Diabetes-Related Microvascular and Macrovascular Diseases in the Physical Therapy Setting

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Physical therapists commonly treat people with diabetes for a wide variety of diabetes-associated impairments, including those from diabetes-related vascular disease. Diabetes is associated with both microvascular and macrovascular diseases affecting several organs, including muscle, skin, heart, brain, and kidneys. A common etiology links the different types of diabetes-associated vascular disease. Common risk factors for vascular disease in people with diabetes, specifically type 2 diabetes, include hyperglycemia, insulin resistance, dyslipidemia, hypertension, tobacco use, and obesity. Mechanisms for vascular disease in diabetes include the pathologic effects of advanced glycation end product accumulation, impaired vasodilatory response attributable to nitric oxide inhibition, smooth muscle cell dysfunction, overproduction of endothelial growth factors, chronic inflammation, hemodynamic dysregulation, impaired fibrinolytic ability, and enhanced platelet aggregation. It is becoming increasingly important for physical therapists to be aware of diabetes-related vascular complications as more patients present with insulin resistance and diabetes. The opportunities for effective physical therapy interventions (such as exercise) are significant.

Diabetes mellitus (DM) is a global health issue affecting children, adolescents, and adults. According to the World Health Organization, approximately 180 million people worldwide currently have type 2 DM (formerly called adult-onset diabetes); over 95% of people with diabetes have this form. The number of people with type 2 DM is estimated to double by 2030.[1] In the year 2000, death from diabetes-associated complications accounted for approximately 6% of worldwide mortality.[2] Additionally, the economic burden of diabetes in the United States in 2002 was estimated to be $132 billion.[3]

Diabetes is a disease that is strongly associated with both microvascular and macrovascular complications, including retinopathy, nephropathy, and neuropathy (microvascular) and ischemic heart disease, peripheral vascular disease, and cerebrovascular disease (macrovascular), resulting in organ and tissue damage in approximately one third to one half of people with diabetes.[4] Because of the progressive nature of the disease, physical therapists will increasingly encounter patients with prediabetes (ie, impaired glucose tolerance or insulin resistance), early type 2 DM without or with only a few vascular complications, and more advanced disease with several vascular complications. For additional information describing the epidemiology of these problems in people with DM, see the perspective article by Deshpande et al[5] in this issue.

Diabetes-associated vascular alterations include anatomic, structural, and functional changes leading to multiorgan dysfunction.[6] As physical therapists increasingly become first-line providers of treatment for musculoskeletal and movement disorders in people with diabetes, it will be important for clinicians to be keenly aware of the underlying vascular deficits in conditions such as diabetic neuropathy, retinopathy, nephropathy, and cardiovascular and peripheral vascular diseases in their treatment programs, even if these conditions are not the reasons for referral. Additionally, physical therapists will play an important role in the care of people with diabetes because numerous interventions provided by physical therapists (such as therapeutic exercise) can assist in alleviating symptoms, slow the metabolic progression to overt type 2 DM, and reduce morbidity and mortality associated with these complications.[7–10]

Diabetic microvascular (involving small vessels, such as capillaries) and macrovascular (involving large vessels, such as arteries and veins) complications have similar etiologic characteristics. Chronic hyperglycemia plays a major role in the initiation of diabetic vascular complications through many metabolic and structural derangements, including the production of advanced glycation end products (AGE), abnormal activation of signaling cascades (such as protein kinase C [PKC]), elevated production of reactive oxygen species (ROS, oxygen-containing molecules that can interact with other biomolecules and result in damage), and abnormal stimulation of hemodynamic regulation systems (such as the renin-angiotensin system [RAS]).

The objectives of this article are to briefly describe the epidemiology of, the comorbidities and risk factors associated with, the pathogenesis of, and the physical therapy management associated with microvascular and macrovascular complications of diabetes. In a significant portion of the article, the term “diabetes” includes both type 1 DM and type 2 DM, which have much the same vascular pathology and etiology.

Microvascular Complications of Diabetes

Diabetic Retinopathy

Diabetic retinopathy (DR) is a microvascular complication that can affect the peripheral retina, the macula, or both and is a leading cause of visual disability and blindness in people with diabetes.[1] The severity of DR ranges from nonproliferative and preproliferative to more severely proliferative DR, in which the abnormal growth of new vessels occurs.[11] Total or partial vision loss can occur through a vitreous hemorrhage or retinal detachment, and central vision loss can occur through retinal vessel leakage and subsequent macular edema.[12] The prevalence of DR increases with prolonged duration of diabetes.[13] In studies including people with both type 1 diabetes and type 2 diabetes, after 30 years of diabetes, most patients had some form of DR, and over half had proliferative DR; people with type 1 diabetes and taking insulin had the highest prevalence of DR, and people with type 2 diabetes diagnosed after age 30 had the lowest prevalence of DR.[14–16] Diabetic retinopathy also recently was seen in approximately 10% of people with insulin resistance (prediabetes) and was associated with the presence of hypertension and a higher body mass index.[17] Other studies of DR showed associations with younger age of onset, tobacco use, insulin treatment, abnormal blood lipid (ie, total cholesterol, low-density lipoprotein [LDL], and triglyceride) levels, pregnancy, renal disease, elevated homocysteine levels,[18] and a diet high in fat (Table).[19–21]

The earliest histological marker of DR is the loss of pericytes.[22] Pericytes are elongated contractile cells that wrap around endothelial cells of small vessels[23] and assist in providing maintenance of capillary tone (ie, dilatation and constriction),[24] capillary

Table.
Risk Factors for Diabetes-Associated Microvascular and Macrovascular Complications

Risk Factor	Retinopathy	Neuropathy	Nephropathy	Cardiovascular Disease	Cerebrovascular Disease	Peripheral Vascular Disease
Hyperglycemia	Yes	Yes	Yes	Yes	Yes	Yes
Hyperinsulinemia					Yes	
Age	Yes	Yes	Yes	Yes		
Tobacco use	Yes	Yes	Yes	Yes	Yes	
Insulin treatment	Yes					
Dyslipidemia	Yes	Yes	Yes	Yes		
Pregnancy	Yes					
Renal disease	Yes					
Elevated homocysteine level	Yes					
High-fat diet	Yes					
Chronic diabetes mellitus		Yes				Yes
Hypertension		Yes		Yes	Yes	Yes
Obesity				Yes		Yes
Atrial fibrillation					Yes	
Heart failure					Yes	
Proteinuria			Yes		Yes	
Microalbuminuria		Yes	Yes		Yes	
Hyperuricemia					Yes	
Blood inflammatory molecules					Yes	
Elevated blood fibrinogen level						Yes
Physical inactivity				Yes		Yes
Elevated height		Yes				
Ketoacidosis		Yes				
Carotid artery stenosis					Yes	

growth, and protection against ROS damage.[25] Therefore, the loss of pericytes with DR would interfere with capillary constriction (producing chronically dilated vessels), new capillary generation, and processes that protect vessels against continuous exposure to noxious molecules (ie, normal homeostasis). Other microvascular changes that occur with DR include capillary basement membrane thickening (Fig. 1),[26] increased permeability of endothelial cells, and formation of microaneurysms (ie, weakening of vessel walls that results in the projection of a balloonlike sac) (Fig. 2).[27]

The most significant factor in the development and progression of DR in people with diabetes appears to be poor glycemic (blood sugar) control.[28,29] Under hyperglycemic conditions, which are frequently seen in people with diabetes, impairment of retinal blood flow, increased inflammatory cell adhesion to retinal blood vessels, and capillary blockage can result in hypoxia and damage to the retina.[30]

Diabetic Neuropathy

Approximately one half of people with diabetes have some form of peripheral neuropathy (PN), either polydiabetic or monodiabetic neuropathy.[31] People with diabetes also frequently have autonomic neuropathy, including cardiovascular autonomic dysfunction, which is manifested as abnormal heart rate (HR) and vascular control.[32] Physical therapists commonly encounter diabetes-associated PN in the evaluation and treatment of balance and movement disorders because these disorders frequently affect lower-extremity sensation and can cause lower-extremity pain in people with diabetes. Loss of lower-extremity sensation coupled with impaired peripheral vascular function can contribute to lower-

