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TEACHERS' TOPICS

Microvascular and Macrovascular Complications of Diabetes Mellitus

Keecia D. King, PharmD, Jocelyn D. Jones, PharmD, and Jessica Warthen, PharmD

College of Pharmacy and Pharmaceutical Sciences, Florida A&M University

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Approximately 7 out of every 10 of the 1.7 million Americans who die each year die of a chronic disease such as diabetes mellitus.[1] Hyperglycemia may lead to diabetic complications causing damaging effects to the kidneys, nervous system, ocular function, cardiovascular system, and circulatory system, and leading to nephropathy, neuropathy, retinopathy, cardiovascular disease, cerebrovascular disease, and peripheral vascular disease. Healthcare professionals should make a collaborative effort to detect, evaluate, and treat long-term complications of diabetes. The purpose of this paper is to convey the pivotal role of pharmacists in the management of diabetic complications. As pharmacy faculty members and professors, our role is to educate pharmacy students on the signs and symptoms of disease, current treatment modalities, and the medical literature on the prevention and treatment of complications. Pharmacy students learn about diabetes in the didactic sequence of learning and during the experiential experience.

Keywords: diabetes, microvascular, macrovascular

INTRODUCTION

Diabetes is a national as well as global epidemic in terms of incidence, healthcare costs, and overall complications. As reported by the Center for Disease Control (CDC), over 18 million people in the United States have been diagnosed with the disease; 13 million are aware of the diagnosis and 5.2 million are unaware. Currently, diabetes is the sixth leading cause of death in the United States, and diabetic patients have twice the death rate of people without the disease.[2] The financial impact continues to rise as more people are affected. In 2002, the total cost of care (direct and indirect) equaled approximately $130 billion.[2] The prevalence of diabetes has increased among all racial groups and ethnic backgrounds. Among those 20 years and older, diabetes has been identified in American Indians and Alaska Natives (14.9%), African Americans (11.4%), Caucasians (8.4%), and Hispanic/Latino Americans (8.2%).[2]

The results from the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) convincingly demonstrated the importance of glycemic control for the prevention of microvascular complications of diabetes.[3,4] Uncontrolled diabetes has also been associated with heart disease, stroke, end-stage renal disease, nerve disease, dental disease, blindness, and amputations. There is a strong association between hyperglycemia and the incidence and progression of microvascular and macrovascular complications. These complications are believed to be major contributors to morbidity and mortality in patients with diabetes.[5,6] Diabetic complications can be delayed or prevented with continuous glycemic control accomplished by appropriate glucose monitoring, drug therapy, and ongoing disease state management.

Corresponding Author: Keecia D. King, PharmD. Assistant Professor of Pharmacy Practice, Florida A&M University College of Pharmacy and Pharmaceutical Sciences, Jacksonville Practice Division, 900 University Blvd North, Suite 400, Jacksonville, FL 32211. Tel: 904-762-2604. Fax: 904-762-2615. E-mail: keecia.king@famu.edu

OVERVIEW

Diabetes is a metabolic disease in which the body does not produce or does not properly utilize insulin. Type 1 diabetes results from cellular-mediated autoimmune destruction of the beta cells of the pancreas.[7] Insulin injections are necessary for survival. Type 1 diabetes develops most often in children or young adults and accounts for about 5% to 10% of cases of diabetes diagnosed in the United States.[2] Other factors that are involved in the development of type 1 diabetes include genetics and environmental factors.

Type 2 diabetes usually begins as insulin resistance, a disorder in which the cells do not use insulin properly. As the need for insulin rises, the pancreas gradually loses its ability to produce insulin. Diagnosis usually occurs in adult patients age 40 years and above; however, an increased risk and diagnosis of the disease has been identified in children and adolescents. Physical inactivity and unhealthy dietary habits create an environment that promotes obesity and

diabetes. About 90% to 95% of people with diabetes have type 2; approximately 80% are overweight.[2] The risk of developing type 2 diabetes increases with age, obesity, lack of physical activity, and impaired glucose tolerance. The disease is more common among people who have a family history of diabetes; have had gestational diabetes; and are African American, Hispanic American, Asian American, Pacific Islander, or Native American.[2]

Diabetes Complications

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Chronic hyperglycemia is associated with long-term damage and dysfunction of small and large blood vessels resulting in failure of various organs. Common complications resulting from uncontrolled diabetes include heart disease, stroke, blindness, periodontal disease, nervous system damage, and kidney dysfunction.[2] At the time of diagnosis, most patients with type 2 diabetes will have some symptoms of elevated glucose (ie, polyuria, polydipsia, polyphagia), microvascular symptoms (ie, blurred vision, numbness or tingling in hands or feet), and macrovascular complications (ie, cardiovascular disease).[8] These patients have a high mortality rate because of macrovascular complications. In comparison, an increased incidence of microvascular complications is usually not observed until 10 years after the initial diagnosis in type 1 diabetes.

