

Diabetes and Critical Limb Ischemia

Understanding the prevalence, pathology, and common misconceptions associated with this condition may help us to improve upon current limb salvage rates.

BY CAMERON M. AKBARI, MD

Diabetes mellitus is found in more than 6% of the US population, and the incidence continues to increase to epidemic levels, with almost 800,000 new cases diagnosed annually. Multiple epidemiological studies spanning several decades have clearly established the link between diabetes and vascular disease. The Framingham Study of more than 5,000 subjects demonstrated 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 twofold in men and threefold for women. Along the spectrum of lower-extremity arterial occlusive disease, the association with diabetes becomes even greater. For example,

"The prevalence of intermittent claudication is at least two to four times higher among patients with diabetes."

the prevalence of intermittent claudication is at least two to four times higher among patients with diabetes, and among all other cardiovascular risk factors, diabetes continues to impart the strongest association for the development of critical limb ischemia (CLI).

THE DIABETIC FOOT

Foot ulceration is one of the most common and formidable complications of diabetes, affecting almost 20% of all diabetic patients during their lifetime. Despite advances in management, foot problems continue to be the most common cause of hospitalization in diabetic patients, with an annual health care cost of more than \$1 billion. Diabetes remains the single strongest risk factor for limb loss, contributing to half of all lower-extremity amputations in the US, and the relative risk for leg amputation is 40 times greater among diabetic patients. Moreover, up to 50% of diabetic amputees will undergo a second leg amputation within 5 years of the first.

The pathway to foot ulceration and limb loss among patients with diabetes has been well described, and the principle pathogenic mechanisms are neuropathy, microvascular disease, infection, and ischemia. Sensorimotor neuropathy leads to loss of the protective



Figure 1. The common appearance of the diabetic foot, with characteristic metatarsal prominence, intrinsic muscle atrophy, and clawing of the toes.

