

# Peripheral arterial disease in patients with diabetes mellitus

**Peripheral vascular disease is commonly seen in diabetic patients and the disease progression is often more aggressive in this patient group. This article discusses the clinical assessment, and looks at medical and surgical treatment options.**

**E**arly diagnosis and treatment of peripheral arterial disease in patients with diabetes mellitus is vital to reduce the risk of cardiovascular events, minimize the risk of long-term disability, and improve quality of life. However, peripheral arterial disease is still underdiagnosed and under-treated in patients with diabetes despite the recognized association with cardiac and cerebral ischaemic events (Pyorala et al, 1987). Such patients need aggressive risk factor modification (Brun et al, 2000), antiplatelet therapy and potentially revascularization, best delivered by a multidisciplinary team. This article summarizes the recent evidence and recommendations for the management of peripheral arterial disease in patients with diabetes mellitus.

## Extent of the problem

Atherosclerosis is a multisystem problem and the presence of peripheral arterial disease may also indicate disease in cerebrovascular, coronary, renal, intestinal and other arteries with potentially life- or limb-threatening consequences (Munger et al, 1997). Approximately 10% of patients aged 65 years or over are affected by peripheral arterial disease, approximately 12 million patients in the USA. The Framingham Heart Study (Murabito et al, 1997) reported that around 20% of patients with symptomatic peripheral arterial disease had diabetes. On the other hand the prevalence of diabetes has tripled since the mid-1980s and is expected to double again by 2010 (King and Rewers, 1993), which means over one in ten people in northern Europe will develop diabetes in their lifetime. Accordingly, around 1 in 15 of the population will die from vascular disease in relation to diabetes (Andersson and Svardsudd, 1995).

## Pathophysiology

The pathophysiology of peripheral atherosclerotic disease is similar in patients with or without diabetes

despite the differences in the distribution of disease. Diabetes affects nearly every vascular bed and the associated proatherogenic changes include increases in vascular inflammation, derangements in the cellular components of the vasculature and generalized endothelial cell dysfunction, as well as alterations in blood cells and haemostatic factors (Beckman et al, 2002).

## Clinical assessment

### History and examination

The early detection of peripheral arterial disease in patients with diabetes mellitus is essential to initiate optimal risk factor modification to reduce the risk of atherothrombotic events, improve quality of life and decrease disability. Initial assessment should begin with a thorough medical history and physical examination to help identify those patients with cardiovascular risk factors, symptoms of claudication, rest pain or functional impairment. Alternative causes of leg pain, including spinal stenosis, should be excluded. Patients with peripheral arterial disease may present with no symptoms, intermittent claudication, rest pain or gangrene. The clinical stage of symptomatic peripheral arterial disease may be classified using the Fontaine staging system (Dormandy and Rutherford, 2000):

- Stage I represents those who have peripheral arterial disease but are asymptomatic
- Stages IIa and IIb include patients with mild and moderate-to-severe intermittent claudication respectively
- Stage III is those with ischaemic rest pain
- Stage IV patients have distal ulceration and gangrene.

Physical examination consists of inspection looking for nicotine staining, xanthelasma, cold peripheries, marbled skin, trophic changes, venous guttering as a result of poor blood supply, ulceration or gangrene (*Figure 1*), palpation of pulses and auscultation for bruits followed by blood pressure measurements. 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 (*Table 1*). The interdigital spaces should be inspected for fissures, ulcerations and infections (American Diabetes Association, 2003a).

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**Investigations**

**Ankle:brachial pressure index**

Measurement of the ankle:brachial pressure index (ABPI) is reproducible, non-invasive and accurate for the detection and assessment of the severity of peripheral arterial disease (American Diabetes Association, 2003b). It is defined as the ratio of the systolic blood pressure in the ankle divided by the systolic blood pressure at the arm, using a hand-held 5–10 MHz Doppler probe and a blood pressure cuff (Figure 2).