Pathogenesis

Hyperglycemia is considered a major factor in the development of diabetic complications and the adverse effects are recognizable through multiple pathways. The aldose reductase (polyol) pathway, advanced glycation end-product pathway, hexosamine pathway, and protein kinase C pathway provide evidence that elevated blood glucose promotes cellular dysfunction and damage. The polyol pathway converts excess intracellular glucose into sugar alcohols via activity of the enzyme aldose reductase. This enzyme catalyzes the conversion of glucose to sorbitol, and in turn, sorbitol triggers a variety of different intracellular changes in the tissues involved.[9] Advanced glycation end products (AGEs) form at a constant rate in the normal body; however, in diabetes, this process is drastically increased. Three main consequences have been found in association with AGEs inside cells: (1) functional alterations of intracellular proteins, (2) altered interaction with AGE receptors, and (3) altered interactions with matrix and other cells.

The hexosamine pathway becomes activated when glucose levels are high in cells. It processes an upstream glycolytic intermediate, causing a permanent modification of proteins and transcription factors by the product of the pathway, N-acetyl-glucosamine. High levels of intracellular glucose activate the enzyme protein kinase C (PKC). When activated, this PKC enzyme alters cell function.[10,11]

Clinical Manifestations: Microvascular

Over 200,000 people die each year because of diabetes-related complications.[12] Underlying diabetic complications such as nephropathy, neuropathy, retinopathy, cardiovascular disease, and peripheral vascular disease can be present for many years before an actual diagnosis is made.[13,14] In fact, microvascular complications can begin developing at least 7 years before the clinical diagnosis of type 2 diabetes.[15] Conversely, type 1 patients may not develop signs of microvascular complications until 10 years after diagnosis of diabetes.[16]

Nephropathy. Diabetic nephropathy is a clinical syndrome characterized by excessive urinary albumin excretion, hypertension, and renal insufficiency. In the United States, diabetic nephropathy accounts for about 40% of new cases of end-stage renal disease (ESRD).[2] Nephropathy is a frequent complication of type 1 and type 2 diabetes mellitus.[17] Patients who have type 2 diabetes are commonly found to have albuminuria and overt nephropathy soon after or at the time of diabetes diagnosis. Half of patients with type 1 DM who have overt nephropathy will develop ESRD within 10 years and 75% within 20 years.[18] Not all diabetic patients will develop overt nephropathy; however, there are some factors that affect the progression of nephropathy such as cigarette smoking, poor glycemic control, urinary albumin excretion rate, hyperlipidemia, hypertension, genetics, and ethnicity.[19]

A test for the presence of microalbumin should be performed at diagnosis in patients with type 2 diabetes. Individuals with type 1 diabetes should be screened after 5 years of disease duration. After the initial screening and in the absence of previously demonstrated microalbuminuria, a test for the presence of microalbumin should be performed annually. Normal urinary albumin excretion is less than 30 mg/24 hr. Abnormal albumin excretion is defined as either microalbuminuria (30-299 mg/24 hr) or macroalbuminuria (>300 mg/24 hr).[20]

The natural history of diabetic nephropathy has 5 stages, which includes hyperfiltration with normal renal function; histological changes without clinically evident disease; incipient diabetic nephropathy or microalbuminuria; overt diabetic nephropathy (macroalbuminuria, reduced renal function); and renal failure requiring dialysis.[21] A diagnosis of microalbuminuria warrants therapy. Evidence-based treatment for diabetic nephropathy includes lifestyle

changes (ie, proper nutrition, dietary protein restrictions, weight control, smoking cessation, and exercise), optimal glucose control, blood pressure lowering, and drug therapy. There is strong evidence that angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) can cause a reduction in microalbuminuria and may retard progression to overt diabetic nephropathy. Therefore, these drugs should be used as first-line agents for diabetic patients at risk for nephropathy.