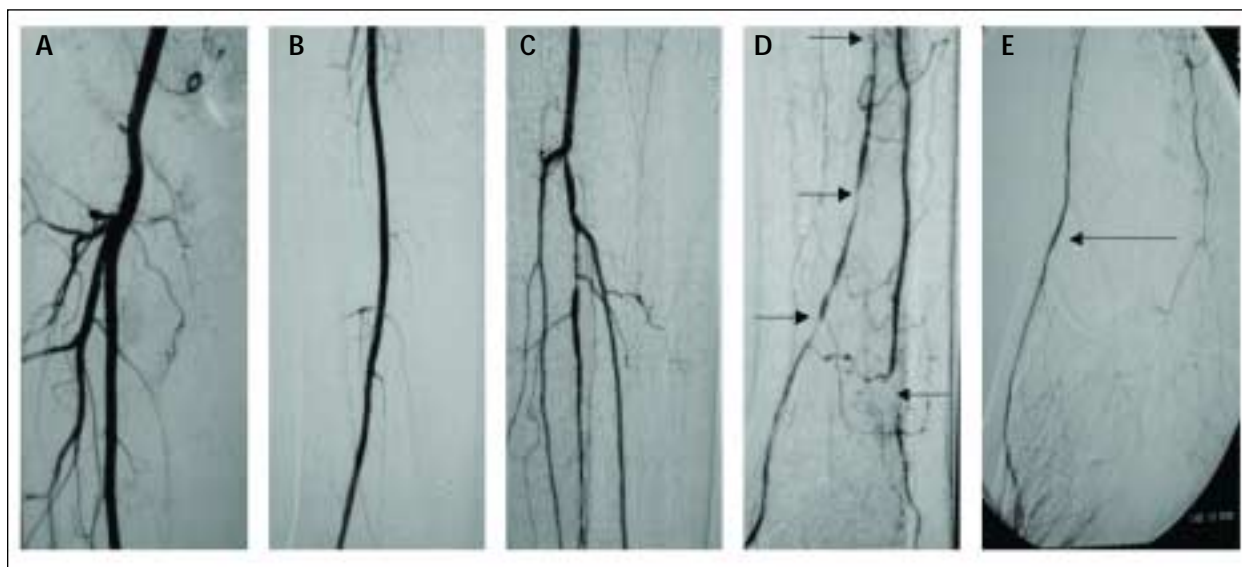


Figure 2. Lower-extremity arteriogram in a patient with diabetes and foot gangrene displaying the classic anatomic pattern of vascular disease in diabetes. Note the normal appearance of the femoral and popliteal arteries (A-C), with extensive occlusive disease of the infrapopliteal (tibial) vessels. Specifically, the peroneal artery becomes occluded after its origin, and the posterior tibial and anterior tibial arteries display multiple occlusions and stenoses (D, arrows). However, the dorsalis pedis artery is patent (E, arrow) and of adequate caliber to allow for successful bypass grafting.

sensation of pain, whereas motor fiber destruction results in small-muscle atrophy in the foot, resulting in the characteristic “claw” foot and metatarsal prominence (Figure 1). This causes abnormal pressure points to develop on the bony prominence without sensation, with subsequent callus formation, cracking, erosion, and ulceration. Additionally, autonomic neuropathy causes loss of sympathetic tone (which results in increased arteriovenous shunting and inefficient nutrient flow) and autonomic denervation of oil and sweat glands leads to dry skin, fissures, and further predisposition to skin breakdown and ulceration.

Some patients may experience a painful variant of distal polyneuropathy. Typical complaints include a “toothache”-like or shooting “electrical shock” pain, which is constant, symmetrically bilateral, and often accompanied by hyperesthesias. Although differentiation from ischemic rest pain is usually possible based on history and physical findings, some patients may have a shared component, and objective quantification of the degree of ischemia becomes important.

Diabetes is also characterized by a microvascular dysfunction, with increased vascular permeability and impaired autoregulation of blood flow and vascular tone. Although multiple theories have been postulated as to the etiology of accelerated microangiopathy, it is likely that several biochemical derangements work syn-

ergistically at multiple areas within the arteriolar and capillary level, including the basement membrane, smooth muscle cell, and the endothelial cell. Thickening of the capillary basement membrane is the dominant structural change in both neuropathy and retinopathy, and in the diabetic foot, capillary basement membrane thickening may theoretically impair the migration of leukocytes and the hyperemic response after injury, thereby increasing the susceptibility of the diabetic foot to infection.

A variety of other microvascular abnormalities may be demonstrated in the diabetic foot. Both capillary blood flow and the maximal hyperemic response to stimuli are reduced in the diabetic foot, suggesting that a functional microvascular impairment is a major contributing factor for diabetic foot problems. Furthermore, diabetes also affects the axon reflex (neurogenic vasodilatation), which further impairs the ability of the diabetic foot to achieve maximal blood flow after injury.

Endothelial function is also abnormal in patients with both insulin-dependent and noninsulin-dependent diabetes mellitus, and multiple mechanisms have been proposed, including abnormalities in the nitric oxide pathway, abnormal production of vasoconstrictor prostanoids, intracellular signaling, reduction in $\text{Na}^+ - \text{K}^+$ ATPase activity, and advanced glycosylated end products.

NOMENCLATURE AND MISCONCEPTION

The microvascular disease of diabetes should not be confused with so-called “small-vessel disease.” This term has been used erroneously to describe the nature and pattern of diabetic vascular disease and refers to the common misconception of an untreatable occlusive lesion in the microcirculation. In common practice, the term has become equated with the futility of limb salvage efforts in patients with diabetes. However, multiple prospective anatomic and physiologic studies, and clinical experience with 2 decades of successful distal revascularization in the diabetic patient, have clearly demonstrated the absence of arteriolar occlusive (small-vessel) disease. Dispelling the notion of small-vessel disease has been fundamental to diabetic limb salvage because arterial reconstruction is almost always possible and successful in these patients.

