INVITED REVIEW

Diabetes and peripheral vascular disease

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Diabetes mellitus is found in as many as 13 million people nationally, or 5.2% of the US population, and more than 650,000 new cases are diagnosed annually.[1] Clinical data that link diabetes to vascular disease are derived from several large epidemiologic studies. The Framingham Study of more than 5000 subjects showed that diabetes is a powerful risk factor for atherosclerotic coronary and peripheral arterial disease, independent of other atherogenic risk factors, with a relative risk averaging two fold for men and three fold for women.[2] The Framingham Study results also confirmed that the risk of stroke is at least 2.5-fold higher in patients with diabetes,[3] a finding that has been confirmed in other large epidemiologic studies.[4,5] Moreover, diabetes is strongly associated with atherosclerosis of the extracranial internal carotid artery and thus imparts an additional independent risk of stroke.[6]

PATHOPHYSIOLOGY OF VASCULAR DISEASE AND COMPLICATIONS OF DIABETES MELLITUS

Overview. Many of the clinical complications of diabetes may be ascribed to alterations in vascular structure and function, with subsequent end-organ damage and death. Specifically, two types of vascular disease are seen in patients with diabetes: a nonoccclusive microcirculatory dysfunction involving the capillaries and arterioles of the kidneys, retina, and peripheral nerves, and a macroangiopathy characterized by atherosclerotic lesions of the coronary and peripheral arterial circulation.[7-10] The former is relatively unique to diabetes, whereas the latter lesions are morphologically similar in both patients with and without diabetes.

Retinopathy is the most characteristic microvascular complication of diabetes, and population-based study results have identified a correlation between its development and the duration of diabetes.[11] Similar correlations have been found with nephropathy, neuropathy, and diabetes,[12] with perhaps the strongest evidence coming from the Diabetes Control and Complications Trial. The results from the Diabetes Control and Complications Trial clearly showed a delay in the development and progression of these microvascular complications with intensive glycemic control, thus supporting the direct causal relationship between hyperglycemia, diabetes, and its microvascular sequelae.[13] These and other clinical trials have provided the rationale for experimental studies investigating the fundamental pathophysiology of microvascular and macrovascular disease in diabetes mellitus.

Microvascular dysfunction in diabetes is manifested by an increased vascular permeability and impaired autoregulation of blood flow and vascular tone. These changes culminate into nephropathy, retinopathy, and neuropathy and most likely contribute to the cardiovascular complications of diabetes. Although multiple theories have been postulated as to the cause of accelerated microangiopathy, it is likely that several biochemical derangements exist in the presence of hyperglycemia and diabetes and that these mechanisms work synergistically to cause microvascular dysfunction. These metabolic alterations produce functional and structural changes at multiple areas within the arteriolar and capillary level, including the basement membrane,[9] the smooth muscle cell,[14] and, in particular, the endothelial cell.[15]

One of the greatest impediments in understanding vascular disease in patients with diabetes is the misconception that they have an untreatable occlusive lesion in the microcirculation.[8] This idea originated from a retrospective histologic study that showed the presence of periodic-acid-Schiff-positive material occluding the arterioles in amputated limb specimens from patients with diabetes.[16] However, subsequent prospective staining and arterial casting studies[17,18] and physiological studies[19] have shown the absence of an arteriolar occlusive lesion. Dispelling the notion of "small vessel disease" is fundamental to the principles of limb sal-

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vage in patients with diabetes because arterial reconstruction is almost always possible in these patients.

Although there is no occlusive lesion in the diabetic microcirculation, other structural changes do exist, most notably, a thickening of the capillary basement membrane. This alteration in extracellular matrix may represent a response to the metabolic changes related to diabetes and hyperglycemia. However, this does not lead to narrowing of the capillary lumen and arteriolar blood flow may be normal or even increased despite these changes.[20] Capillary basement membrane thickening is the dominant structural change in both diabetic retinopathy and neuropathy. In the kidney, nonenzymatic glycosylation reduces the charge on the basement membrane, which may account for transudation of albumin, an expanded mesangium, and albuminuria.[21] Similar increases in vascular permeability occur in the eye and probably contribute to macular exudate formation and retinopathy.

In the diabetic foot, basement membrane thickening may theoretically impair the migration of leukocytes and the hyperemic response after injury and thus may increase the susceptibility of the diabetic foot to infection.[22,23] Although resting total skin microcirculatory flow is similar in both patients with and without diabetes, the capillary blood flow is reduced in diabetes, indicating a maldistribution and functional ischemia of the skin.[24] Moreover, study results of skin microvascular flow have shown reduced maximal hyperemic response to heat in patients with diabetes, suggesting that a functional microvascular impairment is a major contributing factor for diabetic foot problems. All of these changes result in an inability to vasodilate and achieve maximal blood flow after injury.