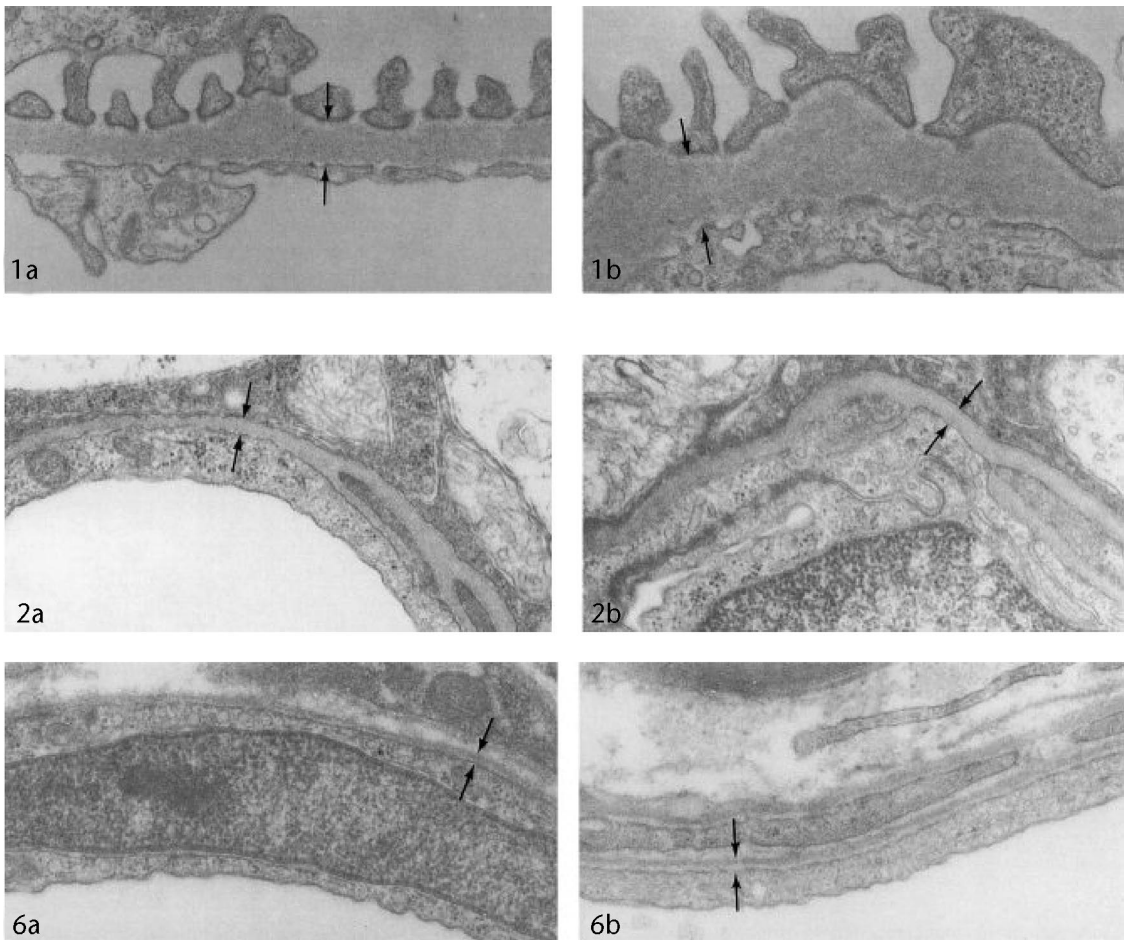

Figure 1.
Representative transmission electron micrographs of capillary basement membranes (opposing arrows) in tissues from 300- to 350-day-old normal mice (a) and age- and sex-matched transgenic diabetic mice (b). Capillary basement membranes are shown in renal glomerulus (1a, 1b), retina (2a, 2b), and peripheral nerve (6a, 6b). All micrographs: ×28,500. Reprinted with permission of Wiley-Liss Inc, a subsidiary of John Wiley & Sons Inc, from: Carlson EC, Audette JL, Veitenheimer NJ, et al. Ultrastructural morphometry of capillary basement membrane thickness in normal and transgenic diabetic mice. *Anat Rec A Discov Mol Cell Evol Biol.* 2003;271: 332–341.

extremity (commonly foot) ulceration.[33] Like those for DR, the risk factors for PN include poor glycemic control (ie, elevated glycation hemoglobin levels and impaired glucose tolerance[34]), age, duration of diabetes, tobacco use, dyslipidemia, and hypertension (especially diastolic) (Table).[35] Other independent risk factors for PN include increased height, presence of cardiovascular disease (CVD), presence of severe ketoacidosis (ie, elevated by-products of fat metabolism in the blood), and presence of microalbuminuria (ie, presence of albumin in urine, indicating early renal dysfunction) (Table).[36] Unlike that of DR, the pathogenesis of PN appears to be related to both vascular and nonvascular metabolic mechanisms, but this theory is controversial.[37–39] For additional information related to the effects of peripheral neuropathy on skin and muscle, see related articles by Mueller et al,[40] LeMaster et al,[41] and Hilton et al[42] in this issue.

Characteristic traits of PN include axonal thickening with progression to axonal loss,[43] basement membrane thickening, pericyte loss,[44,45] loss of microfilaments (ie, cytoskeletal filaments comprising actin and myosin), and decreased capillary blood flow to C fibers,[46] leading to decreased nerve perfusion and endoneurial hypoxia[44,45] (Fig. 1). Neuronal microvasculature is impaired in the presence of hyperglycemia,[47] and this impairment is mediated through the abnormal initiation of signaling cascades,[48,49] potentially leading to the demyelination associated with diabetic PN.[50] Both nonvascular and vascular mechanisms of PN appear to be primarily related to the metabolic aspects (ie, hyperglycemia) of diabetes.

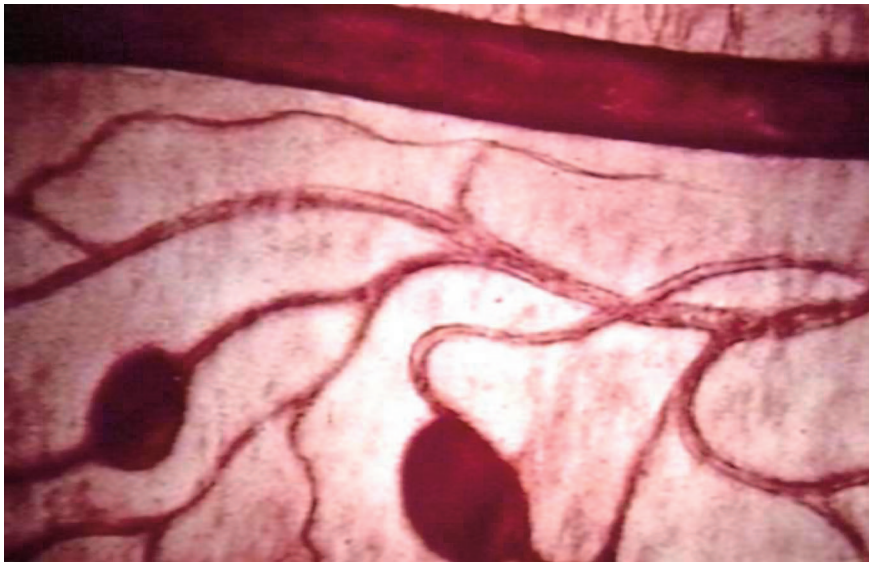

Figure 2.
Microaneurysms in diabetic retinopathy. From the Slice of Life collection, curated by Suzanne Stensaas, University of Utah.

Diabetes-related cardiac autonomic neuropathy is frequently underdiagnosed and can include clinical abnormalities such as resting tachycardia, exercise intolerance, resting HR variability, slow HR recovery after exercise, orthostasis, "silent" myocardial infarction, and increased risk of mortality.[51,52] The prevalence of diabetes-related cardiac autonomic neuropathy is unclear and has been reported to range from 1% to 90%, depending on the outcome variable.[32] Risk factors for diabetes-associated cardiac neuropathy include age, obesity, smoking, poor glycemic control, and hypertension (Table).[53]

Cardiac autonomic dysfunction in people with diabetes has been associated with diabetic cardiomyopathy, a topic beyond the scope of this article. In brief, people with diabetic cardiomyopathy have diastolic filling and relaxation abnormalities frequently later accompanied by systolic dysfunction and heart failure. It is unclear whether cardiac autonomic dysfunction directly mediates diabetic cardiomyopathy, because many of the same risk factors and mechanisms contribute to the development of both conditions.[51]

Diabetic Nephropathy

Diabetic nephropathy (DN) is a serious and progressive complication of both type 1 DM and type 2 DM. The first manifestation of DN is typically microalbuminuria, which progresses to overt albuminuria (ie, increased albumin levels in the urine, indicating more severe renal dysfunction) and eventually to renal failure[54] and is the leading cause of end-stage renal disease (ESRD).[55] Approximately one fourth of people with type 2 diabetes have microalbuminuria or a more advanced stage of DN that worsens at a rate of 2% to 3% per year.[56] Other characteristic features of DN include thickening of glomerular basement membranes (Fig. 1) and glomerular hyperfiltration, leading to mesangial (central part of the renal glomerulus) extracellular matrix expansion and further increases in urinary albumin excretion[57] and progressing to glomerular and tubular sclerosis and renal failure.[58,59] Like those for DR and PN, the risk factors for DN include hyperglycemia, duration of diabetes, age of onset, tobacco use, dyslipidemia, hypertension,[60,61] and obesity (Table).[62]

Macrovascular Complications of Diabetes

Cardiovascular disease (CVD) is the leading cause (~70%) of death in people with type 2 diabetes.[63,64] People with diabetes have a 4-fold-greater risk for having a CVD event than people without diabetes after controlling for traditional risk factors for CVD, such as age, obesity, tobacco use, dyslipidemia, and hypertension.[65,66] These CVD risk factors are common in diabetes, but data suggest that diabetes is an independent risk factor for CVD. People with diabetes also have a 5-fold-greater risk for a first myocardial infarction (MI) and a 2-fold-greater risk for a recurrent MI than people who previously had an MI but do not have diabetes. These data suggest that the risk for an MI in people who have diabetes but who have not had an MI is similar to that in people without diabetes but with a previous MI.[67] Further, people with diabetes have a poorer long-term prognosis after an MI, including an increased risk for congestive heart failure and death.[68] Even people with insulin resistance (ie, the blunted response of tissues [such as muscle, fat, and liver] to insulin that frequently precedes type 2 DM) have an increased risk for CVD.[69] Traditionally, diabetes and CVD were limited primarily to Westernized populations. However, recent evidence suggests that these conditions are rapidly emerging in resource-limited regions of the world,[70] and estimates indicate that 80% of people with diabetes worldwide will die from CVD.[71]