In contrast to the microcirculatory abnormalities, the macroangiopathy of diabetes is similar to that occurring in the nondiabetic population and is due to atherosclerotic occlusive disease. The major difference between these two populations of patients is the pattern and location of the occlusive lesions. Whereas occlusive lesions of the superficial femoral and popliteal segment are commonly found in the nondiabetic patient with limb ischemia, diabetic patients commonly have occlusive disease involving the infrageniculate, or tibial, arteries (Figure 2). However, the foot arteries are almost invariably patent, which allows for extreme distal arterial reconstruction despite extensive tibial or even proximal multisegmental disease (Figure 3). In addition, the popliteal, superficial femoral, and more proximal arteries are less likely to be affected by atherosclerosis, which allows these vessels to serve as an inflow source for distal bypasses.

Conventional use of the term *CLI* has been applied to patients with arterial occlusive disease and either rest pain or tissue loss (Fontaine classification stage III and IV). Along the continuum of lower-extremity vascular disease, CLI is the terminus or end-stage, and represents the most severe manifestation of the disease. Among patients with diabetes, the concept of CLI is modified. Because of the unique biologic

milieu of the diabetic foot, and due to the combined roles of neuropathy and microneurovascular dysfunction, even a moderate degree of ischemia will lead to ulceration and progressive tissue loss. The corollary is also true, in that correction of ischemia (even a moderate degree) in the biologically compromised diabetic foot will lead to healing and improved limb salvage results.

“The absence of a palpable foot pulse strongly suggests underlying ischemia in the diabetic patient with tissue loss in the foot.”

TESTING AND SCREENING

Assessment of the arterial circulation is a fundamental consideration in the overall treatment algorithm for diabetic limb salvage. Advances in the surgical treatment of diabetic arterial occlusive disease, particularly the use of paramalleolar bypass grafting and refined techniques in balloon angioplasty, have markedly decreased the number of patients previously deemed inoperable, thereby highlighting the importance of early and accurate diagnosis in the diabetic foot with suspected CLI. The diabetic foot with tissue loss needs maximal perfusion to heal. Evaluation should consist

chiefly of the physical examination, focused specifically on the status of the foot pulse. The absence of a palpable foot pulse strongly suggests underlying ischemia in the diabetic patient with tissue loss in the foot.

Noninvasive arterial testing has a variable role in the patient with diabetes and suspected CLI. For example, in the patient with no tissue loss and subjective complaints of pain with suspected painful neuropathy, noninvasive testing may be helpful to rule out a shared component of ischemic rest pain. On the other hand, noninvasive tests offer little additional information in the diabetic patient with foot ulceration and nonpalpable pulses. Due to the continuum of biologic compromise and ischemia in the diabetic foot, there simply is



Figure 3. Arteriogram of a popliteal to dorsalis pedis bypass graft.

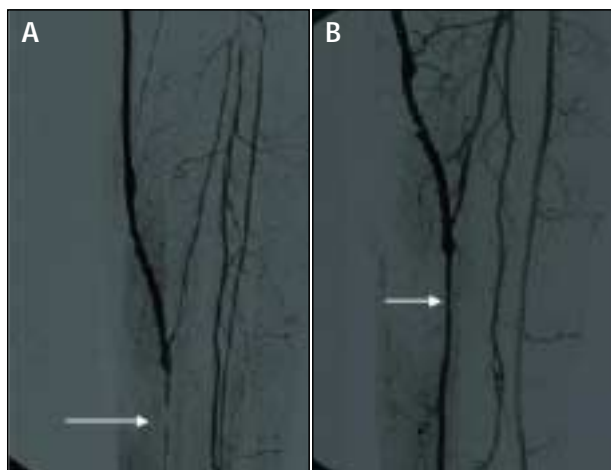


Figure 4. This patient presented 2 years after a successful posterior tibial artery bypass with ultrasound findings suggestive of progressive distal disease and impending graft failure, confirmed by arteriography (A, arrow). Operative intervention was deemed high risk because of a myocardial infarction 1 month earlier, and therefore, percutaneous intervention with angioplasty of the tibial segment was performed successfully (B, arrow).

no fixed number in any test that reliably predicts healing, and false reliance on the results of noninvasive testing may lead to failure of any limb salvage effort. Additionally, all of these tests have significant limitations in the presence of diabetes. For example, medial arterial calcinosis occurs frequently and unpredictably in the diabetic patient, and its presence can lead to artifactually elevated ankle-brachial ratios.