Diabetes also affects the axon reflex. Injury directly stimulates nociceptive C fibers, which results in both orthodromic conduction to the spinal cord and antidromic conduction to adjacent C fibers and other axon branches. One function of this axon reflex is the secretion of several active peptides, such as substance P and calcitonin gene-related peptide, which directly and indirectly (through mast cell release of histamine) cause vasodilation and increased permeability. This neurogenic vasodilatory response is impaired in diabetes, further reducing the hyperemic response when it is most needed: that is, under conditions of injury and inflammation.[25]

The previous changes contribute to an early functional impairment in vascular reserve in the peripheral, coronary, and cerebral circulation of patients with diabetes. With positron emission tomography, myocardial blood flow may be measured at rest and after vasodilator administration, and thus coronary flow reserve (as a measure of endothelial function) may be calculated. Reduced coronary flow reserve and impaired coronary reactivity has been observed in patients with diabetes with angiographically normal coronary arteries and no other detectable microvascular complications, which suggests an early endothelial dysfunction.[26,27] Similarly, cerebrovascular reactivity and reserve capacity may be assessed with transcranial Doppler scanning and acetazolamide, which causes vasodilatation of the brain resistance vessels. Impaired cerebrovascular reserve is also noted in patients with diabetes, particularly among those patients with other microvascular complications.[28]

Endothelial function. The normal endothelium plays an important role in blood vessel wall function and homeostasis by synthesizing and releasing substances, such as prostacyclin, endothelin, prostaglandins, and nitric oxide, which modulate vasomotor tone and prevent thrombosis.[29] There is substantial evidence that endothelial function is abnormal in animal models of diabetes mellitus[30-32] and in patients with both insulin-dependent and non–insulin-dependent diabetes mellitus,[33,34] thus directly implicating either hyperglycemia or hyperinsulinemia as a possible mediator of abnormal endothelium-dependent responses. A variety of mechanisms responsible for vascular dysfunction have been proposed, principally abnormalities in the nitric oxide pathway, abnormal production of vasoconstrictor prostanoids, intracellular signaling, reduction in Na^+,K^+–adenosine triphosphatase (ATPase) activity, and advanced glycosylated end products.[15,27,28,35-37]

In 1980, Furchgott and Zawadzki[38] discovered that arterial vasodilation was dependent on an intact endothelium and its release of a substance they called endothelium-derived relaxing factor, which causes arterial smooth muscle relaxation in response to acetylcholine and other vasodilators.[38] Later identified as endothelial-derived nitric oxide (EDNO), it activates vascular smooth muscle guanylate cyclase, elevates cyclic guanosine monophospate levels, and may increase Na^+,K^+-ATPase activity.[39] A variety of substances other than acetylcholine may cause EDNO-mediated vasodilation. Several in vivo studies with N^G-monomethyl-L-arginine (L-NMMA), an arginine analogue and competitive inhibitor of EDNO synthesis, have shown that the vasodilatory effects of insulin are nitric oxide dependent[40,41] and that insulin mediates EDNO-dependent vasodila-

tion by modulating the synthesis and release of EDNO. Impaired endothelial-dependent vasodilatation in certain insulin-resistant states may be instrumental in the pathogenesis of atherosclerosis and hypertension and is postulated to be the result of diminished insulin-mediated EDNO production and release.[42]

Studies of patients with insulin-dependent and non–insulin-dependent diabetes have shown impaired endothelium-dependent responses to acetylcholine in both groups but an intact response to exogenous nitric oxide donors (ie, sodium nitroprusside) in insulin-dependent diabetes only.[33,34] It thus appears that abnormal nitric oxide release or synthesis predominates in insulin-dependent diabetes, whereas non–insulin-dependent diabetes may be characterized by either a diminished response of smooth muscle to EDNO or increased inactivation of nitric oxide.

