

Diabetes & Cardiovascular Disease Review



A Publication of the
American Diabetes Association /
American College of Cardiology
Make the Link! Initiative

Issue 6:
Peripheral Arterial
Disease in Diabetes

Peripheral Arterial Disease in Diabetes

Peripheral arterial disease (PAD) is a condition characterized by atherosclerotic occlusive disease of the lower extremities. PAD is a major risk factor for lower-extremity amputation and is also accompanied by a high likelihood for symptomatic cardiovascular and cerebrovascular disease. Although much is known about PAD in the general population, the assessment and management of PAD in individuals with diabetes is less clear. At present, there are no established guidelines regarding the care of patients with both diabetes and PAD.

The American Diabetes Association recently conducted a consensus conference to review current knowledge regarding PAD in diabetes. After lectures by experts in the fields of endocrinology, cardiology, vascular surgery, orthopedic surgery, podiatry, and nursing, a vascular medicine panel developed a consensus statement that addressed the epidemiology, impact, biology, and evaluation and treatment of PAD in diabetes.

This article includes excerpts from the statement published in *Diabetes Care* (December 2003). To access the full statement, visit <http://care.diabetesjournals.org/cgi/content/full/26/12/3333>.

Epidemiology and Impact of PAD in Diabetes

PAD affects 12 million Americans. Data from the Framingham Heart Study¹

revealed that 20% of symptomatic patients with PAD had diabetes, but this statistic probably greatly underestimates the prevalence, given that many more people with PAD are asymptomatic. It has been reported that of the people with PAD, over one-half are asymptomatic or have atypical symptoms, about one-third have claudication, and the remainder have more severe forms of the disease.²

The most common symptom of PAD is intermittent claudication, defined as pain, cramping, or aching in the calves, thighs, or buttocks that appears reproducibly with walking exercise and is relieved by rest. More extreme presentations of PAD include rest pain, tissue loss, or gangrene; these limb-threatening manifestations of PAD are collectively termed “critical limb ischemia” (CLI).

PAD is also a major risk factor for lower-extremity amputation, especially in patients with diabetes. Moreover, even for the asymptomatic patient, PAD is a marker for systemic vascular disease involving coronary, cerebral, and renal vessels, leading to an elevated risk of events, such as myocardial infarction (MI), stroke, and death.

Diabetes and smoking are the strongest risk factors for PAD. Other well-known risk factors are advanced age, hypertension, and hyperlipidemia.³

In people with diabetes, the risk of PAD is increased by age, duration of diabetes, and presence of peripheral neuropathy. African Americans and Hispanics with diabetes have a higher prevalence of PAD than non-Hispanic whites, even after adjustment for other known risk factors and the excess prevalence of diabetes. Diabetes is most strongly associated with femoral-popliteal and

tibial (below the knee) PAD, whereas other risk factors (e.g., smoking and hypertension) are associated with more proximal disease in the aorto-ilio-femoral vessels.

The true prevalence of PAD in people with diabetes has been difficult to determine, because most patients are asymptomatic, many do not report their symptoms, there is not uniform agreement on screening modalities, and pain perception may be blunted by the presence of peripheral neuropathy. For these reasons, a patient with diabetes and PAD may be more likely to present with an ischemic ulcer or gangrene than a patient without diabetes.

The reported prevalence of PAD is also affected by the methods by which the diagnosis is sought. Two commonly used tests are the absence of peripheral pulses and the presence of claudication. Both, however, suffer from insensitivity. A more accurate test is the ankle-brachial index (ABI), which involves measuring the systolic blood pressures in the ankles (dorsalis pedis and posterior tibial arteries) and arms (brachial artery) using a handheld Doppler and then calculating a ratio. Simple to perform, it is a noninvasive, quantitative measurement of the patency of the lower-extremity arterial system. The ABI has been validated against angiographically confirmed disease and found to be 95% sensitive and almost 100% specific.⁴ There are some limitations, however, in using the ABI. Calcified, poorly compressible vessels in the elderly and some patients with diabetes may artificially elevate values. The ABI may also be falsely negative in symptomatic patients with moderate aortoiliac stenoses. These issues complicate the evaluation of an individual patient but

What's Inside

- ▶ Reproducible patient page:
All About Peripheral Arterial Disease

are not prevalent enough to detract from the usefulness of the ABI as an effective test to screen for and diagnose PAD in patients with diabetes.