The MICRO-HOPE (Microalbuminuria, Cardiovascular, and Renal Outcomes-Heart Outcomes Prevention Evaluation)[22] study included over 3500 people with diabetes, aged 55 years or older, who had a previous cardiovascular event or at least one other cardiovascular risk factor. Risk reduction of overt nephropathy was a primary study outcome. Patients were randomized to ramipril 10 mg/day or placebo; follow-up was 4.5 years. The ramipril treatment group experienced a 24% risk reduction in the overt development of nephropathy. The vasculoprotective and renoprotective effects of ACE inhibitors have been attributed in part to the ability of these agents to directly lower glomerular capillary pressure.[23]

Angiotensin receptor blockers may be equivalent to ACE inhibitors in renal protection and blood-pressure–lowering effects. The landmark RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan)[24] Study included over 1500 patients from 29 countries with type 2 diabetes, proteinuria, and elevated serum creatinine. Patients received either losartan (50-100 mg daily) or placebo. Patients were allowed to remain on previous antihypertensive therapy (ie, calcium-channel antagonists, diuretics, alpha blockers, beta blockers, and centrally acting agents). The primary endpoint of the study was time to first occurrence of doubling of serum creatinine, ESRD, or death. Follow-up occurred for an average of 3.4 years. The study was ended 13 months ahead of schedule. Because of increasing evidence, interventions aimed at blockade of the renin-angiotensin system provided cardioprotective benefits in diabetic patients with renal impairment. The losartan group demonstrated a 25% risk reduction of a doubling of the serum creatinine concentration, 28% risk reduction of ESRD, and 35% decrease in the level of proteinuria. Losartan significantly reduced the risk of developing the primary composite endpoints.

Neuropathy. Diabetic peripheral neuropathy (DPN) is one of the most prevalent and complicated conditions to manage among diabetic patients. About 60% to 70% of people with diabetes have mild to severe forms of nervous system damage; resulting in impaired sensation or pain in the feet or hands, slowed digestion of food in the stomach, carpal tunnel syndrome, precursor for foot ulcers, and other nerve problems. Diabetes is the major contributing reason for non-traumatic lower extremity amputations (more than 60% of cases).[2]

The most common form of DPN involves the somatic nervous system; the autonomic nervous system may be affected in some patients.[25] Sensorimotor neuropathy is characterized by symptoms such as burning, shooting, and tingling sensations, and allodynia (super-sensitivity or pain from normal stimuli). Autonomic neuropathy can cause gastroparesis, sexual dysfunction, bladder incontinence, and cardiovascular damage. The occurrence of DPN is primarily dependent on the duration of diabetes and level of glycemic control. If diagnosed early, neuropathy can be reversed, or at least controlled. There are 3 proposed stages of neuropathy: functional (reversible, biochemical alteration in nerve function); structural (may be reversible, loss of structural change in nerve fibers); and nerve death (irreversible, critical decrease in nerve fiber density and neuronal death).[26] The best way to manage diabetic neuropathy is through primary prevention, management of early symptoms, and relief of pain.[27,28] There are clinical trials supporting the use of tricylic antidepressants, anticonvulsants, analgesics, and various other agents.

Tricyclic antidepressants. This drug class is the most widely studied for the treatment of DPN. Their mechanism of action inhibits the reuptake of serotonin and norepinephrine in the central nervous system; this inhibitory effect is beneficial in nociceptive pain.[29] Tricyclic antidepressants (TCAs) can be divided into 2 groups: tertiary and secondary amines. Tertiary amines block serotonin reuptake more than norepinephrine reuptake; secondary amines block norepinephrine reuptake more than serotonin reuptake. Commonly associated side effects of TCAs include blurred vision, dry mouth, orthostatic hypotension, constipation, and urinary retention. Secondary amines may be preferred over tertiary amines because they are associated with fewer anticholinergic adverse side effects.

Duloxetine (Cymbalta) is the first drug specifically approved for the management of pain associated with diabetic peripheral neuropathy. This agent is a serotonin-norepinephrine reuptake inhibitor. The treatment dose for DPN is 60 mg once or twice daily. Adverse effects such as nausea, somnolence, dizziness, constipation, dry mouth, hyperhidrosis, decreased appetite, and asthenia are common.[30,31]

Anticonvulsants. Several anticonvulsants (ie, carbamazepine, oxcarbazepine, gabapentin) have been used effectively to treat painful neuropathies. Carbamazepine and oxcarbazepine are thought to depend on neuron stabilization by inhibition of ionic conductance to exert their

anticonvulsant and analgesic effects. The typical dose of carbamazepine used for patients with DPN is 100 mg, once or twice daily, not to exceed 1,200 mg daily.[27] Some adverse effects (ie, dizziness, drowsiness, lightheadedness) appear to be transient; however, at higher doses, ataxia, diplopia, and nystagmus may develop.

Oxcarbazepine, similar to carbamazepine, has a better adverse effect profile and fewer drug interactions. This agent is thought to be comparable to carbamazepine since it has demonstrated efficacy in the treatment of neuralgia.[28] Currently, there are no published studies for the use of oxcarbazepine in the treatment of DPN.