Although there is considerable controversy regarding the role of free radicals in diabetic vascular disease,[43] an increased production of oxygen-derived free radicals has been described in diabetes and may contribute to endothelial dysfunction.[44] Superoxide anions and other oxygen-derived free radicals directly inactivate endothelium-derived nitric oxide.[45] In animal models, endothelium-derived free radicals impair EDNO-mediated vasodilatation and administration of superoxide dismutase and other free radical scavengers normalize EDNO-dependent relaxation in diabetic arteries.[46] Defective endothelium-dependent relaxation in diabetic rat aorta is significantly attenuated by vitamin E, a potent free radical scavenger.[47] In human studies, administration of vitamin C restores and improves endothelium-dependent vasodilation, but not endothelium-independent responses, in patients with both insulin-dependent and non–insulin-dependent diabetes mellitus, thus further suggesting that oxygen-derived free radicals may decrease the bioavailability of EDNO.[48]

A potentially treatable source of oxygen-derived free radicals is hyperlipidemia. Increased levels of low density lipoprotein (LDL) and very low density lipoprotein are common in patients with diabetes. Hyperglycemia promotes the oxidation and nonenzymatic glycation of LDL, which has been strongly implicated in atherogenesis by a variety of mechanisms.[49] In animal models of hypercholesterolemia, the vascular endothelium produces several free radicals, presumably through xanthine oxidase activation, and these endothelial-derived free radicals inactivate EDNO.[50] Moreover, flow-mediated vasodilatation and reactive hyperemia (endothelium-dependent) are more impaired in patients with insulin-dependent diabetes and elevated LDL cholesterol levels, which further supports the relationship of hypercholesterolemia, free radicals, and EDNO.[51]

Advanced glycosylation end products (AGEs) have also been implicated in the pathogenesis of diabetic microvascular complications.[37] These are formed from a reversible reaction between glucose and protein to form Schiff bases, which then rearrange to form stable Amadori-type early glycosylation products. Some of these reversible early glycosylation products may undergo complex rearrangements to form irreversible AGEs. In experimental diabetes, AGEs impair the actions of EDNO and cause an impaired endothelium-dependent response, which is ameliorated by the administration of an AGE inhibitor.[52] AGEs also displace disulfide crosslinkages in collagen and scleral proteins, accounting for the diminished charge in the capillary basement membrane. This may contribute to the increased vascular permeability of diabetes because blockade of a specific receptor for AGE reverses diabetes-mediated vascular hyperpermeability.[53] Moreover, the presence of AGE receptors on both endothelial cells and monocytes, along with AGE deposition in the subendothelium, suggests monocyte deposition into the subendothelial space and secondary complications.[54] Makita et al,[55] with a radioreceptor assay for AGEs in serum and arterial wall, have demonstrated higher AGE levels in patients with diabetes as compared with nondiabetic control subjects, with the highest levels occurring among patients with diabetes with nephropathy.[55] Because at least part of AGE-induced cellular dysfunction is the result of an oxidant-sensitive mechanism, which is inhibited by antioxidants, it is likely that both oxygen-derived free radicals and AGEs each contribute to cause impaired EDNO-dependent vasodilation in diabetes. Taken together, the effects of AGEs on vascular permeability, subendothelial protein deposition, inactivation of nitric oxide, and modification of LDL provide strong evidence of their important role in diabetic vascular disease.

Experimental studies in diabetic animals have also indicated that abnormal endothelial production of vasoconstrictor prostanoids, notably thromboxane A_2 and prostaglandin H_2, may be a cause of endothelial cell dysfunction. Increased levels of thromboxane A_2 have been isolated only from segments of diabetic aortic tissue with intact endotheliums, which suggests that the endothelium is responsible for the increased release, and impaired relaxation to acetylcholine in these segments is restored by treatment with cyclooxygenase inhibitors.[15,35] In humans, however, the role of vasoconstrictor