Treadmill function testing is another non-invasive functional test using a graded treadmill, which is positive when there is more than a 20 mmHg drop in ankle pressure after exercise. Measurement of toe pressures may be useful when there is arterial wall calcification (making ABPI measurement unreliable). Also, a toe pressure of less than 40 mmHg is associated with poor wound healing and may indicate a need for revascularization. Another test is transcutaneous oximetry measurement.

**Colour duplex ultrasound**

Duplex ultrasound can directly visualize vessels and is also useful in the surveillance of post-procedure patients for graft or stent patency. In patients with severe or mixed symptoms likely to need revascularization, further investigation may be necessary to help localize peripheral arterial disease and provide a road map for intervention.

Table 1. Clinical picture and investigations in a patient with peripheral arterial disease			
Symptoms and signs	Acute	Pain	
		Pallor	
		Paraesthesia	
		Paralysis	
		Pulseless	
		Perishing	
	Irreversible	Mottling	
		Muscle tender	
		Motor/sensory	
		Major necrosis	
		Chronic	Claudication
			Rest pain
Ulceration			
Necrosis			
Investigations	Ankle:brachial pressure index, duplex		
	Foot X-ray, magnetic resonance imaging		
	Computed tomography angiography		
	Magnetic resonance angiography		
	Angiography		



**Figure 1. Varying degrees of foot ischaemic tissue loss as a result of peripheral arterial disease. a and b. Non-healing ulceration. c. Wet gangrene of second and third toes. d. Dry gangrene of second and third toes.**

**Magnetic resonance or computed tomography angiography**

Magnetic resonance angiography is non-invasive with minimal risk of renal insult and gives images that are comparable with conventional contrast angiography. The development of computed tomography angiography has dramatically improved image quality and expanded the applications for non-invasive angiography; consequently, the computed tomography angiography is replacing conventional angiography in many peripheral arterial disease imaging studies (Fishman, 2004). Contrast angiography, an invasive test with a small risk of contrast-induced nephrotoxicity, is still needed for patients with suspected pedal ischaemia.

**Management**

Peripheral arterial disease represents generalized atherosclerotic disease and, therefore, modifying cardiovascular risk factors (smoking, diabetes mellitus, hypertension, dyslipidaemia and antiplatelet therapy) is essential and may be the only required intervention. The improvement of peripheral arterial disease symptoms and com-

**Figure 2. Ankle:brachial pressure index and degrees of peripheral arterial disease. Normal if 0.91–1.30; mild obstruction if 0.70–0.90; moderate obstruction if 0.40–0.69; severe obstruction if <0.40; poorly compressible if >1.30 test is unreliable.**



plications may be achieved with various medical or interventional modalities including angioplasty, bypass surgery or amputation in order to improve functional status and quality of life. Cardiovascular risk factors for individuals with peripheral arterial disease are similar to those for people with diabetes alone (Table 2) (Marso and Hiatt, 2006).

**Risk factor modification**

**Tobacco smoking**

Tobacco smoking is the most important risk factor for the development and progression of peripheral arterial disease and there are proven strong correlations between symptoms and the amount and duration of tobacco use (Freund et al, 1993). Cessation of smoking increases long-term survival in peripheral arterial disease patients from 46% to 82% over 10 years (Jonason and Bergstrom, 1987).

**Diabetes mellitus**

The vascular complications of diabetes mellitus may be classified as microvascular (retinopathy, vitreous haemorrhage, renal failure) and macrovascular (myocardial infarction, sudden death, stroke, amputation, or death as a result of peripheral arterial disease). A well-conducted study showed that intensive glycaemic control resulted in a 25% and 16% reduction in microvascular and macrovascular complications respectively, although there were no significant differences in diabetes-related or all-cause mortality (UK Diabetes Prospective Study, 1998a). The American Diabetes Association (2001) recommends a glycosylated haemoglobin level of <7.0% in diabetic individuals in order to prevent microvascular complications. Another study demonstrated that individuals with both peripheral arterial disease and type 2 diabetes had an adjusted risk of death 1.55 times that for individuals with diabetes alone and 1.67 times that for those with peripheral arterial disease alone (Leibson et al, 2004).