With the absence of foot pulses on physical examination, in the setting of tissue loss, poor healing, or gangrene, it can be assumed that ischemia is present and needs to be corrected for limb salvage. If ischemia is suspected, arteriography of the entire lower extremity should be performed. Based on the pattern of vascular disease in the diabetic patient, with sparing of the pedal vessels, the arteriogram must include the foot vessels in both the lateral and anterior views for a complete assessment. Concern about contrast-induced renal dysfunction in the presence of diabetes should not preclude the performance of a high-quality arteriogram of the entire distal circulation. Several prospective studies have documented that the incidence of contrast-induced nephropathy is not higher in the diabetic patient without pre-existing renal disease, particularly with the judicious use of hydration and renal protective agents.

The goal of arterial reconstruction is to restore maximal perfusion to the foot and ideally restore a palpable

foot pulse. Possible approaches include endovascular techniques (angioplasty and stenting), bypass grafting (using autogenous or prosthetic grafts), or a combination of the two. Ultimately, the choice of procedure should be individualized based on the patient's anatomy, comorbidities, and preoperative assessment; the goal is to provide the most durable procedure with the least risk (Figure 4). For example, angioplasty alone may be beneficial to the patient with an isolated iliac artery stenosis or a focal lesion in the superficial femoral artery, but may also be used in combination with an infrainguinal bypass in the diabetic patient with multi-level disease.

CONCLUSION

In the diabetic patient with CLI, the characteristic anatomic pattern of long segment tibial occlusive disease with sparing of the foot vessels usually requires bypass grafting to the dorsalis pedis or distal posterior tibial vessels for limb salvage. Nearly 2 decades of experience with pedal grafts has demonstrated superior patency and limb salvage outcomes. At the same time, more sophisticated and newer techniques in endovascular approaches have allowed for even better outcomes because more options may be offered to the patient with prohibitive comorbidities. Greater flexibility in treatment options, based on patient characteristics and clinical data, will offer the highest success for limb salvage in the patient with diabetes and peripheral vascular disease.

Cameron M. Akbari, MD, is the Director of the Vascular Diagnostic Laboratory and Attending Vascular Surgeon at Washington Hospital Center, Washington, DC. He has disclosed no financial interest in any product or manufacturer mentioned herein. Dr. Akbari may be reached at (202) 877-8050; cameron.akbari@medstar.net. ■

1. LoGerfo FW, Coffman JD. Vascular and microvascular disease of the foot in diabetes. *N Engl J Med*. 1984;311:1615-1619.
2. Akbari CM, LoGerfo FW. Diabetes and peripheral vascular disease. *J Vasc Surg*. 1999;30:373-384.
3. Akbari CM, LoGerfo FW. Peripheral vascular disease in the person with diabetes. In: Porte D, Sherwin RS, Baron AD, eds. *Ellenberg and Rifkin's Diabetes Mellitus*. 6th ed. New York: McGraw-Hill; 2003:845-857.
4. Akbari CM, LoGerfo FW. The micro- and macrocirculation in diabetes mellitus. In: Veves A, ed. *A Clinical Approach to Diabetic Neuropathy*. 1st ed. New York: Humana Press; 1998:319-331.
5. Akbari CM, LoGerfo FW. Saphenous vein bypass to pedal arteries in diabetic patients. In: Yao JST, Pearce WH, eds. *Techniques in Vascular and Endovascular Surgery*. Norwalk: Appleton and Lange; 1998:227-232.
6. Akbari CM, LoGerfo FW. Diabetes and peripheral vascular disease. In: Hobson RW, Veith FJ, Wilson SE. *Vascular Surgery: Principles and Practice*. 3rd ed. New York: Marcel Dekker; 2004:601-610.
7. Akbari CM, Macsata R, Smith BM, et al. Overview of the diabetic foot. *Semin Vasc Surg*. 2003;16:3-11.
8. Akbari CM, Pomposelli FB, Jr, Gibbons GW, et al. Lower extremity revascularization in diabetes: late observations. *Arch Surg*. 2000;135:452-456.