Identifying and treating intermittent claudication in people with diabetes

Edward Jude, Judith Gibbons

Introduction

Intermittent claudication (IC) – pain in the legs on walking that goes away with rest – is more common in people with diabetes than in those without. The appearance of IC symptoms is often the first indication of peripheral arterial disease (PAD; Jude, 2004) or peripheral vascular disease (PVD) in people with diabetes. Early diagnosis of IC, and therefore PAD/PVD, can reduce the substantial morbidity of the condition, which can culminate in limb loss for some patients. Members of the diabetes screening team should play a vital role in identifying people suffering from IC.

The aching, cramping pain of intermittent claudication (IC) may be felt in the calves, feet, thighs or buttocks and is usually relieved by resting for a few minutes. IC occurs when atherosclerosis reduces arterial blood flow to the lower limbs, depriving the leg muscles of the extra oxygen needed during exercise. IC can therefore be seen as a marker for vascular and arterial disease.

The incidence of IC among people aged 55–74 years is 4.6 % (Fowkes et al, 1991). People with diabetes are twice as likely to get IC compared with the general population, as they are more likely to have peripheral arterial disease (PAD) or peripheral vascular disease (PVD; TASC Working Group, 2000); and 20 % of patients with PAD have diabetes (American Diabetes Association, 2003).

Risk factors for IC include dyslipidaemia and hypertension, but the most important risk factors are smoking and diabetes (Krentz et al, 2003). The longer a patient has diabetes and the longer the condition is poorly controlled, the more likely they are to have problems with their arteries and develop IC. Some diabetes patients with PAD will not have any IC symptoms because they will be masked by peripheral neuropathy (Jude et al, 2001). However, for those patients who do have symptoms the pain will prevent them exercising, which will make their diabetes worse. IC has a significant adverse effect on health-related quality of life. Since patients can only walk short distances they are often unable to perform daily activities (Hiatt, 2001), which can lead to limitations on lifestyle, social isolation and unemployment (Binnie et al, 1999).

Around 10 % of IC patients progress to critical limb ischaemia and 2 % require amputation (Dormandy, 1991). However, IC patients with diabetes have a greater risk of progression (TASC Working Group, 2000). A Scandinavian study showed that the rate of progression to critical limb ischaemia over 6 years was 40 % for those with diabetes versus 15 % for those without diabetes (Jonason and Ringqvist, 1985).

Importance of identifying patients with IC

Patients may only occasionally walk far enough to feel the pain of IC and even then they will often dismiss it as muscle cramp, a part of getting older, a part of their diabetes or arthritis. However, IC symptoms can indicate arterial disease elsewhere in the body, such as the coronary or carotid arteries, and the patient may be at risk of angina, a transient ischaemic attack or stroke (TASC Working Group, 2000). Furthermore, as the PAD progresses,
patients can develop ischaemic leg pain or peripheral neuropathy. The main complication of peripheral neuropathy is foot ulcers, which can lead to increased morbidity and mortality and can be the leading cause of hospitalisation in people with diabetes (Boyko et al, 1996). Patients should be assessed for neuropathy by examining the foot, asking about symptoms and checking the sensation with a 10 g monofilament and 128 Hz tuning fork (Boulton et al, 1998). The peripheral circulation in the lower limb should be assessed by palpating the dorsalis pedis on the dorsum of the foot and the posterior tibial behind the medial malleolar. Those with absent pulses have a higher risk of foot ulceration. Early detection and treatment of these ulcers can prevent amputation (Jude and Boulton, 1999).

**How to identify IC patients**

At the diabetes patient’s annual review it is worthwhile asking a few questions about pain on walking, possibly using the format of the Edinburgh Claudication Questionnaire (Table 1). If a patient has pain in his or her legs after a period of exercise which disappears after a short rest but reappears after the same period of exercise this will indicate the patient has IC, particularly if foot pulses are not palpable. Foot pulses will often be weak or absent in patients with IC as well as those with non-symptomatic PAD.

