

Clinical review

Intermittent claudication

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BMJ 2006;333:1002-5

Intermittent claudication is pain affecting the calf, and less commonly the thigh and buttock, that is induced by exercise and relieved by rest. Symptom severity varies from mild to severe. Intermittent claudication occurs as a result of muscle ischaemia during exercise caused by obstruction to arterial flow. It is a common problem, with a prevalence of 0.6-10%¹ which increases significantly with age. Almost a fifth of the population over the age of 65 has intermittent claudication,² and, as a result of demographic changes in many developed countries, its prevalence in the general population is likely to rise dramatically over the next 20 years.

Intermittent claudication has a negative impact on various aspects of quality of life³ and on affected people's ability to continue to work. Its socioeconomic impact has not been evaluated but is likely to be considerable. More importantly, people with intermittent claudication have a significantly increased mortality risk. However, many people with the condition do not consult a doctor, and often doctors are unaware that their patients have the condition.^{w1} Early diagnosis and risk factor control by primary care doctors is critical to reducing the mortality associated with claudication. This review presents current knowledge on the diagnosis, natural course, and management of intermittent claudication.

Search strategy

I searched the *Cochrane Library* for relevant systematic reviews on management of intermittent claudication and used clinical evidence to assess clinically relevant benefits and harms of different treatments. I performed Medline searches to find relevant reviews on the natural course, diagnosis, and treatment of the condition.

Who gets it?

In the vast majority of cases atherosclerosis is the underlying pathology in intermittent claudication. Cigarette smoking is by far the most potent risk factor for development of peripheral atherosclerosis and intermittent claudication (fig 1), increasing the risk at least threefold, and the higher the numbers of pack years the more severe the disease.⁴ Other major risk factors are increasing age,⁵ diabetes,⁶ hypertension,⁴ hyperlipidaemia,^{w2} and hyperhomocysteinaemia.^{w3} In younger patients intermittent claudication may be caused by conditions such as popliteal artery entrapment,^{w4} cystic adventitial disease,^{w5} fibromuscular dysplasia,^{w6} and external compression syndromes

Summary points

Intermittent claudication is a common condition and in most cases is easily diagnosed

It is associated with a significantly increased risk of death from cardiovascular disease

Only a small proportion of patients with claudication require revascularisation

The main treatment aim is to reduce the risk of mortality from cardiovascular events

Smoking cessation, control of hypertension and diabetes, and prescription of statins and antiplatelet drugs are key elements for treating the condition

Exercise, angioplasty, and bypass surgery can improve symptoms of claudication

(which occur in high intensity athletes such as professional cyclists).^{w7}

How is it diagnosed?

The diagnosis of intermittent claudication is based on a classic history of cramping muscle pain that occurs after the same degree of exercise and which is quickly relieved by rest. However, other conditions such as nerve root compression, spinal stenosis, hip arthritis, symptomatic Baker's cyst, venous claudication, and chronic compartment syndrome may mimic the symptoms of intermittent claudication. Typically the pain from nerve root compression tends to radiate down the back of the leg and is described as sharp lancinating pain, which is sometimes relieved by adjusting the position of the back (such as leaning forward). In spinal stenosis motor weakness may be present. Concomitant lumbosacral spine disease and peripheral arterial disease may cause difficulty in identifying which of the two conditions is the main cause of symptoms.

Absent or reduced peripheral pulses or the presence of audible bruits supports the diagnosis of intermittent claudication, but some patients with the

P+ *References w1-w22 are on bmj.com*

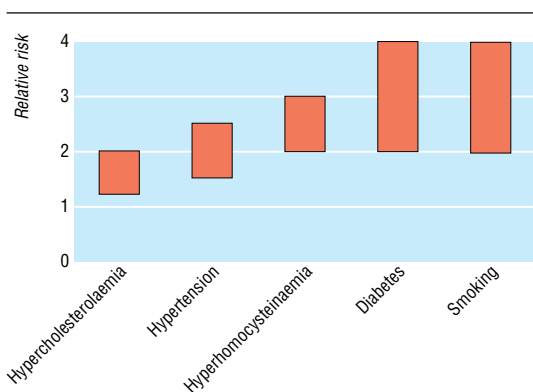


Fig 1 Effects of various risk factors on relative risk of developing intermittent claudication^{4 6 w2 w3}

