reports and advise patients of disease progression and prognosis.

Background retinopathy includes such features as small hemorrhages in the middle layers of the retina. They clinically appear as "dots" and therefore are frequently referred to as "dot hemorrhages." Hard exudates are caused by lipid deposition that typically occurs at the margins of hemorrhages. Microaneurysms are small vascular dilatations that occur in the retina, often as the first sign of retinopathy. They clinically appear as red dots during retinal examination. Retinal edema may result from microvascular leakage and is indicative of compromise of the blood-retinal barrier. The appearance is one of grayish retinal areas. Retinal edema may require intervention because it is sometimes associated with visual deterioration.[8]

Proliferative retinopathy is characterized by the formation of new blood vessels on the surface of the retina and can lead to vitreous hemorrhage. White areas on the retina ("cotton wool spots") can be a sign of impending proliferative retinopathy. If proliferation continues, blindness can occur through vitreous hemorrhage and traction retinal detachment. With no intervention, visual loss may occur. Laser photocoagulation can often prevent proliferative retinopathy from progressing to blindness; therefore, close surveillance for the existence or progression of retinopathy in patients with diabetes is crucial.[8]

Diabetic nephropathy

Diabetic nephropathy is the leading cause of renal failure in the United States. It is defined by proteinuria > 500 mg in 24 hours in the setting of diabetes, but this is preceded by lower degrees of proteinuria, or "microalbuminuria."

Microalbuminuria is defined as albumin excretion of 30–299 mg/24 hours. Without intervention, diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy. This progression occurs in both type 1 and type 2 diabetes.

As many as 7% of patients with type 2 diabetes may already have microalbuminuria at the time they are diagnosed with diabetes.[9] In the European Diabetes Prospective Complications Study, the cumulative incidence of microalbuminuria in patients with type 1 diabetes was ~ 12% during a period of 7 years.[9,10] In the UKPDS, the incidence of microalbuminuria was 2% per year in patients with type 2 diabetes, and the 10-year prevalence after diagnosis was 25%.[9,11]

The pathological changes to the kidney include increased glomerular basement membrane thickness, microaneurysm formation, mesangial nodule formation (Kimmelstiel-Wilson bodies), and other changes. The underlying mechanism of injury may also involve some or all of the same mechanisms as diabetic retinopathy.

Screening for diabetic nephropathy or microalbuminuria may be accomplished by either a 24-hour urine collection or a spot urine measurement of microalbumin. Measurement of the microalbumin-to-creatinine ratio may help account for concentration or dilution of urine, and spot measurements are more convenient for patients than 24-hour urine collections. It is important to note that falsely elevated urine protein levels may be produced by conditions such as urinary tract infections, exercise, and hematuria.

Initial treatment of diabetic nephropathy, as of other complications of diabetes, is prevention. Like other microvascular complications of diabetes, there are strong associations between glucose control (as measured by hemoglobin A_{1c} [A1C]) and the risk of developing diabetic nephropathy. Patients should be treated to the lowest safe glucose level that can be obtained to prevent or control diabetic nephropathy.[9,11,12] Treatment with angiotensin-converting enzyme (ACE) inhibitors has not been shown to prevent the development of microalbuminuria in patients with type 1 diabetes but has been shown to decrease the risk of developing nephropathy and cardiovascular events in patients with type 2 diabetes.[9,13]

In addition to aggressive treatment of elevated blood glucose, patients with diabetic nephropathy benefit from treatment with antihypertensive drugs. Renin-angiotensin system blockade has additional benefits beyond the simple blood pressure–lowering effect in patients with diabetic nephropathy. Several studies have demonstrated renoprotective effects of treatment with ACE inhibitors and antiotensin receptor blockers (ARBs), which appear to be present independent of their blood pressure–lowering effects, possibly because of decreasing intraglomerular pressure. Both ACE inhibitors and ARBs have been shown to decrease the risk of progression to macroalbuminuria in patients with microalbuminuria by as much as 60–70%. These drugs are recommended as the first-line pharmacological treatment of microalbuminuria, even in patients without hypertension.[9]

Similarly, patients with macroalbuminuria benefit from control of hypertension. Hypertension control in patients with macroalbuminuria from diabetic kidney disease slows decline in glomerular filtration rate (GFR). Treatment with ACE inhibitors or ARBs has been shown to further decrease the risk of progression of kidney disease, also independent of the blood pressure–lowering effect.