People with diabetes (particularly type 2 DM) frequently have many traditional risk factors for CVD, including central obesity, dyslipidemia (ie, elevated serum triglyceride, LDL,

and free fatty acid levels and low high-density lipoprotein levels), and hypertension.[72] The combination of central adiposity, dyslipidemia, hyperglycemia, and hypertension in the general population is termed "metabolic syndrome."[73] These factors, along with the independent risk factor of diabetes, can act both independently and cumulatively over time to significantly increase risk for CVD. The combination of hyperglycemia, insulin resistance, dyslipidemia, hypertension, and chronic inflammation can injure the vascular endothelium, leading to macrovasculopathy and CVD in people with type 2 DM.[74]

Cerebrovascular Disease

Stroke is the third leading cause of death in the United States, after CVD and cancer,[75] and is an event very familiar to physical therapists. Diabetes is an independent risk factor across all ages[76] for stroke; the risk in people with diabetes is up to 2- to 4-fold greater, more so in white people and women.[75,77–79] Diabetes is also a risk factor for sudden and eventual death from stroke,[80,81] and people who have diabetes and who have a stroke have more severe neurological deficits and disability,[82–84] a poorer long-term prognosis,[85] and a higher incidence of stroke recurrence than people without diabetes.[86]

As in CVD, the presence of diabetes adversely affects the cerebrovascular circulation by increasing the risk of intracranial and extracranial (eg, carotid artery) atherosclerosis.[87,88] People with diabetes have an increased incidence of traditional risk factors for stroke, including hypertension, dyslipidemia, heart failure, and atrial fibrillation.[89] However, after these factors are controlled for, diabetes remains a strong predictor for stroke, suggesting that the presence of diabetes carries an independent risk for stroke apart from the increased presence of traditional risk factors (Table).[80]

As in other diabetes-related complications, hyperglycemia appears to be a significant factor in stroke. Hyperglycemia is a significant predictor of fatal and nonfatal stroke[90] and death from stroke.[91] Hyperinsulinemia (ie, elevated blood insulin levels) also appears to be a risk factor for stroke,[92,93] although this relationship is still unclear.[94] The presence of DR, proteinuria, microalbuminuria, and hyperuricemia (ie, elevated blood uric acid levels) are other diabetes-related factors associated with an increased risk for stroke (Table).[91,95,96] Finally, elevated blood levels of chronic inflammatory markers are associated with an increased risk for stroke in people with diabetes.[97]

Peripheral Artery Disease

Currently in the United States, more than 3.5 million people (African-American > white > Hispanic people) with diabetes have peripheral artery disease (PAD).[98] Peripheral artery disease is characterized by occlusion of the lower-extremity arteries,[99] which can cause intermittent claudication and pain, especially upon exercise and activity,[100] and which can result in functional impairments[101] and disability.[102] Physical therapists frequently encounter people with diabetes-related PAD because of these functional impairments and because of common events of more severe PAD: foot ulceration and lower-extremity amputation.[103] Because people with diabetes are 15 times more likely to have lower-extremity amputation than people without diabetes,[104] physical therapists frequently treat people with diabetes-related amputations. As the incidence of diabetes increases, physical therapists will more frequently see, treat, and prescribe exercise for these people. An elevated awareness of PAD is needed among physical therapists because death in people with diabetes and PN is frequently attributed to CVD.[105] Moreover, lower-extremity amputation is more common in people with diabetes and PAD than in people without diabetes but with PAD[106]; these data suggest that physical therapists should carefully assess lower-extremity blood flow (ie, peripheral pulses) and skin integrity for all patients with diabetes, especially those with known PAD.

Peripheral artery disease, like the aforementioned vascular diseases, is related to the duration and severity of diabetes.[106,107] Hyperglycemia, specifically, glycation hemoglobin, has been shown to be an independent risk factor for PAD.[108] In addition to diabetes, other risk factors for PAD include hypertension, tobacco use, obesity (ie, waist-to-hip ratio), elevated serum fibrinogen levels, dyslipidemia, a history of CVD, and physical inactivity (Table).[109,110]

Common Mechanisms for Microvascular and Macrovascular Diseases in Diabetes

One common pathogenic mechanism for microvascular disease is rooted in chemical reactions between by-products of sugars and proteins that occur over the course of days to weeks and eventually produce irreversible cross-linked protein derivatives called AGE.[111] These derivatives can exhibit a wide range of effects on surrounding tissues, including modification (eg, thickening) of collagen[112] and endothelium.[113] Specifically, in DR, AGE can induce growth inhibition and programmed cell death (ie, apoptosis) of retinal pericytes,[114] induce overproduction of endothelial growth factors (including vascular endothelial growth factor, insulin-like growth factor 1, basic fibroblast growth factor, and hepatocyte growth factor),[115,116] increase pathologic angiogenesis (neovascularization),[117] and

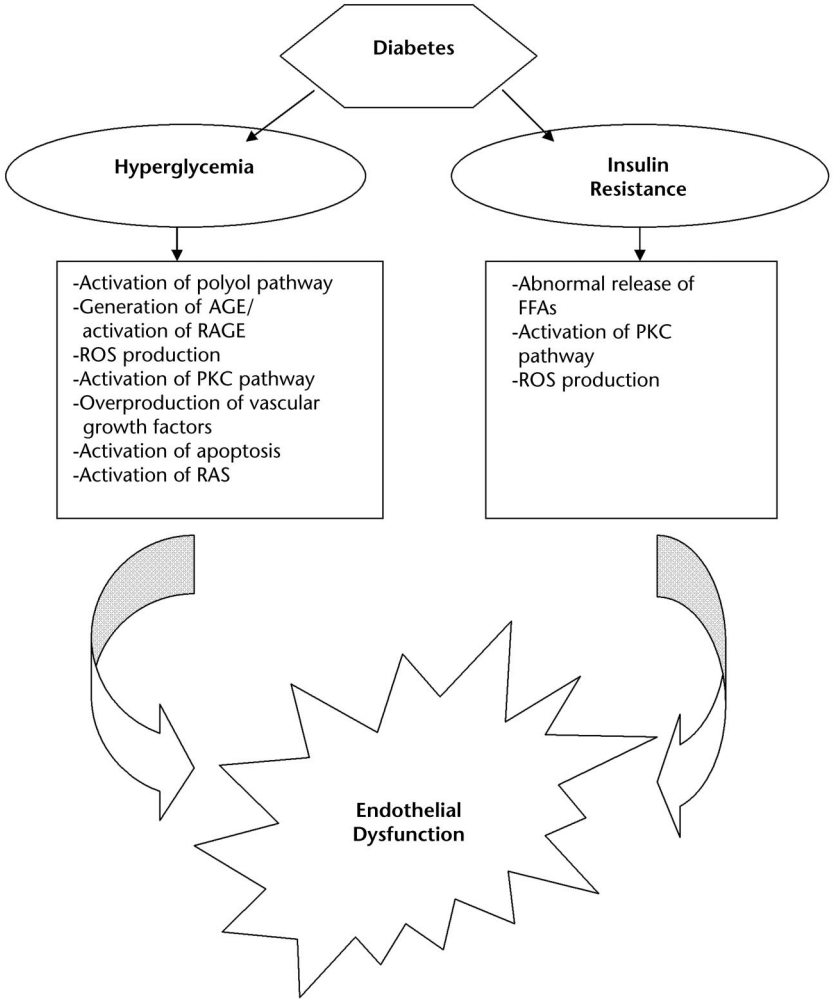

Figure 3.
Potential mechanisms for diabetes-associated endothelial dysfunction. AGE=advanced glycation end products, RAGE=receptors for AGE, ROS=reactive oxygen species, PKC=protein kinase C, RAS=renin-angiotensin system, FFA=free fatty acid.

increase vascular inflammation[118]; all of these actions lead to an increased risk for microthrombosis formation, capillary blockage, and retinal ischemia.[119] Neovascularization, vitreous hemorrhage, and increased levels of vascular endothelial growth factor can further lead to retinal fibrosis and detachment and loss of vision.[12] In addition, AGE can bind to immunoglobulin protein receptors for AGE and produce a cascade of signaling events that lead to endothelial cell dysfunction[120] (Fig. 3).