condition will have normally palpable pulses and no bruits. A low ankle-brachial pressure index (< 0.9) also supports the diagnosis. However, the presence of palpable pulses or a normal resting ankle-brachial pressure index (> 0.9) does not rule out the diagnosis. If the clinical history is highly suggestive of intermittent claudication and the ankle-brachial pressure index is normal, an exercise ankle-brachial pressure index should be performed. If a substantial drop in ankle pressure is observed after exercise and at the same time as symptoms develop, a diagnosis of intermittent claudication can confidently be made.^{w8} In patients with an ankle-brachial pressure index > 1.3 the result is likely to be artefactual secondary to heavily calcified vessels, and a toe-ankle brachial pressure index should be calculated.

What is the prognosis?

Patients with intermittent claudication have a significantly higher mortality than age matched controls, about 12% a year (fig 2).⁶ Of these deaths, 66% are due to heart disease, and 10% are due to strokes. Increasing age, cigarette smoking, diabetes and lower ankle-brachial pressure index are independent risk factors for mortality.

The natural course of intermittent claudication is benign for the leg affected, with few patients ever requiring intervention or amputation. Only one in four patients with intermittent claudication will develop any deterioration in symptoms. Multiple longitudinal studies have shown that the amputation rate in this group of patients is only 1-7% at 5-10 years.^{7 w9 w10} At 10 years, fewer than one in five patients will undergo any form of revascularisation of the leg.⁷

How is it treated?

People with peripheral arterial disease have the same risk of death from cardiovascular causes as those with a history of coronary or cerebrovascular disease.⁸ Treatment of intermittent claudication should therefore be on two fronts. Firstly, treatment should be targeted at reducing the risk from cardiovascular events through secondary prevention. Secondly, treatment should aim to improve the symptoms of claudication.

Tips for non-specialists

- Recognise the symptoms of intermittent claudication early
- Ideally, confirm the diagnosis by measuring ankle-brachial pressure indices in the community
- Identify risk factors for atherosclerosis and start treatments to control them—smoking cessation, diabetic control, antiplatelet drugs, antihypertensives, statins—and encourage exercise
- Refer patients to a specialist if the diagnosis is uncertain or if claudication is disabling

Secondary risk factor modification

Smoking cessation

Smoking cessation reduces the risk of death from cardiovascular causes. Patients with peripheral arterial disease who continue to smoke have an increased rate of progression of atherosclerosis as well as an increased risk of amputation.⁹ With regard to symptoms of intermittent claudication, a systematic review of observational studies found only inconclusive results as to whether smoking cessation improved walking distance or reduced symptom progression.^{w11} Nevertheless, the consensus opinion is that smoking cessation is a key part of treating intermittent claudication. There is clear evidence that use of nicotine replacement therapy,¹⁰ bupropion, and nortriptyline¹¹ increases the proportion of patients successfully stopping smoking by 50-100%.

Antiplatelet drugs

There is clear evidence that antiplatelet drugs reduce major cardiovascular events. They also reduce the risk of arterial occlusion and the requirement for revascularisation procedures.^{w12 w13} Various guidelines, including those of the Scottish Intercollegiate Guidelines Network, recommend antiplatelet treatment for patients with peripheral arterial disease.^{w12 w14}

Statins

Statins reduce the risk of cardiovascular events in this group of patients.¹³ There is also some evidence that statins improve the symptoms of claudication, increasing walking distance and pain-free walking time.¹³ Unless there is a major contraindication, all patients should be prescribed statins.^{w14}

Diabetes control

The prevalence of diabetes is higher among patients with intermittent claudication than in the general

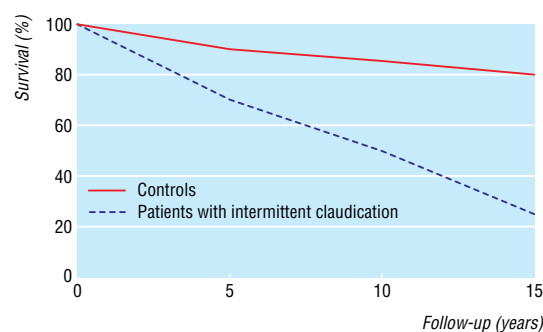


Fig 2 Survival in patients with intermittent claudication compared with age matched healthy controls⁶