Using the ABI, one survey⁵ found a prevalence of PAD to be 20% in people with diabetes >40 years of age. Moreover, another survey of patients with diabetes >50 years of age showed a prevalence of PAD of 29%.⁶

Impact of PAD. The impact of PAD can be assessed by its progression, its symptoms, and the excess cardiovascular events associated with systemic atherosclerosis. Approximately 27% of patients with PAD demonstrate progression of symptoms over a 5-year period, with limb loss occurring in 4%. While the majority of patients remain stable in their lower-limb symptomatology, there is a striking excess cardiovascular event rate over the same 5-year time period, with 20% sustaining nonfatal events (MI and stroke) and a 30% mortality rate.⁷ For individuals with CLI, the outcomes are worse: 30% will have amputations and 20% will die within 6 months.⁸ The natural history of PAD in patients with diabetes has not specifically been studied longitudinally, but it is known from prospective clinical trials of risk interventions that the cardiovascular event rates in patients with PAD and diabetes are even higher than those of their nondiabetic counterparts.

Diagnosing PAD is of clinical importance for two reasons: 1) to identify a

patient who has a high risk of subsequent MI or stroke regardless of whether PAD symptoms are present and 2) to treat symptoms of PAD, which may be associated with functional disability and limb loss. PAD is often more subtle in its presentation in patients with diabetes than in individuals without diabetes. In contrast to the focal and proximal atherosclerotic lesions of PAD found typically in other high-risk patients, in diabetic patients, the lesions are more likely to be more diffuse and distal. Importantly, PAD in diabetes is usually accompanied by peripheral neuropathy with impaired sensory feedback. Thus, a classic history of claudication may be less common. However, a patient may elicit more subtle symptoms, such as leg fatigue and slow walking velocity, and simply attribute them to getting older. It has been reported that patients with PAD and diabetes experience worse lower-extremity function than patients with PAD alone.⁹ Also, diabetes patients who have been identified with PAD are more prone to the sudden ischemia of arterial thrombosis or may have a pivotal event leading to neuroischemic ulceration or infection that rapidly results in an acute presentation with critical limb ischemia and risk of amputation. By identifying a patient with subclinical disease and instituting preventative measures, it may be possible to avoid acute, limb-threatening ischemia.

PAD in diabetes also adversely affects quality of life, contributing to long-term disability and functional impairment that is often severe. Patients with claudication have a slower walking speed (generally <2 mph) and a limited walking distance. This may result in a “cycle of disability” with progressive deconditioning and loss of function. Finally, there are significant economic costs of health care, reduced productivity, and personal expenses associated with a chronic manifestation of atherosclerotic disease such as PAD.

Diagnosis and Evaluation of PAD in Diabetes

The initial assessment of PAD in patients with diabetes should begin with a medical history and physical examination to help identify those patients with PAD risk factors, symptoms of claudication, rest pain, and/or functional impairment. There

Table 2.

Criteria for Testing for PAD Using the ABI

1. Perform a screening ABI in patients with diabetes who are >50 years of age, and, if normal, repeat the test every 5 years.
2. Consider a screening ABI in patients with diabetes who are <50 years of age and have other PAD risk factors (e.g., smoking, hypertension, hyperlipidemia, or duration of diabetes >10 years).
3. Perform a diagnostic ABI in any patient with symptoms of PAD.

are many alternative causes of leg pain on exercise, including spinal stenosis, and they should be excluded. PAD patients present along a spectrum of severity, ranging from no symptoms, intermittent claudication, and rest pain to nonhealing wounds and gangrene.