Combination treatment with an ACE inhibitor and an ARB has been shown to have additional renoprotective effects. It should be noted that patients treated with these drugs (especially in combination) may experience an initial increase

in creatinine and must be monitored for hyperkalemia. Considerable increase in creatinine after initiation of these agents should prompt an evaluation for renal artery stenosis.[9,14]

Diabetic neuropathy

Diabetic neuropathy is recognized by the American Diabetes Association (ADA) as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes."[15] As with other microvascular complications, risk of developing diabetic neuropathy is proportional to both the magnitude and duration of hyperglycemia, and some individuals may possess genetic attributes that affect their predisposition to developing such complications.

The precise nature of injury to the peripheral nerves from hyperglycemia is not known but likely is related to mechanisms such as polyol accumulation, injury from AGEs, and oxidative stress. Peripheral neuropathy in diabetes may manifest in several different forms, including sensory, focal/multifocal, and autonomic neuropathies. More than 80% of amputations occur after foot ulceration or injury, which can result from diabetic neuropathy.[16] Because of the considerable morbidity and mortality that can result from diabetic neuropathy, it is important for clinicians to understand its manifestations, prevention, and treatment.

Chronic sensorimotor distal symmetric polyneuropathy is the most common form of neuropathy in diabetes. Typically, patients experience burning, tingling, and "electrical" pain, but sometimes they may experience simple numbness. In patients who experience pain, it may be worse at night. Patients with simple numbness can present with a painless foot ulceration, so it is important to realize that lack of symptoms does not rule out presence of neuropathy. Physical examination reveals sensory loss to light touch, vibration, and temperature. Abnormalities in more than one test of

peripheral sensation are > 87% sensitive in detecting the presence of neuropathy. Patients also typically experience loss of ankle reflex.[16] Patients who have lost 10-g monofilament sensation are at considerably elevated risk for developing foot ulceration.[17]

Pure sensory neuropathy is relatively rare and associated with periods of poor glycemic control or considerable fluctuation in diabetes control. It is characterized by isolated sensory findings without signs of motor neuropathy. Symptoms are typically most prominent at night.[16]

Mononeuropathies typically have a more sudden onset and involve virtually any nerve, but most commonly the median, ulnar, and radial nerves are affected. Cranial neuropathies have been described but are rare. It should be noted that nerve entrapment occurs frequently in the setting of diabetes. Electrophysiological evaluation in diabetic neuropathy demonstrates decreases in both amplitude of nerve impulse and conduction but may be useful in identifying the location of nerve entrapment. Diabetic amyotrophy may be a manifestation of diabetic mononeuropathy and is characterized by severe pain and muscle weakness and atrophy, usually in large thigh muscles.[16]

Several other forms of neuropathy may mimic the findings in diabetic sensory neuropathy and mononeuropathy. Chronic inflammatory polyneuropathy, vitamin B_{12} deficiency, hypothyroidism, and uremia should be ruled out in the process of evaluating diabetic peripheral neuropathy.[16]

Diabetic autonomic neuropathy also causes significant morbidity and even mortality in patients with diabetes. Neurological dysfunction may occur in most organ systems and can by manifest by gastroparesis, constipation, diarrhea, anhidrosis, bladder dysfunction, erectile dysfunction, exercise intolerance, resting tachycardia, silent ischemia, and even sudden cardiac death.[16] Cardiovascular autonomic dysfunction is associated

with increased risk of silent myocardial ischemia and mortality.[18]

There is no specific treatment of diabetic neuropathy, although many drugs are available to treat its symptoms. The primary goal of therapy is to control symptoms and prevent worsening of neuropathy through improved glycemic control. Some studies have suggested that control of hyperglycemia and avoidance of glycemic excursions may improve symptoms of peripheral neuropathy. Amitriptyline, imiprimine, paroxetine, citalopram, gabapentin, pregablin, carbamazepine, topiramate, duloxetine, tramadol, and oxycodone have all been used to treat painful symptoms, but only duloxetine and pregablin possess official indications for the treatment of painful peripheral diabetic neuropathy.[16] Treatment with some of these medications may be limited by side effects of the medication, and no single drug is universally effective. Treatment of autonomic neuropathy is targeted toward the organ system that is affected, but also includes optimization of glycemic control.