Advanced glycation end products also play a role in DN through AGE-mediated programmed cell death of mesangial cells and altered extracellular matrix proteins that appear to contribute to both glomerular hyperfiltration[116] and sclerosis.[121] The formation of AGE also may stimulate the oversecretion of growth factors such as insulin-like growth factor 1 and transforming growth factor β and further contribute to glomerular fibrosis,[122] leading to a decrease in available glomerular surface area for filtration.[123]

Other mechanisms involved in microvascular disease include the PKC pathway (a family of multifunctional enzymes involved in signal transduction and gene expression of growth factors and inflammatory signals[124] that may increase vascular permeability) and the polyol pathway (the enzymes aldose reductase and sorbitol dehydrogenase, which catalyze reactions that can lead to sorbitol accumulation-associated osmotic and oxidative stress damage to the endothelium[125]) (Fig. 3). Peripheral nerve damage in DN, including neuronal degeneration and impairment of regeneration of thinly myelinated fibers, is also mediated by AGE accumulation, the activation of the polyol and PKC pathways, and the deleterious effects of ROS.[126,127]

Additionally, the RAS[128] plays a role in microvascular disease because it can alter glomerular hemodynamics and mediate sclerosis in DN. Other enzymatic pathways are involved in the development and progression of microvascular disease but are not discussed here. For an in-depth discussion of these pathways, see more detailed reviews.[129,130]

The pathogenesis of macrovascular disease in diabetes is multifactorial; however, the common recipient of injury is the vascular endothelium (Fig. 4). Diabetes initially impairs the ability of the vascular endothelium to vasodilate through inhibition of the nitric oxide (NO, a gas molecule that maintains arteriolar vasodilatation) pathway.[131] The presence of hyperglycemia inhibits the enzyme responsible for the production of NO (ie, endothelial nitric oxide synthase [eNOS]) and increases the production of ROS, leading to further inhibition of eNOS.[132,133] The vascular endothelium also loses its ability to produce NO-activated tissue plasminogen activator, a fibrinolytic (anti-clotting) protein that inhibits the ability of inflammatory cells to

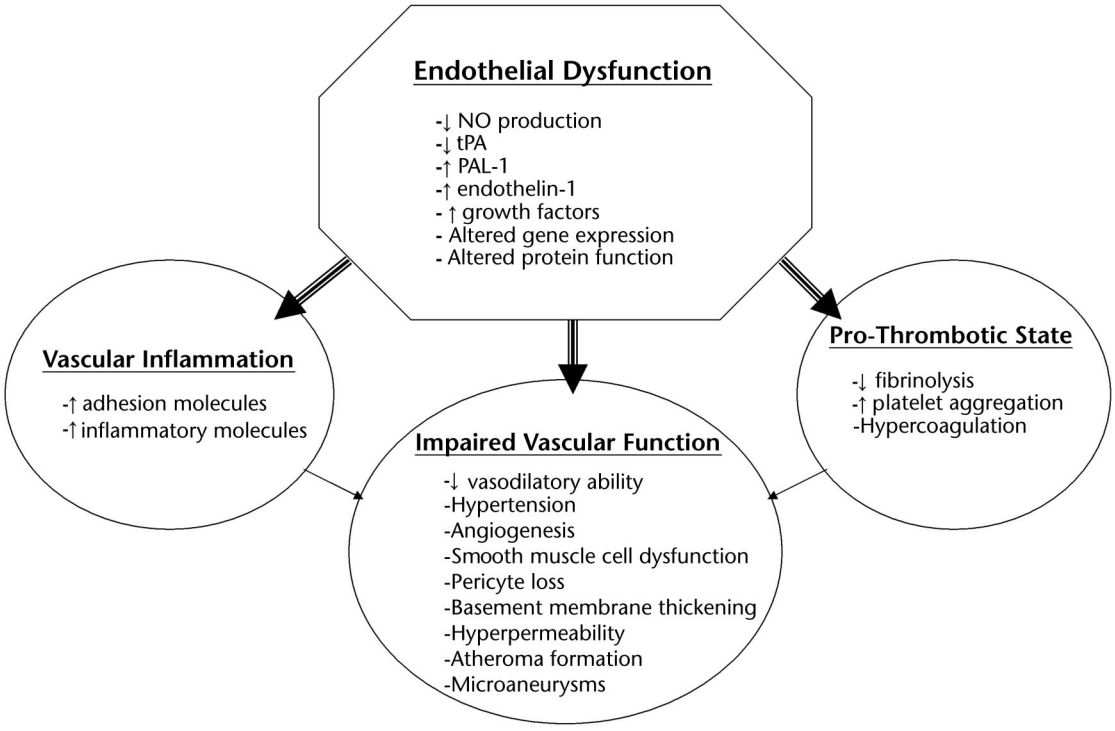

Figure 4.
Potential mechanisms for diabetes-associated vascular abnormalities. NO=nitric oxide, tPA-1=tissue plasminogen activator-1, PAI-1=plasminogen activator inhibitor-1.

"stick" to the endothelial surface.[134] Insulin resistance also can contribute to a decrease in NO production and the subsequent impaired vasodilatory response. In addition, insulin resistance can lead to an increase in the release of free fatty acids from adipose tissue[135] and stimulate the PKC pathway, which can directly and indirectly inhibit eNOS activity through increased ROS generation.[136] The production of AGE (from hyperglycemia) also inhibits NO production, further impairing the vasodilatory response in diabetes.[137] In addition to the reduction in the vasodilatory response in diabetes, an overproduction of vasoconstrictor substances occurs; these substances include endothelin 1, which has direct vasoconstrictive effects on the endothelium as well as indirect fluid volume effects, including the stimulation of water and salt retention and the activation of the RAS.[138]

Another factor involved in the development and progression of macrovascular disease in diabetes is impaired platelet function, which may lead to increased risks for thrombus formation, atherosclerosis progression, and plaque rupture.[134] Hyperglycemia-stimulated PKC pathway effects on NO and ROS generation and diabetes-associated impaired fibrinolytic capacity may contribute to this increased coagulative state.[139,140] Another diabetes-related mechanism for macrovascular disease is a hyperinflammatory state. Inflammatory cells (eg, monocytes and T lymphocytes) enter damaged endothelial cells and migrate into the deeper layers (intima media) of vessels, ingesting oxidized LDL and forming foam cells.[141] Foam cells are the central component of atherosclerotic fatty streaks, an early marker of macrovascular disease (Fig. 2). The levels of adhesion molecules (ie, proteins that recruit inflammatory cells) are also elevated in people with diabetes, thereby facilitating the process of foam cell formation.[142] Finally, diabetes is associated with smooth muscle cell dysfunction.[74] Although the precise mechanism for smooth muscle cell dysfunction in diabetes is unclear, it may be associated with similar mechanisms for endothelial cell dysfunction, including activation of the PKC pathway, AGE deposition, and AGE receptor activation as well as overproduction of growth factors.[136] In the development of atherosclerosis, activated smooth muscle cells in the medial layer of arteries migrate to the atherosclerotic fatty streaks in the intimal layer and produce an extensive extracellular matrix, solidifying the streaks and reciprocally reducing the protective strengthening function in the medial layer, making the atherosclerotic plaque unstable and prone to rupture.[143] These hyperglycemia-stimulated events act in conjunction

over time to produce atheroma and eventual atherosclerosis.[72]

Many of the mechanisms for CVD appear to affect the cerebrovasculature in a similar manner, but this theory is under debate.[144] However, a unique effect of diabetes on neurons and glial cells occurs during ischemia (such as during a transient ischemic attack or stroke). This relationship has been demonstrated through the relationship between hyperglycemia and increased intracellular acidosis.[145] Neuronal intracellular acidosis occurs during an ischemic event as a result of elevated anaerobic metabolism, which leads to neuron and glial cell damage.[145,146] Acidosis may induce intracellular damage through ROS generation, intracellular signaling disruption, and activation of DNA-splitting enzymes.[146] Hyperglycemia also is associated with increased levels of excitatory amino acids (eg, glutamate), which may induce neuronal cell death through the activation of glutamate receptors, the influx of excess calcium, and mitochondrial (cell energy powerhouse) injury.[146,147] This process may lead to a poorer outcome of stroke in people with diabetes.

Role of Physical Therapists in Diabetes-Related Microvascular and Macrovascular Diseases

Diabetes-related comorbidities are conditions that physical therapists will encounter during the evaluation and treatment of movement and functional disorders in people with diabetes. Besides improving movement and function, in general, physical therapists may improve the quality of life for people with diabetes and macrovascular and microvascular diseases through the use of interventions that address pain, poor endurance, obesity, and increased risk for microvascular and macrovascular diseases. Specifically, the prescription and monitoring of an individualized exercise program are essential in a management program, regardless of the severity of diabetes. Exercise therapy may greatly benefit many patients with diabetes by reducing hyperglycemia, insulin resistance, dyslipidemia, and hypertension; these reductions may translate into an improved vascular disease risk profile in children, adolescents, and adults with diabetes.[148–150] Exercise also may aid in weight loss, specifically, loss of trunk fat, and also may improve glycemic and lipemic control in people with diabetes.[151] Additionally, exercise may improve physical function[152] and quality of life in people with diabetes.[153] Caution should be observed in patients who have proliferative DR, microalbuminuria, and cardiac autonomic dysfunction and who are starting aerobic exercise programs, because exercise, particularly resistance exercise, increases retinal blood pressure, reduces kidney blood flow, and stresses autonomic control of HR and contractility.[154] For additional information related to the metabolic effects of exercise in people with DM, see related articles by Turcotte and Fisher[155] and Gulve[156] in this issue.