**Hypertension**

It is widely accepted that hypertension increases the risk of cardiovascular disease associated with diabetes. The heart outcomes prevention evaluation (HOPE) study

showed that ramipril, an angiotensin-converting enzyme inhibitor, significantly reduced the rate of cardiovascular death, myocardial infarction and stroke in a broad range of high-risk patients without hypertension (Yusuf et al, 2000). Furthermore, the UK Prospective Diabetes Study (1998b) showed that although diabetes endpoints were significantly reduced by tight blood pressure control, there was no effect on the risk of amputation as a result of peripheral arterial disease. Nevertheless, consensus still strongly supports aggressive blood pressure control (<130/80 mmHg) in patients with peripheral arterial disease and diabetes in order to reduce cardiovascular risk.

**Dyslipidaemia**

Several large trials with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors have shown significant reductions in cardiovascular event rates in patients with peripheral arterial disease and co-existing coronary artery disease (Pedersen et al, 1998). Simvastatin reduced the total mortality by 43% in patients with diabetes compared with 29% in those without diabetes (Pyorala et al, 1997). Similarly, in a subgroup analysis of the same study, the reduction in cholesterol level by simvastatin was associated with a 38% reduction in the risk of new or worsening symptoms of intermittent claudication. Although there are no direct data on treating dyslipidaemia in patients with both diabetes and peripheral arterial disease, published guidelines recommend a target low-density lipoprotein cholesterol level of <70 mg/dl in this very high-risk group (Grundy et al, 2004).

**Antiplatelet therapy**

The risk of cardiovascular morbidity and mortality in peripheral arterial disease patients with diabetes relates to platelet activity and inflammation. This can be modulated by antiplatelet agents in order to prevent thrombus formation and the resultant vascular events. The Antiplatelet Trialists' Collaboration (1994a) reported a 27% reduction in the odds ratio in the composite primary endpoint of myocardial infarction, stroke and vascular death in patients taking antiplatelet therapy compared with control subjects. Furthermore, aspirin has been shown to significantly improve vascular graft patency in patients with peripheral arterial disease treated with bypass surgery or peripheral angioplasty (Antiplatelet Trialists' Collaboration, 1994b). In summary, patients with diabetes should be on an antiplatelet agent (e.g. aspirin or clopidogrel), those patients with both diabetes mellitus and peripheral arterial disease may benefit more from taking clopidogrel (CAPRIE Steering Committee, 1996).

**Treatment of intermittent claudication**

Symptomatic patients should receive risk modification treatment in addition to exercise rehabilitation and potentially pharmacological agents in case of claudicat-

**Table 2. Risk factors and treatment goals for patients with diabetes and peripheral arterial disease**

Risk factor	Relative risk increase for peripheral arterial disease	Treatment goal
Smoking	2.5	Cessation
Diabetes	4.0	Glycosylated haemoglobin <7%
Dyslipidaemia	1.1 (per 10 mg/dl increase)	Low-density lipoprotein <100 mg/dl (2.6 mmol/litre)
Hypertension	1.5	Blood pressure <130/80 mmHg

ing. Severe claudication or critical leg ischaemia when dealing with rest pain or tissue loss mandates the addition of invasive intervention in the form of angioplasty or vascular reconstruction and debridement with or without amputation. In all patients, preventive foot care and pre-emptive infection management is crucial for limb and life.

### Exercise rehabilitation

Many randomized controlled trials have demonstrated the benefit of supervised exercise training in individuals with peripheral arterial disease (Leng et al, 2000). The best results with exercise therapy are achieved under supervision, and should consist of repetitive daily walks with intermittent periods of rest and weekly increases in walking time and distance (Cheetham et al, 2004). Exercise therapy has minimal associated morbidity and is likely to improve the cardiovascular risk factor profile. Drug therapy can be added as an adjunct to the exercise programme, although this combination has not been well studied. Cilostazol (100 mg twice daily), a phosphodiesterase inhibitor, is probably the most effective agent available and has been shown to improve maximal walking distance by 40–50% compared with placebo (Dawson et al, 1998).