Gabapentin has been extensively studied for the treatment of DPN. In a 12-week prospective, randomized, crossover study, gabapentin was compared to amitriptyline.[32] The main study outcome measured pain relief by pain scale with verbal description and global pain score assessment. There was no significant difference in pain relief with gabapentin versus amitriptyline. Therefore, gabapentin may be used as an alternative agent for DPN; however, it does not appear to offer a considerable advantage over amitriptyline and cost is a key factor. A derivative of gabapentin, pregabalin (Lyrica), has received approval from the Food and Drug Administration (FDA) for treating neuropathic pain associated with DPN; clinical trials are forthcoming.[33]

Analgesics. Data supporting the widespread use of opioid analgesics for the treatment of chronic neuropathic pain are limited. Additionally, there are few trials evaluating the long-term safety and efficacy of opioid analgesics. In one randomized, controlled study,[34] more than 150 patients with moderate to severe pain due to diabetic neuropathy were evaluated. Initial treatment was either one 10 mg tablet of oxycodone controlled-release or placebo every 12 hours. The dose was increased every 3 days to a maximum of 6 tablets (60 mg) every 12 hours, and based on patient response, treatment lasted up to 6 weeks. The primary efficacy variable was overall average daily pain intensity during study days 28 to 42. The average pain intensity was slightly better with opioid therapy. The average dose for pain relief was 37 mg/day. The treatment group (96%) reported more opioid-related adverse events than the placebo group (68%). Opioids may be an option for therapy in patients with neuropathic pain. However, their role may be limited due to the risk of physical dependence, tolerance, adverse effects, and degree of pain relief.

Tramadol is an opioid-like, centrally acting, synthetic non-narcotic analgesic with norepinephrine and serotonin properties. Its efficacy and safety have been evaluated for the treatment of pain of diabetic neuropathy. In a multicenter, randomized, double-blind study,[35] more than 130 patients were treated with tramadol (average dose 210 mg/day, divided into 4 doses) or placebo. Primary efficacy was based on pain intensity scores at day 42 of the study or at the time of discontinuation. Patients in the tramadol group demonstrated a clinically and statistically significant reduction in pain intensity. The most frequently occurring adverse events with tramadol were nausea, constipation, headache, and somnolence.

Alternative approaches to treatment. Mexiletine, an oral congener of lidocaine, targets hyperexcitable peripheral nerve cells that cause pain, such as burning, tingling, and allodynia.[27,28,36] Its clinical efficacy for treating DPN is variable. The initial dose of mexiletine is 200 mg every 8 hours, titrated 50-100 mg every 2-3 days to a maximum dose of 1,200 mg/day. Common adverse effects include headache, stomach upset, dizziness, and nervousness. This agent should not be used in patients with second- or third-degree heart block.

Capsaicin, a chili pepper extract, is commonly used as a topical agent for local pain relief, without systemic toxicity.[28,36] The analgesic effect is produced through its action on the unmyelinated primary afferent nerves by depleting substance P, a peptide thought to be involved in pain transmission. Adverse effects such as a burning, stinging sensation appear to be transient. Patients should be advised that repeated use is necessary for pain relief and to wash hands thoroughly after each application.

Clonidine blocks the effects of norepinephrine at alpha receptors that become active in neuropathic pain.[27,36] Some patients are unable to tolerate the adverse effects which may include dry mouth, dizziness, sedation, postural hypotension. Oral and transdermal clonidine has been used for pain relief. The initial dose of oral clonidine is usually 0.1 mg once or twice daily, and should be titrated slowly to an effective dose, not to exceed 2.4 mg/day. Patients on clonidine should avoid abrupt withdrawal of therapy.

Retinopathy. Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20-74 years. By the end of the first 2 decades of disease, nearly all patients with type 1 diabetes will have evidence of retinopathy. Nearly 20% of patients with type 2 diabetes will have retinopathy at the time of diagnosis of diabetes.[2] Up to 90% of blindness due to diabetes is preventable with regular eye examinations and timely treatment.[37] As a general recommendation, all diabetic patients should have annual dilated eye examinations. Early detection of any visual problems is critical.