A thorough walking history will elicit claudication symptoms. Because these symptoms are often not reported, patients should be asked specifically about them. Two important components of the physical examination are visual inspection of the foot and palpation of peripheral pulses. Dependent rubor, pallor on elevation, absence of hair growth, dystrophic toenails, and cool, dry, fissured skin are signs of vascular insufficiency and should be noted. The interdigital spaces should be inspected for fissures, ulcerations, and infections.¹⁰

Palpation of peripheral pulses should be a routine component of the physical examination and should include assessment of the femoral, popliteal, and pedal vessels. It should be noted that pulse assessment is a learned skill and has a high degree of interobserver variability, with high false-positive and false-negative rates. The dorsalis pedis pulse is reported to be absent in 8.1% of healthy individuals, and the posterior tibial pulse is absent in 2.0%. Nevertheless, the absence of both pedal pulses, when assessed by a person experienced in this technique, strongly suggests the presence of vascular disease.

Noninvasive evaluation for PAD: ABI. As stated earlier, the ABI is a reproducible

Table 1.

Diagnostic Criteria for PAD Using the ABI

ABI	
0.91–1.30	Normal
0.70–0.90	Mild obstruction
0.40–0.69	Moderate obstruction
<0.40	Severe obstruction
>1.30*	Poorly compressible

*Suggests poorly compressible arteries at the ankle level due to medial arterial calcification and renders the diagnosis of PAD by ABI alone less reliable.

and reasonably accurate, noninvasive measurement for the detection of PAD and the determination of disease severity.

ABI is measured by placing the patient in a supine position for 5 minutes. Systolic blood pressure is measured in both arms, and the higher value is used as the denominator of the ABI. Systolic blood pressure is then measured in the dorsalis pedis and posterior tibial arteries by placing the cuff just above the ankle. The higher value is the numerator of the ABI in each limb. The diagnostic criteria for PAD based on the ABI are listed in Table 1, and criteria for testing for PAD using the ABI are included in Table 2.

Additional evaluation. Additional testing may include the following:

Vascular lab evaluation, segmental pressures, and pulse volume recordings: Performed in the patient with diagnosed PAD to assess location and severity. These tests also should be considered for patients with poorly compressible vessels or patients with a normal ABI where there is high suspicion of PAD.

Treadmill functional testing: To help with diagnosis in patients with atypical symptoms or a normal ABI with typical symptoms of claudication; may also be used as an evaluation of treatment efficacy and as an assessment of physical function.

Other studies: Further studies (e.g., toe pressure, transcutaneous partial pressure of oxygen) may help with clinical decision-making regarding revascularization. Sonography or magnetic resonance angiogram may also be valuable for patients in whom revascularization is being considered.

Medical Treatments

Treatment of systemic atherosclerosis associated with PAD. Although there is little prospective data showing that treating cardiovascular risk factors will improve cardiovascular outcomes in people with both PAD and diabetes specifically, consensus strongly supports such interventions, given that both PAD and diabetes are associated with significantly increased risks of cardiovascular events.

Cigarette smoking. Cigarette smoking is the single most important modifiable risk factor for the development and exacerbation

of PAD. In patients with PAD, tobacco use is associated with increased progression of atherosclerosis as well as increased risk of amputation.¹¹ Smoking cessation intervention, including medications if required, counseling, and avoidance of all tobacco products, is essential.

Glycemic control. Hyperglycemia may be a cardiovascular risk factor in individuals with PAD; however, evidence for the benefit of tight glycemic control in ameliorating PAD is lacking. In the U.K. Prospective Diabetes Study (UKPDS), intensive glycemic control reduced diabetes-related endpoints and diabetes-related deaths.¹² However, it was not associated with a significant reduction in the risk of amputation due to PAD. In fact, the major reduction in adverse endpoints was due to improved microvascular rather than macrovascular endpoints. Although it is likely that many patients with PAD were included in this study, the prevalence of PAD was not defined; therefore, conclusions may not directly relate to patients with diabetes and PAD. Nevertheless, good glycemic control (A1C <7.0%) should be a goal of therapy in all patients with PAD and diabetes to prevent microvascular complications.

Hypertension. Hypertension is associated with the development of atherosclerosis as well as with a two- to threefold increased risk of claudication.¹³ In the UKPDS, diabetes endpoints and risks of strokes were significantly reduced, and risk of MI was nonsignificantly reduced by tight blood pressure control.¹⁴ Risk for amputation due to PAD was not reduced. In general, the effects of treating hypertension on atherosclerotic disease or on cardiovascular events have not been directly evaluated in patients with both PAD and diabetes. Nevertheless, consensus strongly supports aggressive blood pressure control (<130/80 mmHg) in patients with PAD and diabetes to reduce cardiovascular risk.