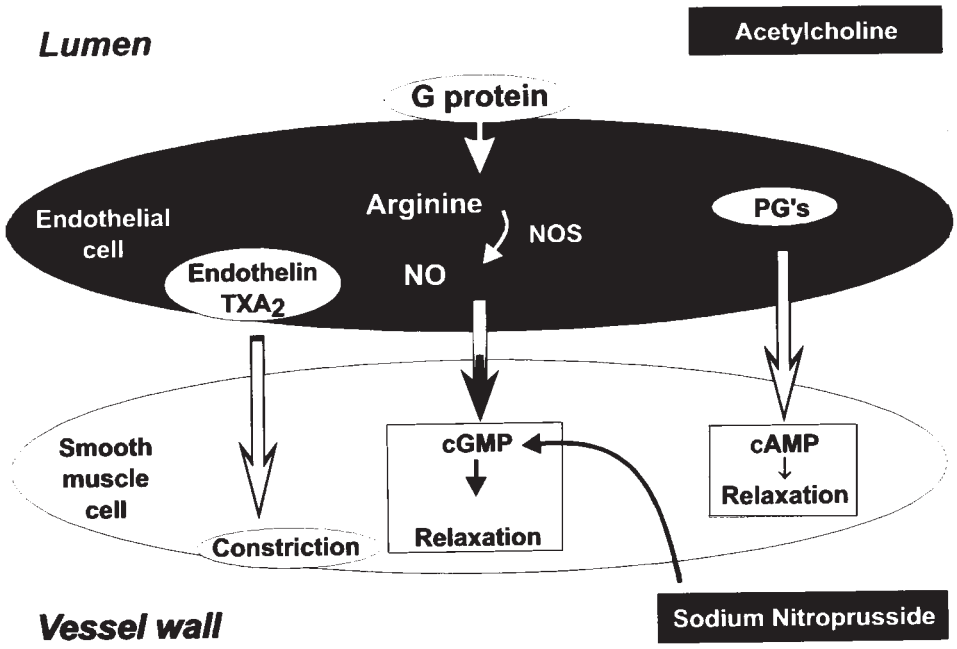

Fig 1. Depiction of role of endothelial nitric oxide *(NO)* and nitric oxide synthetase *(NOS)* in vasodilatory response to acetylcholine (endothelium-dependent response). In contrast, sodium nitroprusside, as exogenous nitric oxide donor, directly activates cyclic guanosine monophospate *(cGMP)* with resultant vasorelaxation. *TXA_2,* Thromboxane A_2; *PGs,* prostaglandins.

prostanoids is less clear. Flow-dependent vasodilation in healthy subjects, which may be used as an index of endothelial function, is abolished by L-NMMA but unaffected by aspirin, thus showing that it is entirely mediated by EDNO and independent of vasoactive prostanoids.[56] Moreover, the attenuated endothelium-dependent vasodilation after acetylcholine administration seen in patients with diabetes is not affected by pretreatment with cyclooxygenase inhibitors.[33,34]

The microcirculation and neuropathy. Several lines of evidence have indicated that microcirculation is also implicated in the pathogenesis of diabetic neuropathy, and in fact, the cause of diabetic neuropathy is a complex interplay between metabolic and microvascular defects. Hyperglycemia induces an increase in the polyol pathway by which glucose is metabolized to sorbitol via aldose reductase. Increased aldose reductase activity impairs myo-inositol uptake, which leads to decreased Na^+,K^+ ATPase activity and loss of electrical conduction in neural tissue.[57,58]

There is also a relationship between aldose reductase, Na^+,K^+-ATPase activity, and nitric oxide in the pathogenesis of diabetic neuropathy. First, Na^+,K^+-ATPase activity in normal arteries is dependent on an intact endothelium, which suggests a stimulatory action by EDNO.[59] Second, hyperglycemia causes decreased Na^+,K^+-ATPase activity in normal rabbit aorta, an effect that is preventable with the administration of aldose reductase inhibitors or with the raising of plasma myo-inositol levels.[30] Third, the administration of L-NMMA, an EDNO inhibitor, decreases Na^+,K^+-ATPase activity in the aortic wall.[24] In addition, L-NMMA administration reverses the protective effects of aldose reductase inhibitor treatment on nerve conduction velocity.[60] It therefore seems likely that microvascular endothelial dysfunction plays a significant role in the pathogenesis of diabetic neuropathy and that at least part of this is caused by the metabolic derangements of diabetes.

Recent studies from our laboratory have helped further define the relationship between microcirculation, diabetes, and neuropathy.[61,62] With laser Doppler scan imaging to measure the vasodilatory response to acetylcholine (endothelium-dependent) and sodium nitroprusside (an exogenous nitric oxide donor, endothelium-independent), we have found that the endothelium-dependent vasodilatation and

the axon reflex are impaired in the presence of diabetes and neuropathy but the endothelium-independent response is spared (Fig 1). This dysfunction may be attributed to an impaired production of nitric oxide. This is also correlated anatomically (with immunostaining techniques), in that expression of endogenous endothelial nitric oxide synthetase is reduced in patients with diabetic neuropathy.[62]

Other causes for diabetic neuropathy include a localized nerve "hypoxia," as the result of reduced endoneurial blood flow, increased vascular resistance,[63,64] and decreased endothelial production of nitric oxide.[60] Although microvascular dysfunction has been mainly implicated, the role of peripheral vascular disease remains considerable because it appears likely that a decrease in total limb blood flow would potentiate nerve ischemia.[65,66] Studies from the authors' clinical laboratory have shown that reversal of hypoxia (by arterial reconstruction) halts the progression of neuropathy, lending further support to the role of hypoxia in the pathogenesis of nerve dysfunction in diabetes mellitus.[67,68]