Macrovascular Complications of Diabetes

The central pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system. In response to endothelial injury and inflammation, oxidized lipids from LDL particles accumulate in the endothelial wall of arteries. Angiotensin II may promote the oxidation of such particles. Monocytes then infiltrate the arterial wall and differentiate into macrophages, which accumulate oxidized lipids to form foam cells. Once formed, foam cells stimulate macrophage proliferation and attraction of T-lymphocytes. T-lymphocytes, in turn, induce smooth muscle proliferation in the arterial walls and collagen accumulation. The net result of the process is

the formation of a lipid-rich atherosclerotic lesion with a fibrous cap. Rupture of this lesion leads to acute vascular infarction.[19]

In addition to atheroma formation, there is strong evidence of increased platelet adhesion and hypercoagulability in type 2 diabetes. Impaired nitric oxide generation and increased free radical formation in platelets, as well as altered calcium regulation, may promote platelet aggregation. Elevated levels of plasminogen activator inhibitor type 1 may also impair fibrinolysis in patients with diabetes. The combination of increased coagulability and impaired fibrinolysis likely further increases the risk of vascular occlusion and cardiovascular events in type 2 diabetes.[20]

Diabetes increases the risk that an individual will develop cardiovascular disease (CVD). Although the precise mechanisms through which diabetes increases the likelihood of atherosclerotic plaque formation are not completely defined, the association between the two is profound. CVD is the primary cause of death in people with either type 1 or type 2 diabetes.[21,22] In fact, CVD accounts for the greatest component of health care expenditures in people with diabetes.[22,23]

Among macrovascular diabetes complications, coronary heart disease has been associated with diabetes in numerous studies beginning with the Framingham study.[24] More recent studies have shown that the risk of myocardial infarction (MI) in people with diabetes is equivalent to the risk in nondiabetic patients with a history of previous MI.[25] These discoveries have lead to new recommendations by the ADA and American Heart Association that diabetes be considered a coronary artery disease risk equivalent rather than a risk factor.[26]

Type 2 diabetes typically occurs in the setting of the metabolic syndrome, which also includes abdominal obesity, hypertension, hyperlipidemia, and increased coagulability. These other factors can also act to promote CVD. Even

in this setting of multiple risk factors, type 2 diabetes acts as an independent risk factor for the development of ischemic disease, stroke, and death.[27] Among people with type 2 diabetes, women may be at higher risk for coronary heart disease than men. The presence of microvascular disease is also a predictor of coronary heart events.[28]

Diabetes is also a strong independent predictor of risk of stroke and cerebrovascular disease, as in coronary artery disease.[29] Patients with type 2 diabetes have a much higher risk of stroke, with an increased risk of 150–400%. Risk of stroke-related dementia and recurrence, as well as stroke-related mortality, is elevated in patients with diabetes.[20]

Patients with type 1 diabetes also bear a disproportionate burden of coronary heart disease. Studies of have shown that these patients have a higher mortality from ischemic heart disease at all ages compared to the general population. In individuals > 40 years of age, women experience a higher mortality from ischemic heart disease than men.[21] Observational studies have shown that the cerebrovascular mortality rate is elevated at all ages in patients with type 1 diabetes.[30]

The increased risk of CVD has led to more aggressive treatment of these conditions to achieve primary or secondary prevention of coronary heart disease before it occurs. Studies in type 1 diabetes have shown that intensive diabetes control is associated with a lower resting heart rate and that patients with higher degrees of hyperglycemia tend to have a higher heart rate, which is associated with higher risk of CVD.[22] Even more conclusively, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study demonstrated that during 17 years of prospective analysis, intensive treatment of type 1 diabetes, including lower A1C, is associated with a 42% risk reduction in all cardiovascular events and a 57% reduction in the risk of nonfatal MI, stroke, or death from CVD.[31]

There has not been a large, long-term, controlled study showing decreases in macrovascular disease event rates from improved glycemic control in type 2 diabetes. Modification of other elements of the metabolic syndrome, however, has been shown to very significantly decrease the risk of cardiovascular events in numerous studies. Blood pressure lowering in patients with type 2 diabetes has been associated with decreased cardiovascular events and mortality. The UKPDS was among the first and most prominent study demonstrating a reduction in macrovascular disease with treatment of hypertension in type 2 diabetes.[32,33]

There is additional benefit to lowering blood pressure with ACE inhibitors or ARBs. Blockade of the renin-angiotensin system using either an ACE inhibitor or an ARB reduced cardiovascular endpoints more than other antihypertensive agents.[13,20,34] It should be noted that use of ACE inhibitors and ARBs also may help slow progression of diabetic microvascular kidney disease. Multiple drug therapy, however, is generally required to control hypertension in patients with type 2 diabetes.