If IC is suspected, and the correct equipment is available, a diagnosis can be confirmed by taking the ankle brachial pressure index (ABPI) – the ratio between Doppler-recorded systolic blood pressure in the lower and upper limb extremities (Table 2). An ABPI of <0.9 is taken to diagnose PAD (Table 3). However, in some people with diabetes the ABPI may be of limited value, as calcified, non-compressible arteries can give an ankle pressure much higher than the brachial pressure (Jude and Boulton, 1999). These patients should be referred to a vascular laboratory for alternative tests, such as toe systolic pressure. Toe digital arteries are less likely to be calcified, so pressure measurements more reliably reflect pressure within the digital artery. Transcutaneous oxygen pressure (TcPO2) can also be used to diagnose PAD and a pressure of <30 mmHg would be seen as abnormal (Jude and Boulton, 1999). The patient with occlusive disease has significantly reduced TcPO2 measurements; this has been used to determine the possibility of ulcer healing and optimal amputation.

**Table 1. The Edinburgh Claudication Questionnaire for diagnosing intermittent claudication (from Leng and Fowkes, 1992).**

<table>
<thead>
<tr>
<th>If a patient describes pain or discomfort in the legs when they walk, ask:</th>
<th>Reply and interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does this pain ever begin when you are standing still or sitting?</td>
<td>No, patient has intermittent claudication (IC)</td>
</tr>
<tr>
<td>Do you get pain if you walk uphill or hurry?</td>
<td>Yes, patient has IC</td>
</tr>
<tr>
<td>Do you get pain if you walk at an ordinary pace on the level?</td>
<td>Yes, patient has IC</td>
</tr>
<tr>
<td>What happens if you stand still?</td>
<td>Pain goes away, patient has IC</td>
</tr>
<tr>
<td>Does the pain disappear within ten minutes or less if you stand still?</td>
<td>Yes, patient has IC</td>
</tr>
<tr>
<td>Where do you get the pain or discomfort?</td>
<td>Claudication pain occurs typically in the calf, atypically in the buttock or thigh. In the absence of calf pain, pain in the shins, hamstrings, feet or joints, or pain that appears to radiate, all suggest a diagnosis other than IC.</td>
</tr>
</tbody>
</table>
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Role of the podiatrist: An opportunity to identify IC patients

The podiatrist should ask patients about pain in their legs at regular foot checks. During foot screening, questions that will distinguish between ischaemic pain (claudication or rest pain) and neuropathic pain should be asked (Table 4).

Referral to diabetologists and vascular surgeons

Mild to moderate claudication is best treated medically by managing risk factors such as stopping smoking, weight reduction, treating hyperlipidaemia and hypertension, and achieving good glycaemic control as well as an optimal exercise programme. Good foot care education should also form part of the treatment package. Patients are therefore best managed by the diabetologists initially and referred to the vascular surgeon when symptoms worsen or complications set in. A significant number of patients seen by diabetologists will probably already have progressed beyond IC to critical limb ischaemia. However, screening for IC should still be included at the patient’s annual review.

Who should identify these patients?

Ideally GPs who are already managing patients with diabetes should pick up IC. Diabetologists and podiatrists (community or diabetes clinic based) are the most likely members of the diabetes care team to screen for PAD and identify IC patients. A significant number of patients seen by diabetologists will probably already have progressed beyond IC to critical limb ischaemia. However, screening for IC should still be included.

Table 2. Determining ankle brachial pressure index (ABPI) values.

Using blood pressure cuffs and a handheld Doppler ultrasound machine:

- Measure systolic blood pressure in the brachial artery of each arm.
- Measure systolic blood pressure in both the posterior tibial and dorsalis pedis arteries in each leg.
- Divide the highest of the ankle pressure readings for each leg by the highest of the brachial pressure readings for the corresponding arm to give the right and left ABPIs, which will indicate the severity of the condition.