DIABETES AND CEREBROVASCULAR DISEASE

Compelling data from several large clinical studies have shown that diabetes is a major risk factor for stroke and that the incidence of ischemic stroke is at least 2.5-fold higher in patients with diabetes.[3-5] Moreover, the mortality and severity of stroke is higher among patients with diabetes.[69,70] The relative risk of stroke increases even further among patients with diabetes with established retinopathy, neuropathy, or nephropathy, thus suggesting that the presence of diabetes introduces additional microvascular and cerebrovascular pathophysiology, which may increase the frequency and severity of stroke in these patients.[71,72]

Elevated blood glucose levels are toxic to infarcted brain tissue, and stroke severity is greater in patients with hyperglycemia.[73,74] Among patients with diabetes, poor glycemic control doubles the risk of ischemic stroke, even after adjustment for other variables.[75] Abnormal cerebral blood flow may be seen in experimental diabetes, and among patients with diabetes and no history of cerebrovascular disease, single photon emission tomography scanning has shown multiple subclinical alterations in cerebral blood flow.[76] Hyperglycemia alone causes both a decrease in cerebral blood flow and an impaired cerebral vasodilatory response.[77] As noted previously, altered cerebral vascular reactivity occurs among patients with long-standing diabetes and may reflect a generalized cerebrovascular microangiopathy involving the brain resistance arterioles.[28]

Acute hyperglycemia and glucose exposure may also impair the autoregulation of cerebral blood flow. In vitro exposure of isolated cerebral arteries to high glucose concentrations causes vasodilation and inhibition of arterial tone, suggesting that both cerebrovascular tone and control of cerebral blood flow may be impaired during acute hyperglycemia.[78] Moreover, because removal of the endothelium abolishes this effect, this appears to be an endothelial-dependent and nitric oxide–mediated mechanism.

Multiple cerebrovascular metabolic abnormalities also contribute to the worse stroke outcome in hyperglycemia and diabetes.[79] Anaerobic metabolism of glucose during ischemia produces lactate, which accumulates inside brain cells and results in lower intracellular pH and cell death. As noted earlier, AGEs accumulate as a consequence of diabetes and may also contribute to the increased stroke severity in patients with diabetes because systemic administration of AGEs into animals with focal brain infarction increases the cerebral infarct size and damage.[80]

Because of the worse prognosis of stroke in patients with diabetes, efforts should be directed toward the reduction of the risk of stroke in these patients, including reduction or elimination of concomitant risk factors. In addition, among selected symptomatic and asymptomatic patients with a high-grade internal carotid artery stenosis, carotid endarterectomy has been shown to reduce the risk of stroke.[81,82] Because diabetes is associated with multiple cerebrovascular abnormalities, the safety of carotid endarterectomy in patients with diabetes may be questioned.[83] A recent report from the authors' institution summarized the experience with carotid endarterectomy in patients with diabetes.[84] During a 6-year period, 732 carotid endarterectomy procedures were performed, 284 (39%) of which were in patients with diabetes mellitus. The total operative mortality rate was 0.3%. There were 11 perioperative neurologic events (1.5%; eight strokes, and three transient ischemic attacks) during the entire period, six (2.1%) of which were among patients with diabetes and five (1.1%) of which were among patients without diabetes, a difference that was not statistically significant. Of the eight strokes, three (1.0%) occurred in patients with diabetes and five (1.1%) in patients without diabetes, which again was not statistically significant. Moreover, it was shown that diabetes is not an independent risk factor for postoperative cardiac morbidity among patients who undergo carotid endarterectomy. These results showed that carotid