Diabetic retinopathy can progress from mild nonproliferative abnormalities, to moderate and severe nonproliferative diabetic retinopathy, and finally, to proliferative diabetic retinopathy.[38] Nonproliferative retinopathy

produces blood vessel changes within the retina: bleeding (hemorrhages), weakened blood vessel walls (microaneurysms), leakage of fluid (edema or exudate), and loss of circulation. It generally does not interfere with vision.[39] However, if left untreated it can progress to proliferative retinopathy. This is very serious and severe. It occurs when new blood vessels branch out or proliferate in and around the retina. It can cause bleeding into the fluid-filled center of the eye or swelling of the retina and lead to blindness.[38]

The duration of diabetes is probably the strongest predictor for development and progression of retinopathy. However, adequate control of blood glucose, blood pressure, and lipid levels can significantly decrease the progression and morbidity of diabetic retinopathy.[40] For patient requiring treatment, laser photocoagulation is effective at slowing the progression of retinopathy and reducing visual loss. However, it does not restore lost vision. Another option for treatment, vitrectomy, is a complex, high-risk surgical procedure. The technique involves draining the inside of the eye to remove any blood, debris, and scar tissue, or to alleviate traction on the retina. Both of these treatments can be effective. Neither treatment can restore lost vision, but they can prevent further eyesight loss.[38]

Clinical Manifestations: Macrovascular

Diabetes exerts a heavy toll on the vascular system. The hallmark of diabetic macrovascular disease is accelerated by atherosclerosis involving the aorta and large- and medium-sized arteries. Macrovascular disease causes accelerated atherosclerosis among diabetics, resulting in increased risk of myocardial infarction, stroke, and lower-extremity gangrene.[41] Macrovascular complications associated with diabetes include cardiovascular, cerebrovascular, and peripheral arterial diseases.

Cardiovascular. People with diabetes are 2 to 4 times more likely to develop cardiovascular disease (CVD) than those without diabetes.[42] However, the risk of coronary artery disease is increased in patients with poor glycemic control. In patients with insulin resistance, the disease tends to accelerate to atherogenesis long before the onset of hyperglycemia. There are several risk factors that may contribute to the development of coronary heart disease (CHD), including lifestyle (eg, cigarette smoking and diet), hyperglycemia, hypertension, and high cholesterol. Additional mechanisms that contribute to the increased risk of CHD and worse outcomes in persons with diabetes include endothelial dysfunction, hypercoagulability, impaired fibrinolysis, platelet hyperaggregability, oxidative stress, sympathovagal imbalance, and glucose toxicity.[43] The presence of insulin resistance is associated with a significantly greater risk for the development of cardiovascular disease (CVD), even in the absence of diabetes. Insulin resistance is associated with the development of CVD risk factors including hypertension, artherogenic dyslipidemia, microalbuminuria, and a pro-inflammatory, prothrombotic vascular environment. Lowering the risk for macrovascular complications remains complex and involves more than lowering glucose levels.

The ultimate goal is prevention; however, aggressive management and treatment of risk factors are vital. The American Diabetic Association recommends maintaining an HbA1c level of $<$7%, an FPG of $<$100 mg/dL, and a glucose level of $<$140 mg/dL as determined by an oral glucose tolerance test (OGTT).[44] Maintaining these levels can be accomplished using any of the antidiabetic agents including sulfonylureas, meglitinides, biguanides, thiazolidinediones, alpha glucosidase inhibitors, and/or insulin. Aspirin at a dose of 81-325 mg daily should be added for cardiovascular (CV) protection for primary and secondary prevention. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) recommends that diabetic patients maintain a blood pressure of $<$130/80 mm Hg. The antihypertensive agents recommended for treatment include thiazide diuretics, ACE Inhibitors, ARBs, and non-dihydropyridine calcium channel blockers.[45] The National Cholesterol Education Panel (NCEP) recommends that diabetic patients maintain low-density lipoprotein cholesterol $<$100mg/dl (ideally $<$70mg/dl), triglycerides $<$150mg/dL, and HDL $>$40mg/dL (men) and $>$50 mg/dL (women). Maintaining these levels can be accomplished with HMG-CoA reductase inhibitors (statins), bile acid sequestrants, fibric acid derivatives, nicotinic acid, or cholesterol absorption inhibitors.[46]

Cerebrovascular. Cerebrovascular disease is a term encompassing many disorders that affect the blood vessels of the central nervous system. These disorders result from either inadequate blood flow to the brain (ie, cerebral ischemia) or from hemorrhages into the parenchyma or subarachnoid space of the central nervous system (CNS). Various terms have been used to describe cerebrovascular events. For example, the term transient ischemic attack (TIA) describes the clinical condition in which a patient experiences a temporary focal neurologic deficit such as slurred speech, aphasia, weakness or paralysis of a limb, or blindness. These symptoms are rapid in onset, lasting $<$24 hours (usually 2 to 15 minutes). Reversible ischemic neurologic deficit is similar to a TIA; however, the deficit improves over no more than 72 hours and may not completely resolve. Cerebral infarction is a

neurologic event causing permanent damage. Cerebral hemorrhage is a cerebrovascular disorder that involves escape of blood from blood vessels into the brain and its surrounding structures. There are 700,000 new or recurrent cerebrovascular events per year. The incidence of stroke is significantly greater among blacks compared with whites.[47] Sudden confusion, loss of coordination, unilateral weakness, and numbness are warning signs of a cerebrovascular event. The risk factors that may predispose a patient to a stroke include smoking, obesity, hypertension, dyslipidemia, and transient ischemic attacks.