### Treatment of critical leg ischaemia

Critical leg ischaemia, as defined by the European Working Group (1992), is the presence of ischaemic rest pain requiring analgesia for more than 2 weeks, or ulceration, or gangrene of the lower extremity with an absolute ankle systolic blood pressure of <50 mmHg and/or toe systolic pressure of <30 mmHg. Critical leg ischaemia is a precursor of limb loss and requires urgent treatment. There is a place for conservative management including limited debridement of ulcers, the provision of appropriate footwear, use of non-adherent dressings, institution of adjunctive wound healing techniques and treatment of infection (unloading of the foot and administration of antibiotics) (American Diabetes Association, 2003c). Revascularization and correction of the underlying ischaemia should precede debridement in order to avoid larger non-healing wounds.

### Revascularization

Many patients may not experience optimal improvement in symptoms with medical therapy alone (American Diabetes Association, 2003c). Over recent years, revascularization has emerged as an important strategy for management of these patients. Revascularization is the definitive therapy for the management of patients with critical leg ischaemia, with the aim of healing ischaemic ulcers and preventing limb loss. Two general revascularization techniques exist: endovascular interventions and open surgical procedures (bypass, endarterectomy and combination of traditional and endovascular procedures). Endovascular revascularization has increased in

popularity in recent years. In general, endovascular revascularization is more appropriate in patients with relatively focal disease in arteries above the knee (Dormandy and Rutherford, 2000); however, short-term success rates for opening long totally occluded vessels and below-the-knee arteries are improving. To date, the best results have been achieved in the aortoiliac vessels, where 1-year patency rates of 80–90% have been demonstrated (American Diabetes Association, 2003c). Angioplasty is still recommended as first line for superficial femoral artery disease as it is less invasive and does not exclude further bypass options, although 2-year data showed the superiority of bypass over endovascular option for superficial femoral artery disease (Adam et al, 2005).

In diabetes, open surgical revascularization tends to have greater durability than endovascular procedures. Such patients need close clinical follow up and possibly preemptive intervention for failing graft. Although most ischaemic limbs can be revascularized, the lack of a target vessel, unavailability of an autogenous vein or irreversible gangrene may mean that some cannot. In these patients, amputation may be a better option than prolonged medical treatment (UK Prospective Diabetes Study, 1998b).

### Amputation

Amputation may represent an acceptable treatment option not a failure for patients facing a prolonged course of treatment with poor prognosis for limb salvage. It is indicated when there is overwhelming infection that threatens the patient's life, or when necrosis secondary to a major arterial occlusion has destroyed the limb.

### Conclusions

Peripheral arterial disease is a common cardiovascular complication in patients with diabetes mellitus. The risk of developing peripheral arterial disease is much higher in patients with diabetes, and the disease is more severe and progresses more rapidly than in individuals without diabetes. Because the major threat to patients with diabetes and peripheral arterial disease is from cardiovascu-

## KEY POINTS

- Peripheral arterial disease is commonly seen in diabetic patients
- Assessment should include detailed history and clinical examination, particularly as atherosclerosis may affect multiple sites.
- Investigations include ankle:brachial pressure index, colour duplex ultrasound and digital subtraction arteriography.
- Clinicians should be alert to the possibility of osteomyelitis.
- All patients should have aggressive modification of cardiovascular risk factors with lifestyle changes and pharmacotherapy.
- Revascularization may be performed by percutaneous angioplasty or bypass surgery.

lar events, the primary therapeutic goal is to modify atherosclerotic risk factors. A supervised exercise programme and cilostazol are the preferred first treatment steps for the management of symptomatic peripheral arterial disease. Revascularization has an important role to play in the management of patients for whom risk factor modification and pharmacological treatment prove inadequate. **BJHM**

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