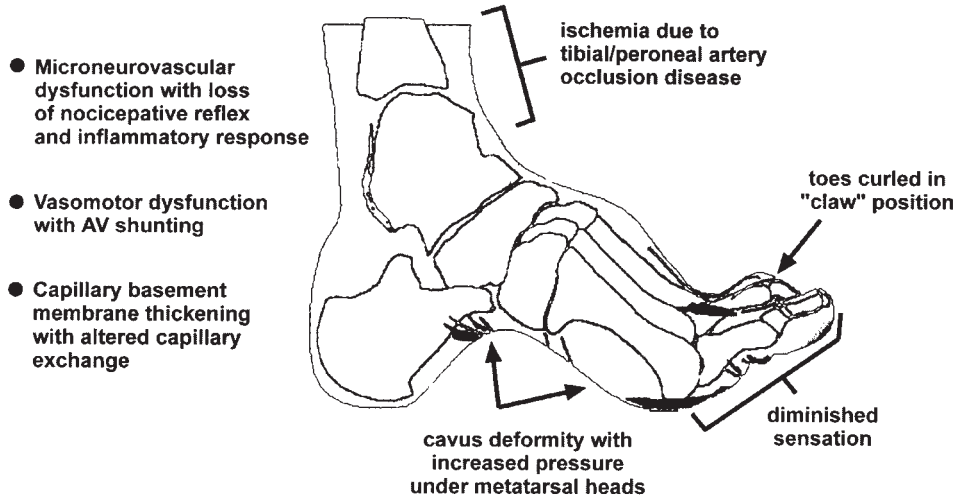

Fig 2. Underlying mechanisms of diabetic foot ulceration. Sensorimotor neuropathy leads to diminished sensation and small muscle atrophy in foot, resulting in flexed metatarsals, metatarsal head prominence, and clawing of toes. Altered architecture of foot, coupled with ischemia and microvascular dysfunction, ultimately leads to ulceration.

endarterectomy may be safely performed in patients with diabetes, with neurologic morbidity and mortality rates that are comparable with those of the nondiabetic population.

THE DIABETIC FOOT

Problems of the diabetic foot are the most common cause for hospitalization in patients with diabetes, with an annual health care cost of more than $1 billion.[85] Diabetes is a contributing factor in half of all lower extremity amputations in the United States, and the relative risk for amputation is 40 times greater in people with diabetes.[86] Diabetic foot ulceration will affect 15% of all individuals with diabetes during their lifetime and is clearly a significant risk factor in the pathway to limb loss.[87] The principal pathogenetic mechanisms in diabetic foot disease are neuropathy, infection, microvascular dysfunction, and ischemia; acting together, they contribute to the sequence of tissue necrosis, ulceration, and gangrene (Fig 2).

As discussed previously, the cause of diabetic neuropathy is unknown and most likely multifactorial. Peripheral neuropathy is a common complication of diabetes, afflicting as many as 50% to 60% of all patients[88,89] and is present in more than 80% of patients with diabetes with foot lesions, thus further emphasizing the direct relationship between neuropathy and foot ulceration.[90] Broadly classified as focal and diffuse neuropathies, the latter is more common and includes the autonomic and chronic sensorimotor polyneuropathies, which both contribute to foot ulceration.

The spectrum of infection in diabetic foot disease ranges from superficial ulceration to extensive gangrene with fulminant sepsis. Classical signs of infection may not always be present in the infected diabetic foot because of the consequences of neuropathy, alterations in the foot microcirculation, and leukocyte abnormalities. Fever, chills, and leukocytosis may be absent in up to two thirds of patients with diabetes with extensive foot infections, and hyperglycemia is often the sole presenting sign.[91] Therefore, a complete examination of the infected areas is mandatory and the wound should be thoroughly inspected, including unroofing of all encrusted areas, to determine the extent of involvement.

Most infections are polymicrobic, the most common pathogens being *staphylococci*, *streptococci*, and *enterococci*; anaerobes and gram-negative bacilli are also commonly cultured.[92] Cultures should be obtained from the base of an ulcer or abscess cavity after debridement. Osteomyelitis is common in diabetic foot ulceration, appearing in almost 70% of benign-appearing ulcers[93] and should be presumed if the bone is palpated on probing in an open ulcer.[94]

Ischemia is a fundamental consideration to the vascular surgeon faced with the diabetic foot.[95] The combination of motor and sensory neuropathy along with loss of the neurogenic inflammatory

response and microcirculatory dysfunction results in a biologically compromised foot. Even moderate ischemia may lead to ulceration under these circumstances, and thus the concept of ischemia must be modified in making decisions about arterial reconstruction. The biologically compromised foot necessitates maximum circulation to heal an ulcer. This leads to three significant principals: (1) all diabetic foot ulcers should be evaluated for an ischemic component; (2) correction of a moderate degree of ischemia will improve healing in the biologically compromised diabetic foot; and (3) whenever possible, the arterial reconstruction should be designed to restore normal arterial pressure to the target area.

Treatment of the diabetic foot should be directed towards the pathogenic factors outlined previously. In general, this can be broken down into a few simple guidelines:[96]

1. Prompt control of infection. This assumes first priority in the management of any diabetic foot problem.
2. Evaluation for ischemia.
3. Prompt arterial reconstruction once active infection has resolved.
4. Secondary procedures, such as further debridement, toe amputations, local flaps, and even free flaps, may then be carried out separately in the fully vascularized foot.