Results of the Heart Outcomes Prevention Evaluation (HOPE) study showed that ramipril, an ACE inhibitor, significantly reduced the rate of cardiovascular death, MI, and stroke in a broad range of high-risk patients without hypertension.¹⁵ Of the 9,297 patients in this study, 4,051 had PAD. Patients with PAD had a similar reduction in the cardiovascu-

lar endpoints when compared with individuals without PAD, thus demonstrating that ramipril was effective in lowering the risk of fatal and nonfatal ischemic events among all patients. Nonetheless, the potential benefit of ACE inhibitors has not been studied in prospective, randomized trials in patients with PAD. Such trials are needed before making definite treatment recommendations regarding the use of an ACE inhibitor as a unique pharmacological agent in the treatment of PAD.

Dyslipidemia. Although treating dyslipidemia decreases cardiovascular morbidity and mortality in general, no studies have directly studied the treatment of lipid disorders in patients with PAD. In a meta-analysis of randomized trials in patients with PAD and dyslipidemia treated by a variety of therapies, Leng et al.¹⁶ reported a nonsignificant reduction in mortality and no change in nonfatal cardiovascular events. However, the severity of claudication was reduced by lipid-lowering treatment. Similarly, in a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S), the reduction in cholesterol level by simvastatin was associated with a 38% reduction in the risk of new or worsening symptoms of intermittent claudication.^{17,18} In the Heart Protection Study, adults with coronary disease, other occlusive arterial disease, or diabetes were randomly allocated to receive simvastatin or placebo.¹⁹ A significant reduction in coronary death rate was observed in people with PAD, but the reduction was no greater than the effect of the drug on other subgroups. Thus, although there are no data showing direct benefits of treating dyslipidemia in individuals with both PAD and diabetes, dyslipidemia in diabetes patients should be treated according to published guidelines, which recommend a target LDL cholesterol level <100 mg/dl. Following this guideline, it is our belief that lipid-lowering treatment may not only decrease cardiovascular deaths, but may also slow the progression of PAD in diabetes.

Antiplatelet therapy. The Antiplatelet Trialists' Collaboration reviewed 145 randomized studies in an effort to evaluate the efficacy of prolonged treatment with antiplatelet agents (in most cases, aspirin).²⁰ This meta-analysis combined data from >100,000 patients, including

70,000 high-risk patients with evidence of cardiovascular disease. A 27% reduction in odds ratio in the composite primary endpoint (MI, stroke, and vascular death) was found for high-risk patients compared with control subjects. However, when a subset of >3,000 patients with claudication was analyzed, effects of antiplatelet therapy were not significant. Thus, the use of aspirin to prevent cardiovascular events and death in patients with PAD is considered equivocal; however, aspirin therapy for people with diabetes is recommended.²¹

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study evaluated aspirin versus clopidogrel in >19,000 patients with recent stroke, MI, or stable PAD.²² The study results showed that 75 mg clopidogrel per day was associated with a relative risk reduction of 8.7% compared with the benefits of 325 mg aspirin per day for a composite endpoint (MI, ischemic stroke, and vascular death). More striking, in a subgroup analysis of >6,000 patients with PAD, clopidogrel was associated with a risk reduction of 24% compared with aspirin. Clopidogrel was shown to be as well tolerated as aspirin. Based on these results, clopidogrel was approved by the U.S. Food and Drug Administration (FDA) for the reduction of ischemic events in all patients with PAD. In the CAPRIE study, about one-third of the patients in the PAD group had diabetes. In those patients, clopidogrel was also superior to aspirin therapy.

In summary, patients with diabetes should be on an antiplatelet agent (e.g., aspirin or clopidogrel) according to current guidelines.²¹ Individuals with diabetes and PAD may benefit more by taking clopidogrel.

Treatment of symptomatic PAD.

Medical therapy for intermittent claudication currently suggests exercise rehabilitation as the cornerstone of therapy, as well as the potential use of pharmacological agents.