Acute treatment of ischemic stroke. The FDA has approved the use of an intravenous recombinant tissue plasminogen activator (tPA) for treatment of patients with acute ischemic stroke. Other intravenous fibrinolytic agents are currently being investigated. The preliminary results from a randomized trial of ancrod, a fibrinogen-depleting agent derived from snake venom, show promise.[48] Recent studies have focused on the use of antiplatelet agents in acute ischemic stroke.[49] Data from 2 large trials involving almost 40,000 patients indicated that the early use of aspirin in patients with acute ischemic stroke who were not treated with a fibrinolytic agent was associated with a small but significant reduction in mortality and stroke recurrence.[50-51] These studies in combination would suggest that for every 1000 stroke patients treated with aspirin, about 9 deaths or nonfatal recurrences would be prevented in the first few weeks, and approximately 13 fewer patients would be dead or dependent at 6 months. Aspirin should not be given for the first 24 hours in patients receiving a fibrinolytic agent because doing so has been associated with an increased risk of intracranial hemorrhage (ICH) and death.

Intracerebral Hemorrhage Management. The current consensus for treatment of intracerebral hemorrhage management (ICH) is antihypertensive treatment with parenteral agents for systolic pressure higher than 160 to 180 mm Hg or diastolic pressures higher than 105 mm Hg.[48] Nitroprusside is the agent most commonly recommended because it can affect a rapid and consistent lowering of the blood pressure to the desired level. Nitroprusside provides a fast onset, is titratable, and has no effect on mental status. Labetolol is another option. Seizure prophylaxis (phenytoin 18 mg/kg or fosphenytoin 15 to 20 mg phenytoin equivalent/kg) should be considered for patients with ICH, especially those with lobar hemorrhage.

Peripheral Arterial Disease. Peripheral arterial disease (PAD) is an atherosclerotic occlusive disease. It is the major risk factor for lower extremity amputations. The abnormal metabolic state accompanying diabetes results in changes in the state of arterial structure and function predisposing people to PAD.[52] The risk of development of PAD increases threefold to fourfold in patients with diabetes mellitus.[53] In the Framingham cohort, glucose intolerance contributed more as a risk factor for claudication than it did for coronary artery disease or stroke.[54] Risk factors for the development of PAD include diabetes, hypertension, hyperlipidemia, cigarette smoking, and age. In people with diabetes, the risk of PAD is increased by age, duration of diabetes, and presence of peripheral neuropathy. Elevated levels of C-reactive protein (CRP), fibrinogen, homocysteine, apolipoprotein B, lipoprotein (a), and plasma viscosity are potential risk factors for PAD. The 2 cardinal symptoms of PAD are intermittent claudication and pain at rest. Intermittent claudication is characterized by pain, ache, a sense of fatigue, or other discomfort that occurs in the affected leg during exercise, particularly walking, and resolves with rest. Pain at rest occurs in patients with critical limb ischemia in whom the resting metabolic needs of the tissue are not adequately met by the available blood supply.[52] In an effort to manage PAD, practitioners must encourage smoking cessation; control diabetes, hypertension, and lipids; promote physical activity and foot care; initiate antiplatelet therapy; and treat symptoms.

A meta-analysis of antiplatelet therapy involving approximately 70,000 high-risk patients with atherosclerosis, including those with a history of acute and prior myocardial infarction, stroke, and transient cerebrovascular ischemia, as well as other high-risk groups such as those with PAD, found that antiplatelet therapy was associated with a 27% odds reduction for subsequent vascular death, myocardial infarction, or stroke.[55] Of the 3295 patients with claudication included in this analysis, a statistically insignificant 18% reduction was noted in the risk of myocardial infarction, stroke, or death after 27 months of antiplatelet therapy.[56] The Swedish Ticlopidine Multicenter Study (STIMS) found that ticlopidine reduced mortality by 29% in patients with claudication.[57] The CAPRIE Trial compared the efficacy of clopidogrel and aspirin in preventing ischemic events in patients with recent myocardial infarction, recent ischemic stroke, or PAD. Notably, of the 6452 patients in the PAD subgroup, clopidogrel treatment reduced adverse cardiovascular events by 23.8%.[58]