Indications for revascularisation in intermittent claudication

- A predicted or observed lack of response to exercise or drug treatment
- Presence of severe disability, patient being unable to work or perform important activities
- Absence of other disease that would limit exercise even if claudication were improved (such as angina, chronic respiratory disease)
- Patient's anticipated natural history and prognosis
- Morphology of lesion makes it suitable for revascularisation

population, and such patients need to be screened for diabetes. Tight control of blood glucose concentration significantly reduces the incidence of cardiovascular events in people with diabetes but has had no effect on the risk of peripheral arterial disease.¹⁴ Intensive therapy reduces the incidence of myocardial infarction but has no effect on the risk of leg amputation.^{w15}

Blood pressure control

Good control of hypertension confers protection against cardiovascular events.^{15 w16} In diabetic patients intensive blood pressure control is more effective at reducing cardiovascular events and mortality.¹⁶ There is, however, no evidence that lowering blood pressure alters the natural course of intermittent claudication, and a Cochrane review concluded that the evidence for the various drug classes is poor for peripheral arterial disease and that no recommendations could be made.^{w17} The joint British recommendations for prevention of coronary heart disease, however, suggest that in peripheral arterial disease the treatment target should be a systolic blood pressure < 140 mm Hg and a diastolic pressure < 85 mm Hg.¹⁷

Symptomatic treatment*Exercise*

Regular exercise, at least three times weekly, has been shown to improve total walking distance and maximal exercise time.¹⁸ There is some suggestion that supervised exercise may be more beneficial than non-supervised exercise.^{w18}

Oral treatment

After 12-24 weeks' treatment, cilostazol significantly improves walking distance compared with placebo. However, the drug is associated with common side effects such as headache, diarrhoea, and palpitations.¹³

Additional educational resources

- Cassar K, Bachoo P. Peripheral arterial disease. *Clin Evid* 2006;(15):164-76
- *Cochrane Database of Systematic Reviews* (www.cochrane.org/review/clibaccess.htm)
- ACC/AHA 2005 guidelines for the management of peripheral arterial disease. *J Am Coll Cardiol* 2006;47:1239-312
- Antithrombotic therapy in peripheral arterial occlusive disease: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004;125:609-26S

Information for patients

- British Heart Foundation. *Peripheral arterial disease. Heart information series number 16.* www.bhf.org.uk/publications/uploaded/download-his16.pdf
- Patient UK. Peripheral vascular disease. www.patient.co.uk/showdoc/23068800

There is no convincing evidence that pentoxifylline, buflomedil, vitamin E, or omega 3 fatty acids have any significant effect on the symptoms of intermittent claudication.^{w19-w22}

Percutaneous transluminal angioplasty

Despite percutaneous transluminal angioplasty being widely used to treat intermittent claudication, its role is still controversial. The 2005 guidelines from the American Heart Association and American College of Cardiology for managing peripheral arterial disease state that, patients with intermittent claudication should not even undergo an evaluation for revascularisation unless they have significant functional impairment with a reasonable likelihood of symptomatic improvement and absence of other disease that might limit activity even if the claudication were improved (see box).^{w14}

There is some evidence that percutaneous angioplasty improves walking distance at six months compared with conservative treatment¹⁵ and that it improves quality of life.¹⁹ A Cochrane review concluded that angioplasty may have some benefit but only a short term one.²⁰ A separate Cochrane review concluded that there is insufficient evidence to conclude whether use of stents provides benefit compared with angioplasty alone for intermittent claudication.²¹

The Transatlantic Inter-Society Consensus Working Group recommends angioplasty only in patients with single stenoses < 3 cm long in the common or external iliac artery, with single stenoses or occlusions ≤ 5 cm long in the femoropopliteal segment, or with multiple lesions each < 3 cm long and not involving the distal popliteal artery.²²

Bypass surgery

As for angioplasty, there is wide variation in opinion as to whether patients with intermittent claudication should be offered surgery. There is little doubt that, for patients with debilitating symptoms who are not suitable for angioplasty, surgery may provide effective treatment, but this may be associated with an increased risk of morbidity (2-30%) and mortality (0-5%). One systematic review has found that surgery improves primary patency after 12-24 months compared with angioplasty, but there was no significant difference at four years.²³

Whatever type of revascularisation is offered, the patients should also be given information about exercise treatment and pharmacotherapy, receive comprehensive risk factor modification and antiplatelet treatment, have a significant disability, and have peripheral arterial disease anatomy such that the procedure being offered has a high chance of immediate and long term success and a low risk of complications.^{w14}

What new treatments can we expect?