Exercise rehabilitation. Randomized controlled trials have demonstrated the benefit of supervised exercise training in individuals with PAD.^{23,24} These programs call for at least 3 months of intermittent treadmill walking three times per week.

Exercise therapy has minimal associated morbidity and is likely to improve the cardiovascular risk factor profile. In nearly all studies, unsupervised exercise regimens have shown lack of efficacy in improving functional capacity.

Pharmacological therapies. Two agents have been approved by the FDA for treating claudication:

- **Pentoxifylline:** Results of postapproval trials suggest that it does not increase walking distance to a clinically meaningful extent.
- **Cilostazol:** Significant benefit has been demonstrated in increasing maximal walking time in addition to improving functional status and health-related quality of life.²⁵ This drug is contraindicated if heart failure is present because of concerns about arrhythmias. In one trial, pentoxifylline was inferior when compared with treatment with cilostazol.²⁶ Cilostazol is the drug of choice if pharmacological therapy is necessary for the management of PAD in patients with diabetes.

Preventative foot care. All patients with diabetes and PAD should receive preventative foot care with regular supervision to minimize the risks of developing foot complications and limb loss.¹⁰

Treatment of the ischemic foot. CLI portends limb loss and requires urgent treatment. The frequent presence of neuropathy strongly influences the clinical presentation. The presence of neuropathy blunts pain perception, allowing a later presentation with more severe lesions than in the nondiabetic patient. In a vicious cycle, the presence of PAD increases nerve ischemia, resulting in worsened neuropathy. In addition, such arterial lesions may progress undetected for long intervals because of the distal distribution, making the severity of the underlying PAD often underestimated. Accordingly, diabetes patients with PAD are more likely to present with advanced disease than nondiabetic patients.

The “neuroischemic” foot—with PAD and neuropathy—is more prone to traumatic ulceration, infection, and gangrene. Each complication requires specific management as well as treatment of the underlying ischemia. In contrast to the plantar location of neuropathic ulcers,

ischemic ulcers are commonly seen around the edges of the foot, including the apices of the toes and the back of the heel. They are generally associated with a pivotal event: trauma or wearing unsuitable shoes. Important aspects of conservative management include debridement, offloading the ulcer, appropriate dressings, and adjunctive wound healing techniques.²⁷ Prompt and timely referral of the patient to appropriate foot care and vascular specialists is critical.

Debridement. Debridement should remove all debris and necrotic material to render infection less likely. The preferred method is frequent sharp debridement with a scalpel, normally undertaken at the hospital bedside or in the outpatient setting. Indications for surgical debridement include the presence of necrotic tissue, localized fluctuance, and drainage of pus or crepitus with gas in the soft tissues on X-ray.

Footwear. With the neuroischemic foot, the chief aim is to protect the foot from pressure and shear. Ulcers may be prevented from healing if the patient wears snug shoes or slip-on styles. It is most important that the shoe does no harm. A shoe that is sufficiently long, broad, and deep and fastens with a lace or strap high on the foot may be all that is needed to protect the margins of the foot and allow healing of the ulcers. Special footwear, such as sandals or braces, may be necessary.

Dressings. Nonadherent dressings should cover diabetic foot ulcers at all times. No single ideal dressing exists, and there is no evidence that any one dressing is better for the diabetic foot than any other. However, the following properties are desirable: ease of removal from the foot and ability to accommodate pressures of walking without disintegrating. Occlusive dressings may lower the risk of infection.

Treatment of infection. Although ulcers often become infected, the signs and symptoms of foot infection are diminished in patients with diabetes. The early warning signs of infection may be subtle because of an impaired neuroinflammatory response. Furthermore, it may be difficult to differentiate between the erythema of cellulitis and the rubor of

Make the Link! Patient Page

All About Peripheral Arterial Disease

What is peripheral arterial disease?

Peripheral arterial disease, also called PAD, occurs when blood vessels in the legs are narrowed or blocked by fatty deposits. Blood flow to your feet and legs decreases. If you have PAD, you have an increased risk for heart attack and stroke. One out of every three people with diabetes over the age of 50 is estimated to have this condition. However, many individuals with warning signs do not realize that they have PAD and therefore do not get treatment.