Results of the ankle brachial pressure index measurement will determine where patients should be referred to and the most appropriate intervention.

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Referral to diabetologists and vascular surgeons

Mild to moderate claudication is best treated medically by managing risk factors such as stopping smoking, weight reduction, treating hyperlipidaemia and hypertension, and achieving good glycaemic control as well as an optimal exercise programme (see below). Good foot care education should also form part of the treatment package. Patients are therefore best managed by the diabetologists initially and referred to the vascular surgeon when symptoms worsen or complications set in. A patient would need referral to the surgeon if there is disabling claudication, ischaemic rest pain, ischaemic foot ulceration or gangrene. In all of the latter cases the patient should ideally be managed in a multidisciplinary diabetic foot clinic with the diabetologist, podiatrist and vascular surgeon. It is
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Results of the ABPI measurement will determine where patients should be referred to and the most appropriate intervention. If the ABPI value is >0.9 the patient does not have PAD. An ABPI value of 0.5–0.9 indicates moderate PAD and the patient should be given lifestyle advice by their GP and be followed up in the diabetic foot clinic. However, if the ABPI value is <0.5, severe PAD is indicated and the patient should be referred to a vascular surgeon.

For some patients with moderate PAD, lifestyle changes (with management of cardiovascular risk factors) will lead to an improvement in symptoms. However, as with many other conditions, patients find it hard to stick to such changes. If IC symptoms do not improve within a few months the patient should be referred to the multidisciplinary diabetic foot clinic.

## Treatment

### Reducing cardiovascular risk

All patients with diabetes diagnosed with IC should be treated by the diabetologist with secondary prevention to reduce cardiovascular risk. Secondary prevention is often associated with an improvement in walking distance. Half of IC patients will improve or not get worse after following lifestyle advice, such as giving up smoking, weight loss, adhering to a proper diet, and regular exercise.

An antiplatelet agent such as aspirin, dipyridamole or clopidogrel will lower the risk of thrombotic vascular events, and has been shown to reduce vascular death in patients with IC by about 25% (Robless et al, 2001). Hypertension should be treated to target (130/80mmHg for people with diabetes; British Hypertensive Society guidelines, Williams et al, 2004), with an angiotensin-converting enzyme (ACE) inhibitor probably being the treatment of choice (Williams et al, 2004). The Heart Outcomes Prevention Evaluation (HOPE) study showed that the ACE inhibitor ramipril reduces cardiovascular related morbidity and mortality in patients with PAD by around 25% (HOPE Investigators, 2000).

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### Table 3. Ankle brachial pressure index (ABPI) value and disease severity (from Olin, 1998).

<table>
<thead>
<tr>
<th>ABPI value</th>
<th>Disease severity</th>
</tr>
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<tbody>
<tr>
<td>0.90–1.30</td>
<td>Normal</td>
</tr>
<tr>
<td>0.70–0.89</td>
<td>Mild</td>
</tr>
<tr>
<td>0.40–0.69</td>
<td>Moderate</td>
</tr>
<tr>
<td>≤0.40</td>
<td>Severe</td>
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</tbody>
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### Table 4. Diabetes foot screening: Comparison of ischaemic and neuropathic pain.

<table>
<thead>
<tr>
<th>Questions to ask the patient</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you get any pains in your legs?</td>
<td>Ischaemic pain</td>
</tr>
<tr>
<td>Do you get any pains in the back of your legs?</td>
<td>Claudication</td>
</tr>
<tr>
<td>If yes to any of these, then:</td>
<td>Severe ache, burning</td>
</tr>
<tr>
<td>What does the pain feel like?</td>
<td>Posterior calf, thigh, buttock</td>
</tr>
<tr>
<td>Show me where it hurts</td>
<td>Walking/exercise, note location and distance</td>
</tr>
<tr>
<td>What brings the pain on and what makes it worse?</td>
<td>Feat and leg</td>
</tr>
<tr>
<td>What can you do to ease the pain?</td>
<td>Rest/stop walking</td>
</tr>
</tbody>
</table>

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PAGE POINTS

1. For some patients with moderate peripheral arterial disease, lifestyle changes (with management of cardiovascular risk factors) will lead to an improvement in symptoms.