Promising potential treatments include debulking procedures that remove atheromatous plaque from arteries using various techniques. Remote superficial femoral artery endarterectomy, minimally invasive atherectomy using a mechanical device, and excimer percutaneous transluminal laser angioplasty are some of the new techniques used to treat stenoses and occlusions of the arteries in the lower limbs. Initial reports are encouraging, but the long term results are unknown.

Efforts continue to develop new drugs to treat peripheral arterial disease and atherosclerosis, and particularly to cause regression of atherosclerotic plaque. These include DG041, a potent antagonist of the EP3 receptor for prostaglandin E₂, and PPAR (peroxisome proliferators activated receptor) and LXR (liver X receptor) agonists which influence the ABCA1 (ATP binding cassette A1) transporter, which has an important role in lipoprotein metabolism.

Therapeutic angiogenesis, the development of new blood vessels to improve the blood flow to the limb, can be achieved with direct administration of angiogenic growth factors. Various growth factors such as vascular endothelial growth factor and hepatocyte growth factors are undergoing trials to assess their potential beneficial effect in leg ischaemia.

Conclusion

Intermittent claudication is the first clinical manifestation of peripheral arterial disease, which in most cases is itself a manifestation of atherosclerosis. The word “peripheral” is probably responsible for the fact that doctors fail to recognise the importance of the condition and patients’ significantly increased risk of death from cardiovascular disease. Intermittent claudication should be seen not as “peripheral” but as an important “central” warning signal to start as early as possible the measures highlighted to reduce the risk of death and major vascular events. Symptomatic treatment of the leg pain should not overshadow the more important aim of reducing cardiovascular risk. Treatment of the condition should not be perceived as solely the responsibility of vascular surgeons and interventionists. Primary care doctors have a major role too—saving lives.

Competing interests: None declared.

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(Accepted 5 October 2006)

doi 10.1136/bmj.39001.562813.DE

One hundred years ago

Doctors and duellists

THE object of the duello is said to be the healing of wounded honour. To try to cure a wound of the spirit, or rather the temper, by a scratch on the skin savours of homoeopathy, but may perhaps be justified by the surgical principle of relieving tension by incision. Owing possibly to climatic influences, honour is more vulnerable in some countries than in others; hence there is more frequent need of curative scarification. It is one of those contradictions in human nature which puzzle the philosopher, that honour of the most morbidly delicate character in certain respects is in others often of a robustness which makes it insensitive to the grief of a wound. When honour has been satisfied by an exchange of scratches and it comes to paying the doctor, the duellist does not always show that punctilious regard for his own dignity which led him to seek vengeance for an affront. . . . A medical practitioner in France was asked to be present at a duel in his professional capacity. He got up early, travelled some miles, flamed the swords, and ministered to his client who was slightly wounded. . . . Some months passed, and, having heard nothing about the matter, he sent in his bill, the amount of which was only fifty francs. The patient apparently found it convenient to reply through his wife, and the lady’s letter

deserves reproduction as a “document” painfully illustrative of human meanness. After some preliminary sentences she goes on: “For the rest, I am told that between men there is a question of delicacy which forbids even the slightest appearance of trade in such a matter, and doctors, no more than the seconds, are brought on the ground by money. Not being versed in such things, however, if you persist in your claim, I shall, to my great regret, be obliged to leave to others the duty of settling this fine point with you. But I have no doubt that, after having thought over the considerations which I have taken the liberty to place before you, you will understand the case without the least difficulty, and you are too intelligent a man to make it necessary for me to discuss with you the useless treatment of an insignificant scratch.” . . . The idea that a doctor is a philanthropist, who should think himself amply rewarded for trouble and loss of time by the mere joy of altruistic labour, is tolerably widespread. But it is new to us that he is expected not only to work for nothing, but to think it a privilege to be allowed to give his professional services to persons having no claim whatever upon him who choose to put what they call their honour to the touch of a sword prick. (*BMJ* 1905;i:672)