What does diabetes have to do with PAD?

If you have diabetes, you're much more likely to have PAD, a heart attack, or a stroke. But you can cut your chances of having those problems by taking special care of your blood vessels.

What are the warning signs of PAD?

Many people with diabetes and PAD do not have any symptoms. Some people may experience mild leg pain or trouble walking and believe that it's just a sign of getting older. Others may have the following symptoms:

- leg pain, particularly when walking or exercising, which disappears after a few minutes of rest
- numbness, tingling, or coldness in the lower legs or feet
- sores or infections on your feet or legs that heal slowly

How do I know whether I'm at high risk for PAD?

Just having diabetes puts you at risk, but your risk is even greater if

- you smoke
- you have high blood pressure
- you have abnormal blood cholesterol levels
- you already have heart disease or have had a heart attack or a stroke
- you're overweight
- you're not physically active
- you're over age 50
- you have a family history of heart disease, heart attacks, or strokes

You can't change your age or your family history, but taking care of your diabetes and the conditions that come with it can lower your chances of having PAD. It's up to you.

Make the Link!
Patient Page

How is PAD diagnosed?

The **ankle brachial index (ABI)** is one test used to diagnose PAD. This test compares the blood pressure in your ankle to the blood pressure in your arm. If the blood pressure in the lower part of your leg is lower than the pressure in your arm, you may have PAD. An expert panel brought together by the American Diabetes Association recommends that people with diabetes over the age of 50 have an ABI to test for PAD. People with diabetes younger than 50 may benefit from testing if they have other PAD risk factors.

These other tests can also be used to diagnosis PAD:

- Angiogram:** A test in which dye is injected into the blood vessels using a catheter and X-rays are taken to show whether arteries are narrowed or blocked.
- Ultrasound:** A test using sound waves to produce images of the blood vessels on a viewing screen.
- MRI (magnetic resonance imaging):** A test using special scanning techniques to detect blockages within blood vessels.

Real-Life Stories from People with Diabetes

Last summer my leg muscles had been hurting, even when I walked a short distance. The pain would stop when I rested but then it would come back. At first, I thought it was just old age. I told my health care team about the pain and also mentioned that there was a sore on my foot that wasn't healing. They did some tests and said I had PAD. Now the pain is gone — I'm taking pills for the PAD and I go for a walk almost every day.

— Sylvia P., age 60 • type 2 diabetes

How is PAD treated?

People with PAD are at very high risk for heart attacks and stroke; therefore, it is very important that cardiovascular risk factors be managed. Follow these steps:

- Get help to quit smoking. Your health care provider can help you.
- Aim for an A1C below 7. The A1C test measures your average blood sugar over the past 2 to 3 months.
- Lower blood pressure to less than 130/80.
- Get your LDL cholesterol below 100.
- Talk to your health care provider about taking aspirin or other antiplatelet medicines. These medicines have been shown to reduce heart attacks and stroke in people with PAD.

Studies have found that exercise, such as walking, can be used both to treat PAD and to prevent it. Medications may help relieve symptoms.

In some cases, surgical procedures are used to treat PAD:

- Angioplasty, also called balloon angioplasty:** A procedure in which a small tube with a balloon attached is inserted and threaded into an artery; then the balloon is inflated, opening the narrowed artery. A wire tube, called a stent, may be left in place to help keep the artery open.
- Artery bypass graft:** A procedure in which a blood vessel is taken from another part of the body and is attached to bypass a blocked artery.

Peripheral Arterial Disease

Continued from page 4

ischemia. The redness of ischemia, which is most marked on dependency, will disappear on elevation of the limb, whereas that of cellulitis will remain irrespective of foot position. Infections in the diabetic foot are often polymicrobial; broad spectrum antibiotics are initially indicated. Severe infections require intravenous antibiotic therapy and urgent assessment of the need for surgical drainage and debridement.

Both wet and dry gangrene can occur in the neuroischemic foot. Wet gangrene is caused by a septic arteritis, secondary to soft tissue infection or ulceration. Gas in the soft tissues is a serious finding that requires an immediate trip to the operating room for open drainage of all infected spaces and intravenous broad-spectrum antibiotics. It is important to emphasize that medical treatment of infection with antibiotics alone is insufficient to resolve the majority of diabetic foot infections.

