Peripheral arterial disease

Peripheral arterial disease (PAD) is expected to become more common in people with diabetes due to the rise in the occurrence of its major risk factors. Diabetes is a major risk factor for PAD; people with diabetes have more than a two-fold increased prevalence of PAD compared with the general population. PAD and peripheral neuropathy in diabetes may lead to diabetic foot ulcers, which can lead to hospital emergencies and result in increased admissions and reduced quality of life. Limb amputations and death can be the end result. Despite the epidemiological and clinical importance of PAD, it remains largely underdiagnosed, and hence undertreated, possibly because it is largely asymptomatic. As it shares many risk factors with cardiovascular disease, once PAD is recognised, a cardiovascular risk assessment should be performed and risk factors addressed.

Author: Mike Kirby, previously Visiting Professor, Faculty of Health and Human Sciences, University of Hertfordshire

Citation: Kirby M (2023) At a glance factsheet: Peripheral arterial disease. *Diabetes & Primary Care* **25**: 79–81

Definition[1]

Peripheral arterial disease (PAD) is a term used to describe a narrowing or occlusion of the peripheral arteries, affecting the blood supply to the lower limbs. Atherosclerosis is the underlying disease process.

Acute limb ischaemia is a sudden decrease in limb perfusion that threatens limb viability. Decreased perfusion and signs and symptoms develop over less than 2 weeks. The sudden reduction in arterial perfusion of the limb is most commonly due to thrombosis within a diseased artery when an atherosclerotic plaque ruptures.

Chronic limb ischaemia can present as intermittent claudication (pain in the lower limb on walking or exercise, relieved by rest, due to diminished circulation) or critical limb ischaemia (circulation is so severely impaired that there is an imminent risk of limb loss). **Chronic limb-threatening ischaemia** may occur and is characterised by chronic, inadequate tissue perfusion at rest, with or without tissue loss. This manifests in ischaemic rest pain.

Prevalence

The prevalence of PAD depends on the diagnostic measurement employed, cut-off values of the test, the limb assessed and the population studied.

In hospital-based studies, PAD is two- to seven-fold more common in people with diabetes than in those without the condition, with estimated rates between 9% and 55% in people with diabetes.[2] A systematic review of studies comparing PAD in people with and without diabetes reported that PAD prevalence ranged between 20% and 50% in those with diabetes, compared with 10% and 26% in those without the condition.[3]

Risk factors

The major risk factors for PAD include **diabetes**, **hypertension**, **smoking** and **hyperlipidaemia**.[4] These are also common in coronary heart disease and cardiovascular disease.

Several pathological mechanisms have been identified in the initiation of atherosclerosis, including endothelial dysfunction, inflammation, platelet aggregation and vascular smooth muscle cell dysfunction, all of which are aggravated by hyperglycaemia.

History and physical examination

In all patients with diabetes, a holistic consultation should include a history of hypertension, dyslipidaemia, tobacco smoking, obesity and the duration of diabetes. A diabetes duration of more than 10 years increases the risk of PAD, together with a longer duration of, and exposure to higher levels of, the other risk factors. History-taking should also focus on the presence of other macrovascular complications, such as cardiovascular disease and coronary heart disease.

Examination should include consideration of differential diagnoses (see overleaf). Symptoms of PAD include intermittent claudication in about 10% of patients; pain at rest, which is indicative of critical limb ischaemia; and about 50% of patients will be asymptomatic.[5]

Examination of the legs in PAD may reveal features of ischaemia such as dependent redness, elevated pallor, and shiny and hairless skin. Peripheral pulses, such as the femoral, popliteal, posterior tibial and dorsalis pedis arteries, should be carefully palpated, and where there is doubt, duplex ultrasound scanning is the gold-standard investigation for comparison, given its very high correlation with digital subtraction angiography in identifying lower-limb PAD.

At an advanced stage, trophic skin changes, ulcers and gangrene may be present. Review the cardiovascular system, including for arterial bruits: femoral, aortic and carotid. Buerger's test is used in an assessment of arterial sufficiency. The vascular angle, which is also called Buerger's angle, is the angle to which the leg has to be raised before it becomes pale, whilst lying down. In a limb with normal circulation, the toes and sole of the foot stay pink, even when the limb is raised by 90 degrees.

Ankle–brachial pressure index

The ankle–brachial pressure index (ABPI) is a sensitive (90%) and specific (98%) screening tool for PAD. The European Society of Cardiology recommends the use of ABPI to screen for PAD in all people with diabetes older than 50 years of age, as well as in younger people with a diabetes duration of more than 10 years, or with other risk factors for PAD such as smoking, hypertension, dyslipidaemia and PAD equivalents.[6]

An ABPI of <0.9 is indicative of PAD, and is associated with a two- to four-fold increase in mortality. An ABPI of >1.3 is indicative of poorly compressible vessels resulting from vascular calcification, and this is also associated with an increased risk of mortality and amputation.