A frequent progression of DN, ESRD, is a significant cause of functional impairments and disability[157] in people with diabetes and an area in which physical therapists may play an increasing role in the treatment of these consequences, because exercise training appears to improve functional and work capacities and increase independence in these people.[158,159] People with ESRD frequently have a low hematocrit and muscle atrophy,[160] which may contribute to their reduced exercise capacity and disability.[161] An impaired glomerular filtration rate has been associated with low exercise capacity[162] and low activity levels.[163] Exercise training has been shown to improve markers of DN, specifically decreasing microalbuminuria.[164]

Peripheral artery disease is another condition that physical therapists frequently encounter in patients with diabetes. The clinical evaluation of PAD in people with diabetes commonly involves palpating for peripheral arterial pulses, but this technique has been shown to have poor accuracy for the determination of PAD.[165] The ankle brachial index (ABI), a sensitive and specific test for determining PAD,[166] is performed by measuring systolic blood pressure in the upper (brachial artery) and lower (dorsalis pedis and posterior tibialis arteries) extremities with a hand-held Doppler probe and dividing the higher ankle systolic pressure by the higher brachial artery pressure.[167] An ABI of less than 0.90 is predictive of PAD, and an ABI of less than 0.50 is associated with impaired physical function (such as walking distance).[166] Although a Doppler probe is not commonly used in the physical therapy setting, clinics that frequently treat people with diabetes-associated PAD may benefit from using this relatively inexpensive tool because it may provide diagnostic and treatment monitoring criteria. Other clinical testing in patients with diabetes-associated PAD may include treadmill testing[168] or the 6-minute walk test[169] to determine walking capacity and time to claudication and pain, if present. Supervised exercise training in people with PAD has been shown to be highly beneficial in terms of walking distance and time, time to claudication and pain, and quality of life[170,171]; is more effective than pharmacologic therapy[172]; and is considered to be first-line therapy in the treatment of PAD.[168] Accordingly, physical therapists are becoming first-line treatment providers for patients with diabetes-related PAD and should be strong advocates of exercise treatment for these patients.

The clinical evaluation and treatment of DN, a common condition in the physical therapy setting, require more specificity. The evaluation of diabetic PN in the clinical setting involves a variety of tests, which may include the measurement of peripheral (typically of the lower extremity, such as the foot) light touch and vibration sense as well as nerve biopsy.[173] The clinical evaluation of vibration sense, a test frequently used in the physical therapy setting, is the strongest predictor of foot insensitivity ulceration.[174] Electrophysiologic nerve conduction testing, occasionally performed in physical therapy clinics but more often performed in physicians' offices, is considered to be the gold standard for measuring nerve function.[175] Nerve biopsy is not considered part of routine clinical testing in DN; however, skin biopsy testing is becoming more frequent in clinics. Skin biopsy testing is minimally invasive and may provide important information, such as nerve density and small-fiber neuropathy,[176] and it may be useful in predicting the progression of the disease.[177] A newly developed noninvasive technique for assessing the presence of DN is corneal confocal microscopy, with which the density and length of the corneal nerve have been shown to be strongly associated with lower-extremity nerve density and which is gaining in popularity.[37] These clinical measurements also may be used to assess the efficacy of specific interventions, including medications, exercise, and weight loss.

Clinical tests to evaluate diabetes-associated cardiac autonomic neuropathy include measurement of resting HR, exercise testing, measurement of blood pressure in response to postural changes (such as moving from a supine position to a standing position), autonomic reflex testing, measurement of 24-hour HR variability, spontaneous baroreflex sensitivity testing, and cardiac radionuclide imaging.[51] Several of these tests, including HR and blood pressure responses to exercise and postural changes, can be performed in the physical therapy setting. A resting HR of $\geq$100 beats per minute is considered to be tachycardia in adults. Orthostatic hypotension is defined as a decrease of greater than 30 mm Hg in systolic blood pressure and a decrease greater than 10 mm Hg in diastolic blood pressure in response to a change from a supine position to a standing position.[178] Patients with diabetes-associated cardiac autonomic neuropathy have a blunted HR response to exercise (ie, they do not attain the age-predicted maximal HR) and a slow HR recovery after peak exercise[52]; the latter is predictive of CVD and all-cause mortality.[52] Physical therapists, therefore, may have to rely more on the patient's perceived exertion than on HR responses for exercise prescription.[179]

Conclusion

Diabetes is associated with both microvascular and macrovascular diseases affecting numerous organs, including skeletal muscle, skin, heart, brain, and kidneys. Common pathogenic mechanisms link the different types of diabetes-associated vascular disease (such as CVD and PAD). Common risk factors for vascular disease in diabetes include hyperglycemia, insulin resistance, dyslipidemia, hypertension, tobacco use, and obesity.

Mechanisms for microvascular disease in diabetes include the pathologic effects of AGE accumulation, overproduction of endothelial growth factors, and abnormal stimulation of the PKC and polyol pathways and the RAS. Mechanisms for macrovascular disease in diabetes include the pathologic effects of AGE accumulation, impaired vasodilatory response attributable to NO inhibition, smooth muscle cell dysfunction, overproduction of endothelial growth factors, chronic inflammation, hemodynamic dysregulation, impaired fibrinolytic ability, and enhanced platelet aggregation (clotting). It is becoming increasingly important for physical therapists to be aware of diabetes-related vascular complications as more patients present with insulin resistance and type 2 DM. The opportunities for effective physical therapy interventions (such as exercise) are significant.

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References

1 World Health Organization. Diabetes facts. Available at: http://www.who.int/mediacentre/factsheets/fs312/en/index.html. Accessed December 13, 2007.

2 World Health Organization. Diabetes action now booklet: a life-threatening condition. Available at: www.who.int/diabetes/BOOKLET_HTML/en/index3.html. Accessed December 13, 2007.

3 Hogan P, Dall T, Nikolov P. Economic costs of diabetes in the US in 2002. *Diabetes Care.* 2003;26:917–932.

4 UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. *Diabetologia.* 1991;34:877–890.

5 Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. *Phys Ther.* 2008;88:1254–1264.

6 Rahman S, Rahman T, Ismail AA, Rashid AR. Diabetes-associated macrovasculopathy: pathophysiology and pathogenesis. *Diabetes Obes Metab.* 2007;9:767–780.

7 Davey Smith G, Bracha Y, Svendsen KH, et al. Incidence of type 2 diabetes in the Randomized Multiple Risk Factor Intervention Trial. *Ann Intern Med.* 2005;142:313–322.

8 Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med.* 2001;344:1343–1350.

9 Eriksson J, Franssila-Kallunki A, Ekstrand A, et al. Early metabolic defects in persons at increased risk for non-insulin-dependent diabetes mellitus. *N Engl J Med.* 1989;321:337–343.

10 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346:393–403.

11 Harding S. Extracts from "concise clinical evidence": diabetic retinopathy. *BMJ.* 2003;326:1023–1025.

12 Sheetz MJ, King GL. Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *JAMA.* 2002;288:2579–2588.

13 Orchard TJ, Dorman JS, Maser RE, et al. Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes.* 1990;39:1116–1124.

14 Kempen JH, O'Colmain BJ, Leske MC, et al. The prevalence of diabetic retinopathy among adults in the United States. *Arch Ophthalmol.* 2004;122:552–563.

15 Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol.* 1984;102:520–526.

16 Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol.* 1984;102:527–532.

17 Tyrberg M, Melander A, Lövestam-Adrian M, Lindblad U. Retinopathy in subjects with impaired fasting glucose: the NANSY-Eye baseline report. *Diabetes Obes Metab.* 2007 Jul 21. [Epub ahead of print]

18 Brazionis L, Rowley K Sr, Itsiopoulos C, et al. Homocysteine and diabetic retinopathy. *Diabetes Care.* 2008;31:50–56.

19 Romero P, Salvat M, Fernandez J, et al. Renal and retinal microangiopathy after 15 years of follow-up study in a sample of type 1 diabetes mellitus patients. *Journal of Diabetes Complications.* 2007;21:93–100.

20 Cundiff DK, Nigg CR. Diet and diabetic retinopathy: insights from the Diabetes Control and Complications Trial (DCCT). *MedGenMed.* 2005;7:3.

21 Cusick M, Chew EY, Chan CC, et al. Histopathology and regression of retinal hard exudates in diabetic retinopathy after reduction of elevated serum lipid levels. *Ophthalmology.* 2003;110:2126–2133.

22 Wilkinson-Berka JL. Diabetes and retinal vascular disorders: role of the renin-angiotensin system. *Expert Rev Mol Med.* 2004;6:1–18.

23 Yamagishi S, Imaizumi T. Pericyte biology and diseases. *Int J Tissue React.* 2005;27:125–135.

24 Rajala U, Pajunpaa H, Koskela P, Keinanen-Kiukaanniemi S. High cardiovascular disease mortality in subjects with visual impairment caused by diabetic retinopathy. *Diabetes Care.* 2000;23:957–961.

25 Yamagishi S, Kobayashi K, Yamamoto H. Vascular pericytes not only regulate growth, but also preserve prostacyclin-producing ability and protect against lipid peroxide-induced injury of co-cultured endothelial cells. *Biochem Biophys Res Commun.* 1993;190:418–425.

26 Carlson EC, Audette JL, Veitenheimer NJ, et al. Ultrastructural morphometry of capillary basement membrane thickness in normal and transgenic diabetic mice. *Anat Rec A Discov Mol Cell Evol Biol.* 2003;271:332–341.