Currently the FDA has approved 2 drugs, pentoxifylline (Trental) and cilostazol (Pletal), for treating claudication in patients with PAD. A meta-analysis, however, concluded that the quality of reported data precluded a reliable estimate of pentoxifylline's efficacy on intermittent claudication.[59] Several trials have reported that cilostazol improves absolute claudication distance by 40% to 50% in comparison to placebo.[60,61] An advisory from

the FDA states that cilostazol should not be used in patients with congestive heart failure since other phosphodiesterase III inhibitors have been shown to decrease survival in these patients.[62]

Clinical Trials

Diabetic Control and Complications Trial.[3] The Diabetic Control and Complications Trial (DCCT) was a clinical study conducted from 1983 to 1993 by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The DCCT was a multicenter, randomized clinical trial designed to compare intensive with conventional diabetes therapy with regard to their effect on the development and progression of the early vascular and neurologic complications of insulin dependent diabetes mellitus (IDDM). The study included 1441 volunteers with IDDM for 1 to 15 years with mild to moderate nonproliferative retinopathy and urinary albumin excretion of less than 200 mg per 24 hours. The study was conducted to answer 2 questions: (1) Will intensive therapy prevent the development of diabetic retinopathy (primary prevention)? (2) Will intensive therapy delay the progression of early diabetic retinopathy (secondary prevention)? The conventional therapy consisted of 1 or 2 daily injections of insulin, including intermediate and rapid-acting insulins, daily self-monitoring of urine or blood glucose, and education about diet and exercise. Patients were examined every 3 months. Intensive therapy included the administration of insulin 3 or more times daily by injection or an external pump. The dosage was adjusted according to the results of self-monitoring of blood glucose performed at least 4 times per day, dietary intake, and anticipated exercise. The patients visited the study center each month and were contacted more frequently by telephone to review and adjust their regimens. In the primary prevention results, the intensive treatment group decreased retinopathy by 76%, nephropathy by 34%, and neuropathy by 69%. In the secondary prevention results, the intensive treatment group decreased retinopathy by 54%, nephropathy by 43%, and neuropathy by 57%. These results show that maintaining the blood glucose levels close to normal possibly slows the onset and progression of microvascular disease. Blood glucose and glycosolated hemoglobin levels were better controlled in the intensive group from month 3 until the end of the study. However, the incidence of severe hypoglycemic episodes was 3 times higher in the intensive group.

United Kingdom Prospective Diabetes Study 33. The United Kingdom Prospective Diabetes Study (UKPDS-33)[4] was a multicenter, prospective, randomized, intervention trial. It was a 20-year study with an 11-year follow up. The subjects included 5,102 patients with newly diagnosed Type 2 diabetes mellitus and a fasting plasma glucose (FPG) level greater than 108 mg/dL on 2 mornings, 1-3 weeks apart. Following recruitment, all eligible subjects participated in a 3-month dietary run-in period during which they were advised to follow a diet high in carbohydrates and fiber and low in saturated fats. Calorie restriction was advised in overweight patients (defined as >120% of ideal body weight). After 3 months, 4,209 asymptomatic patients with FPG levels of 108-270 mg/dL entered the trial. Patients were stratified by ideal body weight. Of the 2,187 patients with ideal body weight >120% ideal body weight, 342 were randomly assigned to intensive treatment with metformin. This part of the UKPDS became known as the Metformin Study and the results were reported separately. The remaining 3,867 patients (nonoverweight and overweight) were randomly assigned to conventional treatment with diet (n = 1138) or intensive treatment (n = 2729) with 1 of 2 sulfonylureas (n = 1573) or insulin (n = 1156). The aim of the conventional regimen was to maintain FPG levels <270 mg/dL without symptoms of hyperglycemia. If marked hyperglycemia was detected, patients were secondarily randomized to receive non-intensive sulfonylurea or insulin therapy, with the additional option of metformin for overweight patients. The aim of the intensive therapy was to maintain FPG levels at <108mg/dL. The primary management in the intensive therapy group was chlorpropamide, 100-500 mg/day; glibenclamide, 2.5-20 mg/day; glipizide, 2.5-40 mg/day, or daily insulin (intermediate or long acting). The median glycosolated hemoglobin level was 7.0% in the intensive therapy group compared with 7.9% in the conventional therapy group ($p = <0.0001$). The diabetes related endpoints included sudden death, death from hypoglycemia or hyperglycemia, myocardial infarction, death from peripheral vascular disease, angina, heart failure, stroke, amputation, renal failure, death from renal failure, retinal photocoagulation, vitreous hemorrhage, blindness in one eye, and cataract extraction. The absolute risk from any diabetes related endpoint was 40.9 per 1000 patient years in the intensive therapy group versus 46.0 per 1000 patient years in the conventional therapy group ($p = 0.029$). Over the 15-year study period, the risk of developing any diabetes-related endpoint was reduced by 12% and myocardial infarction reduced by 16% with the intensive therapy group. Most of the difference in the event rate between the intensive and conventional groups was due to reduction in microvascular complications in the intensive group (relative risk 0.75 95% confidence interval, $p = 0.0099$). There was no difference for any of the endpoints between chlorpropamide, glibenclamide, and insulin-intensive therapy groups. Hypoglycemic