NICE makes the following recommendations for ABPI ratios:[1]

- **Less than 0.5:** Severe arterial disease. Refer the person urgently for specialist vascular assessment.
- **0.5 to less than 0.8:** Presence of arterial disease or mixed arterial/venous disease. Refer the person for specialist vascular assessment.
- **Between 0.8 and 1.3:** No evidence of significant arterial disease.
- **Greater than 1.3:** May suggest presence of arterial calcification, such as in some people with diabetes, rheumatoid arthritis, systemic vasculitis, atherosclerotic disease and advanced chronic renal failure.
- **Greater than 1.5:** Vessels are likely to be incompressible and the result cannot be relied on to guide clinical decisions. Care must be taken in interpreting results in people with these conditions, as ABPI may be misleadingly high.
- If lower-extremity artery disease is clinically suspected, a normal ABPI does not exclude the diagnosis.

Differential diagnosis

Examination should include consideration of differential diagnoses such as pseudo-claudication in spinal stenosis, peripheral neuropathy, nerve root compression, deep venous thrombosis, vasculitis and musculoskeletal causes such as arthritis.

In **chronic peripheral neuropathy** (diabetic neuropathy), pulses will be present unless there is also chronic arterial occlusive disease or vasospasm, and skin temperature will be normal (unlike in acute limb ischaemia).

In **acute compressive peripheral neuropathy** (compartment syndrome), there will be tense muscle compartments, which are not present in acute limb ischaemia. When **deep vein thrombosis** is suspected, pulses are usually palpable (unless chronic arterial occlusive disease, vasospasm or significant oedema is also present), and oedema does not usually occur with acute limb ischaemia. Low cardiac output can exacerbate the clinical picture when in conjunction with chronic lower-extremity PAD.

Nerve root compression causes a sharp lancinating pain, radiating down the leg, exacerbated by sitting, standing or walking, and improved by change in position. **Hip arthritis** tends to cause an aching discomfort in the lateral hip and thigh after exercise, which is not quickly relieved but may improve when not weight-bearing. **Spinal stenosis** is often a bilateral pain and causes weakness affecting the buttocks and posterior leg, which is worse on standing, and relieved by flexing the lumbar spine.

Foot and ankle arthritis may also mimic PAD but causes a typical aching pain in the ankle and foot arch. Symptoms may be influenced by activity level, not quickly resolving, but may be relieved by not bearing weight.

Management

The management of PAD in people with diabetes involves treating both symptoms and cardiovascular risk factors, and lifestyle modification such as regular physical exercise, promotion of a healthy diet, weight reduction and smoking cessation. If medical management fails because of disabling symptoms or in the presence of chronic life-threatening ischaemia, then revascularisation is indicated.

Exercise

Regular physical activity improves claudication distance in PAD. It also improves quality of life and reduces the risk of cardiovascular disease, which often accompanies PAD.

A supervised exercise programme should be offered to all patients with intermittent claudication. NICE CG147 recommends as first-line treatment to offer 2 hours of supervised exercise a week for a 3-month period.[7] This may involve encouraging people to exercise to the point of maximal pain. Supervised exercise is designed to improve symptoms, function and clinical outcomes, and is based primarily on a structured, start-and-stop walking protocol, as is often implemented in cardiac rehabilitation programmes.

Despite the effectiveness of supervised exercise programmes for PAD, there are challenges of awareness, access and implementation. Recent efforts to address these challenges include digital health and hybrid approaches that could reduce barriers to care by delivering structured exercise in more innovative, flexible formats, or remotely.

If supervised exercise is not available, consider suggesting unsupervised exercise (using clinical judgement and taking

into account the person's motivation and comorbidities). For example, advise a regimen of walking until the onset of symptoms (pain threshold), then resting to recover, for approximately 30 minutes, 3–5 times per week.

Medications

Statins, antihypertensives, anti-platelet agents, vasodilators and good glycaemic control can address risk factors, along with smoking cessation.

Naftidrofuryl oxalate can be considered if supervised exercise has not led to satisfactory improvement and the patient prefers not to be referred for consideration of angioplasty or bypass surgery. Review treatment with naftidrofuryl oxalate after 3–6 months; discontinue if there has been no symptomatic benefit.

Cilostazol and pentoxifylline are licensed for the treatment of intermittent claudication; however, naftidrofuryl oxalate results in greater increases in maximum and pain-free walking distance.

NICE TA223 advises naftidrofuryl oxalate 100–200 mg three times a day, with an assessment for improvement after 3–6 months.[8] Treatment with naftidrofuryl oxalate should be started with the least costly licensed preparation. Uncommon side effects include diarrhoea, epigastric pain, nausea, rash, vomiting and, rarely, liver injury and oxalate nephrolithiasis. Cilostazol, pentoxifylline and inositol nicotinate are not recommended for the treatment of intermittent claudication in people with peripheral arterial disease.

Intravenous iloprost is licensed for the treatment of severe chronic lower-limb ischaemia in patients at risk of amputation where surgery has failed or is unsuitable.

Revascularisation

Revascularisation surgery is indicated if claudication impairs quality of life after the failure of exercise therapy and pharmacotherapy in patients whose general condition allows invasive treatment. Strategies include endovascular therapy, open surgery or a combination of the two.

Endovascular therapy is generally recommended for short (<25 cm) occlusive lesions and in people with high surgical risk. It includes balloon dilation (angioplasty), stents and atherectomy. Open surgery is recommended for patients with long (≥25 cm) lesions who are young and fit. Endovascular therapy has continued to evolve, with the modification and development of new technologies, including drug-eluting stents, self-expanding stents, cutting balloons and cryoplasty balloons.[9]

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