27 Hammes HP. Pericytes and the pathogenesis of diabetic retinopathy. *Horm Metab Res.* 2005;37(suppl 1):39–43.

28 Henricsson M, Nilsson A, Janzon L, Groop L. The effect of glycaemic control and the introduction of insulin therapy on retinopathy in non-insulin-dependent diabetes mellitus. *Diabet Med.* 1997;14:123–131.

29 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352:837–853.

30 Kohner EM, Patel V, Rassam SM. Role of blood flow and impaired autoregulation in the pathogenesis of diabetic retinopathy. *Diabetes.* 1995;44:603–607.

31 Dyck PJ, Kratz KM, Karnes JL, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology.* 1993;43:817–824.

32 Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. *Diabetes Care.* 2003;26:1553–1579.

33 Boulton AJ. Foot problems in patients with diabetes mellitus. In: Pickup J, Williams G, ed. *Textbook of Diabetes*. London, United Kingdom: Blackwell Science; 1997:1–58.

34 Sumner CJ, Sheth S, Griffin JW, et al. The spectrum of neuropathy in diabetes and impaired glucose tolerance. *Neurology.* 2003;60:108–111.

35 Dyck PJ, Davies JL, Wilson DM, et al. Risk factors for severity of diabetic polyneuropathy: intensive longitudinal assessment of the Rochester Diabetic Neuropathy Study cohort. *Diabetes Care.* 1999;22:1479–1486.

36 Tesfaye S, Stevens LK, Stephenson JM, et al. Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM Complications Study. *Diabetologia.* 1996;39:1377–1384.

37 Thrainsdottir S, Malik RA, Dahlin LB, et al. Endoneurial capillary abnormalities presage deterioration of glucose tolerance and accompany peripheral neuropathy in man. *Diabetes.* 2003;52:2615–2622.

38 Yang Q, Kaji R, Takagi T, et al. Abnormal axonal inward rectifier in streptozocin-induced experimental diabetic neuropathy. *Brain.* 2001;124:1149–1155.

39 Malik RA, Newrick PG, Sharma AK, et al. Microangiopathy in human diabetic neuropathy: relationship between capillary abnormalities and the severity of neuropathy. *Diabetologia.* 1989;32:92–102.

40 Mueller MJ, Zou D, Bohnert KL, et al. Plantar stresses on the neuropathic foot during barefoot walking. *Phys Ther.* 2008;88:1375–1384.

41 LeMaster JW, Mueller MJ, Reiber GE, et al. Effect of weight-bearing activity on foot ulcer incidence in people with diabetic peripheral neuropathy: Feet First randomized controlled trial. *Phys Ther.* 2008;88:1385–1398.

42 Hilton TN, Tuttle LJ, Bohnert KL, et al. Excessive adipose tissue infiltration in skeletal muscle in individuals with obesity, diabetes mellitus, and peripheral neuropathy: association with performance and function. *Phys Ther.* 2008;88:1336–1344.

43 Dyck PJ, Giannini C. Pathologic alterations in the diabetic neuropathies of humans: a review. *J Neuropathol Exp Neurol.* 1996;55:1181–1193.

44 Ibrahim S, Harris ND, Radatz M, et al. A new minimally invasive technique to show nerve ischaemia in diabetic neuropathy. *Diabetologia.* 1999;42:737–742.

45 Young MJ, Veves A, Walker MG, Boulton AJ. Correlations between nerve function and tissue oxygenation in diabetic patients: further clues to the aetiology of diabetic neuropathy? *Diabetologia.* 1992;35:1146–1150.

46 Malik RA, Tesfaye S, Thompson SD, et al. Endoneurial localisation of microvascular damage in human diabetic neuropathy. *Diabetologia.* 1993;36:454–459.

47 Yagihashi S, Kamijo M, Baba M, et al. Effect of aminoguanidine on functional and structural abnormalities in peripheral nerve of STZ-induced diabetic rats. *Diabetes.* 1992;41:47–52.

48 Cotter MA, Jack AM, Cameron NE. Effects of the protein kinase C beta inhibitor LY333531 on neural and vascular function in rats with streptozocin-induced diabetes. *Clin Sci (Lond).* 2002;103:311–321.

49 Nakamura J, Kato K, Hamada Y, et al. A protein kinase C-beta-selective inhibitor ameliorates neural dysfunction in streptozocin-induced diabetic rats. *Diabetes.* 1999;48:2090–2095.

50 Vlassara H, Brownlee M, Cerami A. Accumulation of diabetic rat peripheral nerve myelin by macrophages increases with the presence of advanced glycosylation end products. *J Exp Med.* 1984;160:197–207.

51 Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation.* 2007;115:387–397.

52 Cheng YJ, Lauer MS, Earnest CP, et al. Heart rate recovery following maximal exercise testing as a predictor of cardiovascular disease and all-cause mortality in men with diabetes. *Diabetes Care.* 2003;26:2052–2057.

53 Witte DR, Tesfaye S, Chaturvedi N, et al. Risk factors for cardiac autonomic neuropathy in type 1 diabetes mellitus. *Diabetologia.* 2005;48:164–171.

54 Drummond K, Mauer M. The early natural history of nephropathy in type 1 diabetes, II: early renal structural changes in type 1 diabetes. *Diabetes.* 2002;51:1580–1587.

55 Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001;345:861–869.

56 Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int.* 2003;63:225–232.

57 Friedman E. Diabetic renal disease. In: Rifkin H, Porte D Jr, eds. *Ellenberg and Rifkin's Diabetes Mellitus: Theory and Practice*. 4th ed. New York, NY: Elsevier; 1990:684–709.

58 Chen S, Hong SW, Iglesias-de la Cruz MC, et al. The key role of the transforming growth factor-beta system in the pathogenesis of diabetic nephropathy. *Ren Fail.* 2001;23:471–481.

59 van Dijk C, Berl T. Pathogenesis of diabetic nephropathy. *Rev Endocr Metab Disord.* 2004;5:237–248.

60 Hasslacher C, Ritz E, Wahl P, Michael C. Similar risks of nephropathy in patients with type I or type II diabetes mellitus. *Nephrol Dial Transplant.* 1989;4:859–863.

61 Linseman DA, Branstetter DG, Yu RL, Aaron CS. Lung tumor induction in A/J mice and clastogenic effects in CD-1 mice of the sequence-selective DNA alkylating agents (+)-CC-1065 and (−)-CC-1065. *Nat Toxins.* 1995;3:32–40.

62 Kramer H, Luke A, Bidani A, et al. Obesity and prevalent and incident CKD: the Hypertension Detection and Follow-Up Program. *Am J Kidney Dis.* 2005;46:587–594.

63 Laakso M. Hyperglycemia and cardiovascular disease in type 2 diabetes. *Diabetes.* 1999;48:937–942.

64 American Heart Association. The heart of diabetes. Available at: http://www.americanheart.org/presenter.jhtml?identifier=3044762. Accessed December 3, 2007.

65 Buyken AE, von Eckardstein A, Schulte H, et al. Type 2 diabetes mellitus and risk of coronary heart disease: results of the 10-year follow-up of the PROCAM Study. *Eur J Cardiovasc Prev Rehabil.* 2007;14:230–236.

66 Bonora E, Formentini G, Calcaterra F, et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabetes Care.* 2002;25:1135–1141.

67 Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med.* 1998;339:229–234.

68 Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation.* 2000;102:1014–1019.

69 Facchini FS, Hua N, Abbasi F, Reaven GM. Insulin resistance as a predictor of age-related diseases. *J Clin Endocrinol Metab.* 2001;86:3574–3578.

70 Mufunda J, Chatora R, Ndambakuwa Y, et al. Emerging non-communicable disease epidemic in Africa: preventive measures from the WHO Regional Office for Africa. *Ethn Dis.* 2006;16:521–526.

71 Turner R, Cull C, Holman R. United Kingdom Prospective Diabetes Study 17: a 9-year update of a randomized, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. *Ann Intern Med.* 1996;124:136–145.

72 Reusch JE, Draznin BB. Atherosclerosis in diabetes and insulin resistance. *Diabetes Obes Metab.* 2007;9:455–463.

73 Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486–2497.

74 Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA.* 2002;287:2570–2581.

75 Centers for Disease Control and Prevention. Stroke. Available at: http://www.cdc.gov/stroke/. Accessed January 5, 2008.

76 Abbott RD, Curb JD, Rodriguez BL, et al. Age-related changes in risk factor effects on the incidence of thromboembolic and hemorrhagic stroke. *J Clin Epidemiol.* 2003;56:479–486.

77 Ohira T, Shahar E, Chambless LE, et al. Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities Study. *Stroke.* 2006;37:2493–2498.

78 Folsom AR, Rasmussen ML, Chambless LE, et al. Prospective associations of fasting insulin, body fat distribution, and diabetes with risk of ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Diabetes Care.* 1999;22:1077–1083.

79 Rohr J, Kittner S, Feeser B, et al. Traditional risk factors and ischemic stroke in young adults: the Baltimore-Washington Cooperative Young Stroke Study. *Arch Neurol.* 1996;53:603–607.

80 Tuomilehto J, Rastenyte D, Jousilahti P, et al. Diabetes mellitus as a risk factor for death from stroke: prospective study of the middle-aged Finnish population. *Stroke.* 1996;27:210–215.