Another target of therapy is blood lipid concentration. Numerous studies have shown decreased risk in macrovascular disease in patients with diabetes who are treated with lipid-lowering agents, especially statins. These drugs are effective for both primary and secondary prevention of CVD, but patients with diabetes and preexisting CVD may receive the highest benefit from treatment. Although it is beyond the scope of this article to review all relevant studies, it should be noted these beneficial effects of lipid and blood pressure lowering are relatively well proven and likely also extend to patients with type 1 diabetes. In addition to statin therapy, fibric acid derivates have beneficial effects. They raise HDL levels and lower triglyceride concentrations and have been shown to decrease the risk of MI in patients with diabetes in the Veterans Affairs

High-Density Lipoprotein Cholesterol Intervention Trial.[20,26,35–39]

Practice Recommendations

Patients with type 1 diabetes of > 5 years' duration should have annual screening for microalbuminuria, and all patients with type 2 diabetes should undergo such screening at the time of diagnosis and yearly thereafter. All patients with diabetes should have serum creatinine measurement performed annually. Patients with microalbuminuria or macroalbuminuria should be treated with an ACE inhibitor or ARB unless they are pregnant or cannot tolerate the medication. Patients who cannot tolerate one of these medications may be able to tolerate the other. Potassium should be monitored in patients on such therapy. Patients with a GFR < 60 ml/min or with uncontrolled hypertension or hyperkalemia may benefit from referral to a nephrologist.[15]

Patients with type 1 diabetes should receive a comprehensive eye examination and dilation within 3–5 years after the onset of diabetes. Patients with type 2 diabetes should undergo such screening at the time of diagnosis. Patients should strive for optimal glucose and blood pressure control to decrease the likelihood of developing diabetic retinopathy or experiencing progression of retinopathy.[15]

All patients with diabetes should undergo screening for distal symmetric polyneuropathy at the time of diagnosis and yearly thereafter. Atypical features may prompt electrophysiological testing or testing for other causes of peripheral neuropathy. Patients who experience peripheral neuropathy should begin appropriate foot self-care, including wearing special footwear to decrease their risk of ulceration. They may also require referral for podiatric care. Screening for autonomic neuropathy should take place at the time of diagnosis in type 2 diabetes and beginning 5 years after the diagnosis of type 1 diabetes. Medication to control the symptoms of painful peripheral neuropathy may be effective in improving quality of life in patients but do not appear to alter the natural course of the disease. For this reason, patients and physicians should continue to strive for the best possible glycemic control.

In light of the above strong evidence linking diabetes and CVD and to control and prevent the microvascular complications of diabetes, the ADA has issued practice recommendations regarding the prevention and management of diabetes complications.

Blood pressure should be measured routinely. Goal blood pressure is < 130/80 mmHg. Patients with a blood pressure ≥ 140/90 mmHg should be treated with drug therapy in addition to diet and lifestyle modification. Patients with a blood pressure of 130–139/80–89 mmHg may attempt a trial of lifestyle and behavioral therapy for 3 months and then receive pharmacological therapy if their goal blood pressure is not achieved. Initial drug therapy should be with a drug shown to decrease CVD risk, but all patients with diabetes and hypertension should receive an ACE inhibitor or ARB in their antihypertensive regimen.[15]

Lipid testing should be performed in patients with diabetes at least annually. Lipid goals for adults with diabetes should be an LDL < 100 mg/dl (or < 70 mg/dl in patients with overt CVD), HDL > 50 mg/dl, and fasting triglycerides < 150 mg/dl. All patients with diabetes should be encouraged to limit consumption of saturated fat, trans fat, and cholesterol. Statin therapy to lower LDL by 30–40% regardless of baseline is recommended to decrease the risk of CVD in patients > 40 years of age. Patients < 40 years of age may also be considered for therapy. In individuals with overt CVD, special attention should be paid to treatment to lower triglycerides or raise HDL. Combination therapy with a statin plus other drugs, such as fibrates or niacin, may be necessary to achieve ideal lipid control, but patients should be monitored closely for possible adverse reactions of therapy.[15]

Aspirin therapy (75–162 mg/day) is indicated in secondary prevention of CVD and should be used in patients with diabetes who are > 40 years of age and in those who are 30–40 years of age if other risk factors are present. Patients < 21 years of age should not receive aspirin therapy because of the risk of Reye's syndrome. Patients who cannot tolerate aspirin therapy because of allergy or adverse reaction may be considered for other antiplatelet agents.[15]

In addition to the above pharmacological recommendations, patients with diabetes should be encouraged to not begin smoking or to stop smoking to decrease their risk of CVD and benefit their health in other ways. It should also be noted that statins, ACE inhibitors, and ARBs are strongly contraindicated in pregnancy.

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