Incision and drainage is the basic tenet of treatment for nearly all infections of the diabetic foot. Sometimes amputation of a toe, toes, or ray(s) may be necessary to establish drainage. Salvage of the diabetic foot is usually possible but may require aggressive debridement and revascularization. Postoperatively, there may be considerable tissue deficit or exposure of bone or tendon. In such circumstances, the foot should be revascularized as indicated and soft tissue deficits may be repaired by reconstructive surgery at a latter stage. A vacuum-assisted wound closure device provides topical subatmospheric pressure that is most helpful in staged procedures.

Dry gangrene is secondary to a severe reduction in arterial perfusion and occurs in chronic critical ischemia. Revascularization should be initially carried out, followed by surgical debridement. If revascularization is not possible, surgical debridement or amputation should be considered if the necrotic toe or any other area of necrosis is painful or if the circulation is not severely impaired. Otherwise, the necrosis should be allowed to autoamputate, because a surgical procedure may result in further necrosis and a higher level of amputation.

Indications for revascularization. The indications for limb revascularization are disabling claudication or CLI (rest pain or tissue loss) refractive to conservative therapy. Disabling claudication is a relative, not absolute, indication and requires significant patient consultation. One must weigh existing symptoms against the risk of the procedure and its expected effect and durability. Although most ischemic limbs can be revascularized, some cannot. Lack of a target vessel, unavailability of the autogenous vein, or irreversible gangrene beyond the mid-foot may preclude revascularization. In such patients, a choice must be made between prolonged medical therapy and primary amputation.

Major amputation in the neuroischemic foot is necessary and indicated only when there is overwhelming infection that threatens the patient's life, when rest pain cannot be controlled, or when extensive necrosis secondary to a major arterial occlusion has destroyed the foot. Using these criteria, the number of major limb amputations should be limited.

Most amputations can be prevented and limbs salvaged through a multi-armed treatment of antibiotics, debridement, revascularization, and staged wound closure. On the other hand, amputation may offer an expedient return to a useful quality of life, especially if a prolonged course of treatment is anticipated with little likelihood of healing. Diabetes patients should have full and active rehabilitation after amputation. Decisions should be made on an individual basis with rehabilitative and quality-of-life issues considered highly.

Conclusions

PAD is a common complication in patients with diabetes. In contrast to PAD in nondiabetic individuals, PAD in diabetic patients is more prevalent and, because of the distal territory of vessel involvement and its association with peripheral neuropathy, it is more commonly asymptomatic. Patients with PAD and diabetes thus may present later with more severe disease and have a greater risk of amputation. Moreover, the presence of PAD is a marker of excess cardiovascular risk. It is important to diagnose PAD in patients with diabetes to elicit symptoms, prevent disability and limb

loss, and identify a patient at high risk of MI, stroke, and death. The diagnosis is made with a determination of the ABI.

Treatment of the patient with diabetes and PAD should be twofold: 1) primary and secondary cardiovascular disease risk factor modification and 2) treatment of PAD symptoms (claudication and CLI) and limiting progression of disease. ■

References

- Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF: Intermittent claudication: a risk profile from the Framingham Heart Study. *Circulation* 96:44-49, 1997
- Hiatt WR: Medical treatment of peripheral arterial disease and claudication. *N Engl J Med* 344:1608-1621, 2001
- Criqui MH: Peripheral arterial disease: epidemiological aspects. *Vascular Medicine* 6 (Suppl. 1):3-7, 2001
- Bernstein EF, Fronck A: Current status of non-invasive tests in the diagnosis of peripheral arterial disease. *Surg Clin North Am* 62:473-487, 1982
- Elhadd TA, Robb R, Jung RT, Stonebridge PA, Belch JFF: Pilot study of prevalence of asymptomatic peripheral arterial occlusive disease in patients with diabetes attending a hospital clinic. *Practical Diabetes Int* 16:163-166, 1999
- Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR: Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 286:1317-1324, 2001
- Weitz JI, Byrne J, Clagett GP, Farkouh ME, Porter JM, Sackett DL, Strandness DE Jr, Taylor LM: Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation* 94:3026-3049, 1996
- Dormandy JA, Rutherford RB: Management of peripheral arterial disease (PAD): TASC Working Group: TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg* 31:S1-S296, 2000
- Dolan NC, Liu K, Criqui MH, Greenland P, Guralnik JM, Chan C, Schneider JR, Mandapat AL, Martin G, McDermott MM: Peripheral artery disease, diabetes, and reduced lower extremity functioning. *Diabetes Care* 25:113-120, 2002
- American Diabetes Association: Preventive foot care in people with diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S63-S64, 2004
- Lassila R, Lepantalo M: Cigarette smoking and the outcome after lower limb arterial surgery. *Acta Chir Scand* 154:635-640, 1988
- UK Prospective Diabetes Study (UKPDS)

- Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
- 13 Stokes J, Kannel WB, Wolf PA, Cupples LA, D'Agostino RB: The relative importance of selected risk factors for various manifestations of cardiovascular disease among men and women from 35 to 64 years old: 30 years of follow-up in the Framingham Study. *Circulation* 75:V65–V73, 1987
- 14 UK Prospective Diabetes Study (UKPDS) Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). *BMJ* 317:703–713, 1998
- 15 Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients: the Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 342:145–153, 2000
- 16 Leng GC, Price JF, Jepson RG: Lipid-lowering for lower limb atherosclerosis (Cochrane Review). *Cochrane Database Syst Rev* 2:CD000123, 2000
- 17 Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 344:1383–1389, 1994
- 18 Kjekshus J, Pedersen TR: Reducing the risk of coronary events: evidence from the Scandinavian Simvastatin Survival Study (4S). *Am J Cardiol* 76:64C–68C, 1995
- 19 MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 360:7–22, 2002
- 20 Antiplatelet Trialists' Collaboration: Collaborative overview of randomised trials of antiplatelet therapy. I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *Br Med J* 308:81–106, 1994
- 21 American Diabetes Association: Aspirin therapy in diabetes (Position Statement). *Diabetes Care* 26 (Suppl. 1):S87–S88, 2003
- 22 CAPRIE Steering Committee: A randomized, blinded, trial of Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE). *Lancet* 348:1329–1339, 1996
- 23 Larsen OA, Lassen NA: Effect of daily muscular exercise in patients with intermittent claudication. *Lancet* 2:1093–1096, 1966
- 24 Leng GC, Fowler B, Ernst E: Exercise for intermittent claudication (Cochrane Review). *Cochrane Database Syst Rev* 2:CD000990, 2000
- 25 Regensteiner JG, Ware JE Jr, McCarthy WJ, Zhang P, Forbes WP, Heckman J, Hiatt WR: Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. *J Am Geriatr Soc* 50:1939–1946, 2002
- 26 Dawson DL, Cutler BS, Hiatt WR, Hobson RW 2nd, Martin JD, Bortey EB, Forbes WP, Strandness DE: A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *Am J Med* 109:523–530, 2000
- 27 American Diabetes Association: Diabetic foot wound care (Consensus Statement). *Diabetes Care* 21:1354–1360, 1999

 **American Diabetes Association**
Cure • Care • Commitment®

Diabetes & Cardiovascular Disease Review

is a bimonthly newsletter of the American Diabetes Association/American College of Cardiology *Make the Link! Diabetes, Heart Disease, and Stroke* Initiative, aimed at reducing the morbidity and mortality associated with diabetic cardiovascular disease. It is published by the American Diabetes Association, 1701 North Beauregard Street, Alexandria, VA 22311.

For more information, contact
MakeTheLink@diabetes.org.

Design: Minker Design

We are grateful to the following companies who have provided educational grants to support the American Diabetes Association/American College of Cardiology *Make the Link!* Initiative: AstraZeneca LP; Aventis Pharmaceuticals; Bristol-Myers Squibb Co.; Eli Lilly and Co.; GlaxoSmithKline; Merck & Co. Inc. and Merck/Schering-Plough Pharmaceuticals; Monarch Pharmaceuticals and Wyeth Pharmaceuticals; Novartis Pharmaceuticals Corp.; and Pfizer Inc.

©2004