81 Haheim LL, Holme I, Hjermann I, Leren P. Nonfasting serum glucose and the risk of fatal stroke in diabetic and nondiabetic subjects: 18-year follow-up of the Oslo Study. *Stroke.* 1995;26:774–777.

82 Ribo M, Molina C, Montaner J, et al. Acute hyperglycemia state is associated with lower tPA-induced recanalization rates in stroke patients. *Stroke.* 2005;36:1705–1709.

83 Parsons MW, Barber PA, Desmond PM, et al. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. *Ann Neurol.* 2002;52:20–28.

84 Megherbi SE, Milan C, Minier D, et al. Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: data from the European BIOMED Stroke Project. *Stroke.* 2003;34:688–694.

85 Sprafka JM, Virnig BA, Shahar E, McGovern PG. Trends in diabetes prevalence among stroke patients and the effect of diabetes on stroke survival: the Minnesota Heart Survey. *Diabet Med.* 1994;11:678–684.

86 Elneihoum AM, Goransson M, Falke P, Janzon L. Three-year survival and recurrence after stroke in Malmo, Sweden: an analysis of stroke registry data. *Stroke.* 1998;29:2114–2117.

87 Fabris F, Zanocchi M, Bo M, et al. Carotid plaque, aging, and risk factors: a study of 457 subjects. *Stroke.* 1994;25:1133–1140.

88 Friedlander AH, Maeder LA. The prevalence of calcified carotid artery atheromas on the panoramic radiographs of patients with type 2 diabetes mellitus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2000;89:420–424.

89 Stegmayr B, Asplund K. Diabetes as a risk factor for stroke: a population perspective. *Diabetologia.* 1995;38:1061–1068.

90 Niskanen L, Turpeinen A, Penttila I, Uusitupa MI. Hyperglycemia and compositional lipoprotein abnormalities as predictors of cardiovascular mortality in type 2 diabetes: a 15-year follow-up from the time of diagnosis. *Diabetes Care.* 1998;21:1861–1869.

91 Sasaki A, Horiuchi N, Hasegawa K, Uehara M. Mortality from coronary heart disease and cerebrovascular disease and associated risk factors in diabetic patients in Osaka District, Japan. *Diabetes Res Clin Pract.* 1995;27:77–83.

92 Shinozaki K, Naritomi H, Shimizu T, et al. Role of insulin resistance associated with compensatory hyperinsulinemia in ischemic stroke. *Stroke.* 1996;27:37–43.

93 Zunker P, Schick A, Buschmann HC, et al. Hyperinsulinism and cerebral microangiopathy. *Stroke.* 1996;27:219–223.

94 Davis TM, Millns H, Stratton IM, et al. Risk factors for stroke in type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 29. *Arch Intern Med.* 1999;159:1097–1103.

95 Guerrero-Romero F, Rodriguez-Moran M. Proteinuria is an independent risk factor for ischemic stroke in non-insulin-dependent diabetes mellitus. *Stroke.* 1999;30:1787–1791.

96 Lehto S, Niskanen L, Ronnemaa T, Laakso M. Serum uric acid is a strong predictor of stroke in patients with non-insulin-dependent diabetes mellitus. *Stroke.* 1998;29:635–639.

97 Engstrom G, Stavenow L, Hedblad B, et al. Inflammation-sensitive plasma proteins, diabetes, and mortality and incidence of myocardial infarction and stroke: a population-based study. *Diabetes.* 2003;52:442–447.

98 American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care.* 2003;26:3333–3341.

99 Kullo IJ, Bailey KR, Kardia SL, et al. Ethnic differences in peripheral arterial disease in the NHLBI Genetic Epidemiology Network of Arteriopathy (GENOA) Study. *Vasc Med.* 2003;8:237–242.

100 Schainfeld RM. Management of peripheral arterial disease and intermittent claudication. *J Am Board Fam Pract.* 2001; 14:443–450.

101 Vogt MT, Cauley JA, Kuller LH, Nevitt MC. Functional status and mobility among elderly women with lower extremity arterial disease: the Study of Osteoporotic Fractures. *J Am Geriatr Soc.* 1994;42:923–929.

102 McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA.* 2004;292:453–461.

103 Adler AI, Boyko EJ, Ahroni JH, Smith DG. Lower-extremity amputation in diabetes: the independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers. *Diabetes Care.* 1999;22: 1029–1035.

104 Dickinson PJ, Carrington AL, Frost GS, Boulton AJ. Neurovascular disease, antioxidants and glycation in diabetes. *Diabetes Metab Res Rev.* 2002;18:260–272.

105 Forsblom CM, Sane T, Groop PH, et al. Risk factors for mortality in type II (non-insulin-dependent) diabetes: evidence of a role for neuropathy and a protective effect of HLA-DR4. *Diabetologia.* 1998; 41:1253–1262.

106 Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. *Diabetes Care.* 2001;24:1433–1437.

107 Al-Delaimy WK, Merchant AT, Rimm EB, et al. Effect of type 2 diabetes and its duration on the risk of peripheral arterial disease among men. *Am J Med.* 2004; 116:236–240.

108 Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med.* 2004;141:421–431.

109 American Heart Association. Peripheral arterial disease risk factors and possible complications. Available at: http://www.americanheart.org/presenter.jhtml?identifier=3020256. Accessed January 5, 2008.

110 Wattanakit K, Folsom AR, Selvin E, et al. Risk factors for peripheral arterial disease incidence in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. *Atherosclerosis.* 2005;180: 389–397.

111 Brownlee M, Cerami A, Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. *N Engl J Med.* 1988;318: 1315–1321.

112 Stitt AW, Jenkins AJ, Cooper ME. Advanced glycation end products and diabetic complications. *Expert Opin Investig Drugs.* 2002;11:1205–1223.

113 Giardino I, Edelstein D, Brownlee M. Nonenzymatic glycosylation in vitro and in bovine endothelial cells alters basic fibroblast growth factor activity: a model for intracellular glycosylation in diabetes. *J Clin Invest.* 1994;94:110–117.

114 Yamagishi S, Hsu CC, Taniguchi M, et al. Receptor-mediated toxicity to pericytes of advanced glycosylation end products: a possible mechanism of pericyte loss in diabetic microangiopathy. *Biochem Biophys Res Commun.* 1995;213:681–687.

115 Campochiaro PA. Retinal and choroidal neovascularization. *J Cell Physiol.* 2000; 184:301–310.

116 Yamagishi S, Amano S, Inagaki Y, et al. Advanced glycation end products-induced apoptosis and overexpression of vascular endothelial growth factor in bovine retinal pericytes. *Biochem Biophys Res Commun.* 2002;290:973–978.

117 Benjamin LE, Hemo I, Keshet E. A plasticity window for blood vessel remodelling is defined by pericyte coverage of the preformed endothelial network and is regulated by PDGF-B and VEGF. *Development.* 1998;125:1591–1598.

118 Chibber R, Ben-Mahmud BM, Chibber S, Kohner EM. Leukocytes in diabetic retinopathy. *Curr Diabetes Rev.* 2007;3:3–14.

119 Boeri D, Maiello M, Lorenzi M. Increased prevalence of microthromboses in retinal capillaries of diabetic individuals. *Diabetes.* 2001;50:1432–1439.

120 Schmidt AM, Stern DM. RAGE: a new target for the prevention and treatment of the vascular and inflammatory complications of diabetes. *Trends Endocrinol Metab.* 2000;11:368–375.

121 Silbiger S, Crowley S, Shan Z, et al. Nonenzymatic glycation of mesangial matrix and prolonged exposure of mesangial matrix to elevated glucose reduces collagen synthesis and proteoglycan charge. *Kidney Int.* 1993;43:853–864.

122 Matsumura T, Yamagishi S, Brownlee M. Advanced glycation end products and the pathogenesis of diabetic complications. In: LeRoith D, Taylor S, Olefsky JM, eds. *Diabetes Mellitus: A Fundamental and Clinical Text*. Philadelphia, PA: Lippincott Williams & Wilkins; 2000: 983–991.

123 Osterby R, Parving HH, Nyberg G, et al. A strong correlation between glomerular filtration rate and filtration surface in diabetic nephropathy. *Diabetologia.* 1988; 31:265–270.

124 Spranger J, Osterhoff M, Reimann M, et al. Loss of the antiangiogenic pigment epithelium-derived factor in patients with angiogenic eye disease. *Diabetes.* 2001;50:2641–2645.

125 Kinoshita JH, Nishimura C. The involvement of aldose reductase in diabetic complications. *Diabetes Metab Rev.* 1988; 4:323–337.

126 Sima AA. New insights into the metabolic and molecular basis for diabetic neuropathy. *Cell Mol Life Sci.* 2003;60: 2445–2464.

127 Vincent AM, Feldman EL. New insights into the mechanisms of diabetic neuropathy. *Rev Endocr Metab Disord.* 2004;5: 227–236.

128 Gilbert RE, Krum H, Wilkinson-Berka J, Kelly DJ. The renin-angiotensin system and the long-term complications of diabetes: pathophysiological and therapeutic considerations. *Diabet Med.* 2003;20: 607–621.

129 Yamagishi S, Imaizumi T. Diabetic vascular complications: pathophysiology, biochemical basis and potential therapeutic strategy. *Curr Pharm Des.* 2005;11: 2279–2299.