2. All patients with diabetes diagnosed with intermittent claudication should be treated by the diabetologist with secondary prevention to reduce cardiovascular risk.
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Patients with hyperlipidaemia should have their cholesterol levels lowered to target. The Heart Protection Study showed that lowering total and LDL-cholesterol by 25% with a statin reduces cardiovascular mortality and morbidity in PAD patients by around a quarter (Heart Protection Study Collaborative Group, 2002).

Exercise

The most effective exercise regimen for IC patients consists of walking sessions approximately 1 hour long, three times a week during which the patient walks to near maximal pain (preferably on a treadmill during supervised therapy), stops until the pain is relieved, and then resumes walking to near maximal pain again (TASC Working Group, 2000). Patients can also be encouraged to carry out foot exercises while sitting – point the toes, and rotate feet to keep calf muscles working. If IC patients adhere to an exercise programme a significant improvement in walking distance can be achieved. Unfortunately, only a minority of patients are able to attend supervised exercise classes and adherence with lifestyle advice is often poor. Many patients will therefore still experience high levels of pain on walking.

Drug treatment

Medication to relieve the pain of IC given in conjunction with lifestyle advice can have an additive effect – reducing the pain encourages adherence to the lifestyle changes. Treating the pain allows patients to walk further, which then acts as a stimulus to improve circulation in the legs, further improving walking distance.

Three indicated therapies are available to improve walking distance in IC – naftidrofuryl, pentoxifylline and cilostazol. However, the only treatment proven to relieve the pain of IC is cilostazol (Pletal). A recent review concluded that cilostazol represents the best evidence-based pharmacological therapy available for the symptoms of IC and should be the first-line treatment for symptom improvement in appropriate patients (Barnett et al, 2004).

Cilostazol has been shown to significantly improve maximal and pain-free walking distance in people suffering from IC whether they have diabetes or not. In a pooled analysis of 436 people with IC who also had diabetes, those who received 100 mg bd of cilostazol increased their maximal walking distances, initial claudication distance and absolute claudication distance significantly compared with placebo (Hittel and Donnelly, 2002; Rendell et al, 2002). People suffering from IC and with diabetes showed no significant differences compared with those without diabetes who had taken cilostazol in these trials with respect to improvements in walking distances and response rates. Mean percentage change in maximal walking distance from baseline was 53% for people with diabetes versus 60% for those without. However, increases in maximal walking distance were slightly lower in patients with diabetes, as these patients had a lower baseline walking distance and a higher incidence of concomitant cardiovascular disease.

Cilostazol is contraindicated in several subpopulations of patients, particularly those with congestive heart failure and severe hepatic or renal impairment.

Interventional therapies

Revascularising therapies, angioplasty, stenting and vascular surgery have a role to play in the management of patients for whom lifestyle changes and pharmacological treatment prove inadequate in controlling symptoms of IC. Surgery is required in those patients with non-healing foot ulcers, severe ischaemia and gangrene.

Conclusion

IC is twice as common in patients with diabetes and is a powerful marker of increased cardiovascular risk. It is therefore important to screen all diabetes patients for PAD, IC and foot ulceration, and also to check their feet regularly and educate them to look out for symptoms of these conditions. While reducing...
cardiovascular risk is a clinical priority, reducing the pain of IC is a priority for patients and can aid adherence with measures to improve lifestyles. Current data would appear to support the use of cilostazol as a promising therapy for patients with IC and diabetes, among the limited options available for these patients.


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While reducing lifestyles to improve with measures can aid adherence for patients and can aid adherence with measures to improve lifestyles.