episodes were more common in the intensive groups ($p < 0.0001$). This trial proved that intensive control of plasma glucose levels in patients with type 2 diabetes by either insulin or sulfonylurea agents reduced the risk of microvascular complications, but not the risk of macrovascular complications.

United Kingdom Prospective Diabetes Study 34. The United Kingdom Prospective Diabetes Study (UKPDS-34)[63] was a multicenter, randomized, controlled trial comparing 411 patients on conventional therapy, primarily with diet alone versus 342 patients on intensive blood-glucose control policy with metformin, aiming for a FPG level below 108 mg/dL. The secondary analysis compared the 342 patients allocated metformin with 951 overweight patients allocated intensive blood-glucose control with chlorpropamide (n = 265), glibenclamide (n = 277), or insulin (n = 409). The primary outcome measures were aggregates of any diabetes-related clinical endpoint, diabetes-related death, and all-cause mortality. The median glycosolated hemoglobin (HbA1c) level was 7.4% in the metformin group compared with 8.0% in the conventional group. Compared with the conventional group, patients allocated metformin, had risk reductions of 32% ($p = 0.002$) for any diabetes-related endpoint, 42% for diabetes-related death ($p = 0.017$), and 36% for all-cause mortality ($p = 0.011$). Among patients allocated intensive blood-glucose control, metformin showed a greater effect than chlorpropamide, glibenclamide, or insulin for any diabetes-related endpoint ($p = 0.0034$), all-cause mortality ($p = 0.021$), and stroke ($p = 0.032$). Since intensive glucose control with metformin appears to decrease the risk of diabetes-related endpoints in overweight diabetic patients, and is associated with less weight gain and fewer hypoglycemic events than are insulin and sulfonylureas, it may be the first-line pharmacological therapy of choice in these patients.

United Kingdom Prospective Diabetes Study 38. The United Kingdom Prospective Diabetes Study (UKPDS-38)[64] was a multicenter, randomized, controlled trial comparing tight control of blood pressure aiming for a blood pressure of <150/85 mm Hg (with the use of captopril or atenolol), with less tight control aiming for a blood pressure of <180/105 mm Hg. The goal was to determine which arm of the study would reduce microvascular and macrovascular complications in patients with type 2 diabetes mellitus. The study included 1148 patients with type 2 diabetes mellitus, aged 25-65 years old, with a blood pressure of ≥160/90 mm Hg or ≥150/85 mm Hg on antihypertensive therapy. Seven hundred fifty-eight patients were randomized to tight blood pressure control group and 390 to the less tight blood pressure control group. The median follow up was 8.4 years. The tight control group received up to the maximum dose of captopril and atenolol. If target blood pressure was not reached with the maximal doses, furosemide, slow-release nifedipine, methyldopa, or prazosin was added. The results revealed a mean blood pressure of 154 ± 16/87 ± 7 mm Hg in the less tight control group and 144 ± 14/82 ± 7 mm Hg in the tight control group ($p < 0.0001$). The absolute risk for any diabetes related endpoint was 50.9 and 67.4 events per 1000 patient years in the tight and less tight control groups, respectively (RR 0.76; 95% CI; $p = 0.0046$). Tight blood pressure control reduced the risk for stroke by 24% ($p = 0.013$), heart failure by 56% ($p = 0.0043$), and microvascular complications by 37% ($p = 0.0092$). Tight blood pressure control was associated with reduction in the risk of diabetes-related mortality and morbidity in hypertensive patients with type 2 diabetes.

SUMMARY

The prevention and treatment of microvascular and macrovascular complications in diabetic patients is of paramount importance. The morbidity and mortality associated with diabetes may be due to under treatment of these complications. Reducing morbidity and mortality and improving quality of life for persons with diabetes is an ongoing challenge. The key to diabetes management is multifaceted. It requires the collaboration of several healthcare disciplines, and most importantly a sincere commitment from the patient.

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