130 Girach A, Manner D, Porta M. Diabetic microvascular complications: can patients at risk be identified? A review. *Int J Clin Pract.* 2006;60:1471–1483.

131 Williams SB, Cusco JA, Roddy MA, et al. Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol.* 1996;27:567–574.

132 De Vriese AS, Verbeuren TJ, Van de Voorde J, et al. Endothelial dysfunction in diabetes. *Br J Pharmacol.* 2000;130: 963–974.

133 Milstien S, Katusic Z. Oxidation of tetrahydrobiopterin by peroxynitrite: implications for vascular endothelial function. *Biochem Biophys Res Commun.* 1999; 263:681–684.

134 Grant PJ. Diabetes mellitus as a prothrombotic condition. *J Intern Med.* 2007;262:157–172.

135 Hennes MM, O'Shaughnessy IM, Kelly TM, et al. Insulin-resistant lipolysis in abdominally obese hypertensive individuals: role of the renin-angiotensin system. *Hypertension.* 1996;28:120–126.

136 Inoguchi T, Li P, Umeda F, et al. High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C–dependent activation of NAD(P)H oxidase in cultured vascular cells. *Diabetes.* 2000;49:1939–1945.

137 Linden E, Cai W, He JC, et al. Endothelial dysfunction in patients with chronic kidney disease results from advanced glycation end products (AGE)-mediated inhibition of endothelial nitric oxide synthase through RAGE activation. *Clin J Am Soc Nephrol.* 2008;3:691–698.

138 Rask-Madsen C, King GL. Mechanisms of disease: endothelial dysfunction in insulin resistance and diabetes. *Nat Clin Pract Endocrinol Metab.* 2007;3:46–56.

139 Assert R, Scherk G, Bumbure A, et al. Regulation of protein kinase C by short-term hyperglycaemia in human platelets in vivo and in vitro. *Diabetologia.* 2001;44:188–195.

140 Carr ME. Diabetes mellitus: a hypercoagulable state. *Journal of Diabetes Complications.* 2001;15:44–54.

141 Hansson GK, Robertson AK, Soderberg-Naucler C. Inflammation and atherosclerosis. *Annu Rev Pathol.* 2006;1:297–329.

142 Williams MD, Nadler JL. Inflammatory mechanisms of diabetic complications. *Curr Diab Rep.* 2007;7:242–248.

143 Suzuki LA, Poot M, Gerrity RG, Bornfeldt KE. Diabetes accelerates smooth muscle accumulation in lesions of atherosclerosis: lack of direct growth-promoting effects of high glucose levels. *Diabetes.* 2001;50:851–860.

144 Mankovsky BN, Ziegler D. Stroke in patients with diabetes mellitus. *Diabetes Metab Res Rev.* 2004;20:268–287.

145 Hoxworth JM, Xu K, Zhou Y, et al. Cerebral metabolic profile, selective neuron loss, and survival of acute and chronic hyperglycemic rats following cardiac arrest and resuscitation. *Brain Res.* 1999;821:467–479.

146 Siesjo BK, Zhao Q, Pahlmark K, et al. Glutamate, calcium, and free radicals as mediators of ischemic brain damage. *Ann Thorac Surg.* 1995;59:1316–1320.

147 Li PA, Shuaib A, Miyashita H. Hyperglycemia enhances extracellular glutamate accumulation in rats subjected to forebrain ischemia. *Stroke.* 2000;31:183–192.

148 Giannini C, de Giorgis T, Mohn A, Chiarelli F. Role of physical exercise in children and adolescents with diabetes mellitus. *J Pediatr Endocrinol Metab.* 2007;20:173–184.

149 O'Gorman DJ, Karlsson HK, McQuaid S, et al. Exercise training increases insulin-stimulated glucose disposal and GLUT4 (SLC2A4) protein content in patients with type 2 diabetes. *Diabetologia.* 2006;49:2983–2992.

150 Sato Y, Nagasaki M, Kubota M, et al. Clinical aspects of physical exercise for diabetes/metabolic syndrome. *Diabetes Res Clin Pract.* 2007;77(suppl 1):S87–S91.

151 Ivy JL. Role of exercise training in the prevention and treatment of insulin resistance and non-insulin-dependent diabetes mellitus. *Sports Med.* 1997;24:321–336.

152 Bruce DG, Davis WA, Davis TM. Longitudinal predictors of reduced mobility and physical disability in patients with type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care.* 2005;28:2441–2447.

153 Smith DW, McFall SL. The relationship of diet and exercise for weight control and the quality of life gap associated with diabetes. *J Psychosom Res.* 2005;59:385–392.

154 Wallberg-Henriksson H, Rincon J, Zierath JR. Exercise in the management of non-insulin-dependent diabetes mellitus. *Sports Med.* 1998;25:25–35.

155 Turcotte LP, Fisher JS. Skeletal muscle insulin resistance: roles of fatty acid metabolism and exercise. *Phys Ther.* 2008;88:1279–1296.

156 Gulve EA. Exercise and glycemic control in diabetes: benefits, challenges, and adjustments to pharmacotherapy. *Phys Ther.* 2008;88:1297–1321.

157 Fried LF, Lee JS, Shlipak M, et al. Chronic kidney disease and functional limitation in older people: health, aging and body composition study. *J Am Geriatr Soc.* 2006;54:750–756.

158 Tawney KW, Tawney PJ, Kovach J. Disablement and rehabilitation in end-stage renal disease. *Semin Dial.* 2003;16:447–452.

159 Boyce ML, Robergs RA, Avasthi PS, et al. Exercise training by individuals with predialysis renal failure: cardiorespiratory endurance, hypertension, and renal function. *Am J Kidney Dis.* 1997;30:180–192.

160 Johansen KL, Shubert T, Doyle J, et al. Muscle atrophy in patients receiving hemodialysis: effects on muscle strength, muscle quality, and physical function. *Kidney Int.* 2003;63:291–297.

161 Moore GE, Brinker KR, Stray-Gundersen J, Mitchell JH. Determinants of VO_2peak in patients with end-stage renal disease: on and off dialysis. *Med Sci Sports Exerc.* 1993;25:18–23.

162 McManus D, Shlipak M, Ix JH, et al. Association of cystatin C with poor exercise capacity and heart rate recovery: data from the Heart and Soul Study. *Am J Kidney Dis.* 2007;49:365–372.

163 Finkelstein J, Joshi A, Hise MK. Association of physical activity and renal function in subjects with and without metabolic syndrome: a review of the Third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis.* 2006;48:372–382.

164 Lazarevic G, Antic S, Vlahovic P, et al. Effects of aerobic exercise on microalbuminuria and enzymuria in type 2 diabetic patients. *Ren Fail.* 2007;29:199–205.

165 Brearley S, Shearman CP, Simms MH. Peripheral pulse palpation: an unreliable physical sign. *Ann R Coll Surg Engl.* 1992;74:169–171.

166 McDermott MM, Greenland P, Liu K, et al. The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. *Ann Intern Med.* 2002;136:873–883.

167 Criqui MH, Denenberg JO, Bird CE, et al. The correlation between symptoms and non-invasive test results in patients referred for peripheral arterial disease testing. *Vasc Med.* 1996;1:65–71.

168 Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary—a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *J Am Coll Cardiol.* 2006;47:1239–1312.

169 Greig C, Butler F, Skelton D, et al. Treadmill walking in old age may not reproduce the real life situation. *J Am Geriatr Soc.* 1993;41:15–18.

170 Gardner AW, Katzel LI, Sorkin JD, et al. Exercise rehabilitation improves functional outcomes and peripheral circulation in patients with intermittent claudication: a randomized controlled trial. *J Am Geriatr Soc.* 2001;49:755–762.

171 Regensteiner JG, Steiner JF, Hiatt WR. Exercise training improves functional status in patients with peripheral arterial disease. *J Vasc Surg.* 1996;23:104–115.

172 Dawson DL, Cutler BS, Meissner MH, Strandness DE Jr. Cilostazol has beneficial effects in treatment of intermittent claudication: results from a multicenter, randomized, prospective, double-blind trial. *Circulation.* 1998;98:678–686.

173 Boulton AJ. Diabetic neuropathy: classification, measurement and treatment. *Curr Opin Endocrinol Diabetes Obes.* 2007;14:141–145.

174 Garrow AP, Boulton AJ. Vibration perception threshold: a valuable assessment of neural dysfunction in people with diabetes. *Diabetes Metab Res Rev.* 2006;22:411–419.

175 Boulton AJ, Malik RA, Arezzo JC, Sosenko JM. Diabetic somatic neuropathies. *Diabetes Care.* 2004;27:1458–1486.

176 Boulton AJ. Treatment of prediabetic neuropathy. *Curr Diab Rep.* 2006;6:415–416.

177 Gibbons CH, Griffin JW, Polydefkis M, et al. The utility of skin biopsy for prediction of progression in suspected small fiber neuropathy. *Neurology.* 2006;66:256–258.

178 The definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *J Auton Nerv Syst.* 1996;58:123–124.

179 Colberg SR, Swain DP, Vinik AI. Use of heart rate reserve and rating of perceived exertion to prescribe exercise intensity in diabetic autonomic neuropathy. *Diabetes Care.* 2003;26:986–990.