DIABETES AND LOWER EXTREMITY VASCULAR DISEASE

Unlike microvascular disease, which is unique to diabetes and its metabolic alterations, the cause of lower extremity ischemia is similar in both patients with and without diabetes and is the result of accelerated atherosclerosis. One notable difference between these populations is the pattern and location of the occlusive atherosclerotic lesion. As noted earlier, there is no evidence for an occlusive lesion at the arteriolar level ("small-vessel disease") in patients with diabetes. However, patients with diabetes are more likely to have atherosclerotic disease affecting the infrageniculate arteries, with sparing of the foot arteries,[97] which allows for successful arterial reconstruction to these distal vessels.

Because the foot vessels are often patent in the patient with diabetes and because of the success of bypass grafting to these vessels, an appropriate evaluation for ischemia is essential in patients with diabetes. Unless recognized and corrected, limb salvage efforts will fail even if infection and neuropathy have been appropriately treated. The most important observation is the presence or absence of a palpable foot pulse; in simplest terms, if the foot pulses are not palpable, it can be assumed that occlusive disease is present.

A variety of noninvasive arterial tests may be ordered. However, in the presence of diabetes, all of these tests have significant limitations. Medial arterial calcinosis occurs frequently and unpredictably in patients with diabetes, and its presence can result in noncompressible arteries with artifactually high segmental systolic pressures and ankle-brachial indices. Lower levels of calcification in the toe vessels support the use of toe systolic pressures,[98] but their use is often limited by the proximity of the foot ulcer to the cuff site. Segmental Doppler wave forms and pulsed volume recordings are unaffected by medial calcification, but evaluation of these waveforms is primarily qualitative and not quantitative. In addition, the quality of the waveforms is affected by peripheral edema, and the presence of ulceration precludes accurate cuff placement. Regional transcutaneous oximetry measurements are also unaffected by medial calcinosis, and recent studies have noted its reliability in predicting healing of ulcers and amputation levels.[99] Limitations, including a lack of equipment standardization, user variability, and a large "gray area" of values, preclude its applicability. Furthermore, transcutaneous oximetry measurements are higher in patients with diabetes with foot ulcers when compared with the nondiabetic population, which further limits the ability of this test to predict ischemia.[100] Therefore, although they have been used to predict healing in patients without diabetes, a high value may not correlate with healing potential in the presence of diabetes.

PRINCIPLES OF ARTERIAL RECONSTRUCTION IN THE DIABETIC FOOT

The limitations of noninvasive vascular testing in patients with diabetes with foot ulceration emphasize the continued importance of a thorough bedside evaluation and clinical judgment. The status of the foot pulse is the most important aspect of the physical examination. An absent foot pulse is an indication for contrast arteriography in the clinical setting of tissue loss, poor healing, or gangrene, even if neuropathy may have been the antecedent cause of skin breakdown or ulceration. Importantly, because the foot vessels are often spared by the atherosclerotic occlusive process, even when the tibial arteries are occluded, it is essential that arteriograms not be terminated at the midtibial level. The complete infrapopliteal circula-

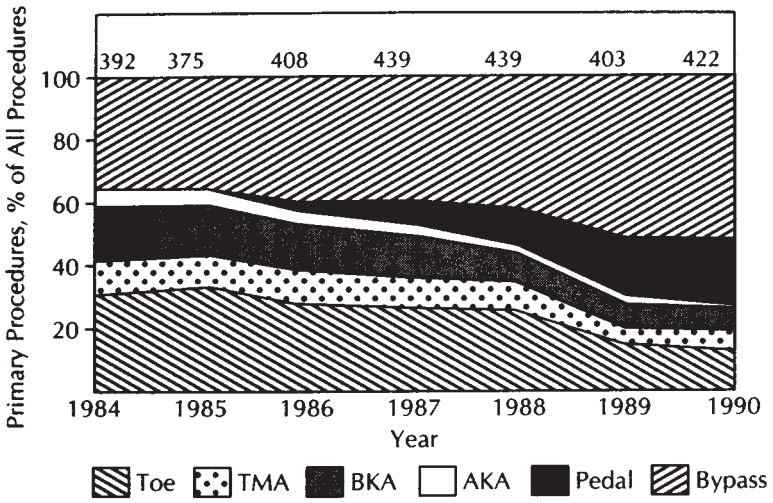

Fig 3. Since 1984, there has been a significant drop in major amputations at the authors' institution, concomitant with a rise in distal lower extremity arterial reconstruction. (With permission from LoGerfo FW, Gibbons GW, Pomposelli FB Jr, et al. Trends in the care of the diabetic foot: expanded role of arterial reconstruction. Arch Surg 1992;127:617-21.).

tion should be incorporated, including the foot vessels. The advent of digital subtraction angiography has greatly helped in the visualization of these distal vessels. Both anteroposterior and lateral foot views should be included. Excessive plantar flexion should be avoided because this may impede flow in the dorsalis pedis artery.

A complete arteriogram will facilitate choosing an outflow artery that will restore a palpable foot pulse. Proximal bypass grafting to the popliteal or tibioperoneal arteries may restore foot pulses. More often, however, because of the pattern of occlusive disease in the patient with diabetes, bypass grafting to the popliteal or even tibial arteries cannot accomplish this goal because of more distal obstruction. Similarly, although excellent results have been reported with peroneal artery bypass grafting,[101] the peroneal artery is not in continuity with the foot vessels and may not achieve maximal flow, particularly to the forefoot, to achieve healing.

Restoration of the foot pulse is a fundamental goal of revascularization in the diabetic foot. Autogenous vein grafting to the dorsalis pedis artery represents a technical advance that provides durable and effective limb salvage.[102] Fundamental to the success of the dorsalis pedis bypass graft is meticulous technique and its appropriate use. The principal indication for the pedal graft is when there is no other vessel that has continuity with the foot, particularly in cases with tissue loss. Although the dorsalis pedis bypass graft may be effectively used for salvage of ischemic heel ulceration,[103] preference should be given to the posterior tibial artery if it is in continuity with the foot. Dorsalis pedis bypass grafting is unnecessary when a more proximal bypass graft will restore foot pulses and should not be done if there is an inadequate length of autogenous vein. In addition, if the dorsum of the foot is extensively infected and the peroneal artery is of good quality on the preoperative arteriogram, preference should be given to peroneal artery bypass grafting.

The distal location of the dorsalis pedis artery theoretically necessitates a long venous conduit, which is often not attainable. However, with the use of the popliteal or distal superficial femoral artery as an inflow site, a shorter length of vein may be used, with excellent long-term patency.[104] This is particularly true in the patient with diabetes, again because of the pattern of atherosclerotic disease. The vein graft to the dorsalis pedis artery can be prepared as an in situ, reversed, or non-reversed vein graft, without any significant difference in outcome.[105] Concomitant angioscopic assessment of the harvested vein should be performed to detect any intraluminal abnormalities.[106] In the absence of saphenous vein, autogenous arm vein grafts may be used and provide comparable limb salvage rates.[107] The authors have had no experience with prosthetic bypass grafting to the dorsalis pedis artery and do not recommend its use.

Because of the presence of medial arterial calcification in patients with diabetes, severe calcification of the outflow artery may be encountered, but this should not preclude attempts at arterial reconstruction.[108] Moreover, active infection in the foot is not a contraindication to dorsalis pedis bypass grafting, as long as the infectious process is controlled and away from the proposed incision area.[109]

We have recently reported our experience with dorsalis pedis arterial bypass grafting in 367 patients during an 8-year period, with a perioperative mortality rate of 1.8%.[110] Tissue loss was an indication for surgery in almost 85% of the patients. Twenty-nine grafts (7.5%) failed within the first 30 days, but 19 were successfully revised when a correctable technical problem was found at reoperation. The actuarial primary and secondary patency and limb salvage rates were 68%, 82%, and 87%, respectively, at 5 years of follow-up.

After successful revascularization, secondary procedures may be performed for both limb and foot salvage. Chronic ulcerations may be treated with ulcer excision, arthroplasty, or hemiphalangectomy. In the patient with extensive tissue loss, both local flaps and free flaps may be used. Because of the architecture of the diabetic foot, underlying bony structural abnormalities are often the cause of ulceration and may be corrected with metatarsal head resection or osteotomy. Heel ulcers may be treated with partial calcanectomy and local (eg, flexor tendon) or even free flap coverage.

SUMMARY

This aggressive and systematic approach to diabetic foot disease has resulted in improved limb salvage among patients with diabetes. At the authors' institution, there has been a significant reduction in every category of lower limb amputation since 1984 (Fig 3).[111] Concomitant with this decrease has been an increase in the number of patients who undergo arterial reconstruction and a greater application of the dorsalis pedis bypass graft. An awareness and understanding of the complex pathophysiology of diabetic microvascular and macrovascular disease will lead to further decreases in lower limb amputation and reduce the overall morbidity and mortality of diabetes in general.

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