ABSTRACT: INTRODUCTION: Peripheral arterial disease (PAD) is a condition characterized by atherosclerotic occlusive disease of the lower extremities. While PAD is a major risk factor for lower-extremity amputation, it is also accompanied by a high likelihood for symptomatic cardiovascular and cerebrovascular disease. Atherosclerosis accounts for more than 90% of cases of PAD, and uncommon vascular syndromes account for the remaining 10%. The femoral and popliteal arteries are affected in 80% to 90% of symptomatic PAD patients, the tibial and peroneal arteries in 40% to 50%, and the aortoiliac arteries in 30%. Although 65–75% of patients with PAD are asymptomatic, the classic presenting symptom is usually described as muscle cramps, fatigue or pain in the lower legs induced by exercise and rapidly relieved by rest; often the symptom location indicates the level of arterial involvement.

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

DIAGNOSIS: PAD can be easily and accurately diagnosed by calculating the ankle-brachial index (ABI). The ABI is defined as the ratio of the systolic blood pressure in the ankle divided by the systolic blood pressure at the arm. The tools required to perform the ABI measurement include a hand-held 5–10 MHz Doppler probe and a blood pressure cuff.

MANAGEMENT: Most patients’ symptoms improve with optimal medical treatment and invasive intervention is often not required. Smoking cessation and exercise are considered the two most important treatments for PAD. CONCLUSION: Symptomatic PAD often impairs a patient’s quality of life and untreated disease can lead to limb loss. Aggressive management of atherosclerotic risk factors, a structured exercise program, use of antiplatelet agents and when indicated percutaneous or surgical revascularizations are the keys for successful management.

KEYWORDS: Peripheral Arterial Disease, Ankle Brachial Index, Claudication.
RISK FACTORS: Diabetes and smoking are the strongest risk factors for PAD. Other well-known risk factors are advanced age, hypertension, and hyperlipidemia.

Potential risk factors for PAD include elevated levels of C-reactive protein (CRP), fibrinogen, homocysteine, apolipoprotein B, lipoprotein (a), and plasma viscosity. An inverse relationship has been suggested between PAD and alcohol consumption.

PATHOPHYSIOLOGY: Atherosclerosis accounts for more than 90% of cases of PAD, and uncommon vascular syndromes account for the remaining 10% [TABLE 1]. The femoral and popliteal arteries are affected in 80% to 90% of symptomatic PAD patients, the tibial and peroneal arteries in 40% to 50%, and the aortoiliac arteries in 30%.

PRESENTATION: Although 65–75% of patients with PAD are asymptomatic, the classic presenting symptom is IC which is usually described as muscle cramps, fatigue or pain in the lower legs induced by exercise and rapidly relieved by rest; often the symptom location indicates the level of arterial involvement. Less commonly, patients may present with critical limb ischaemia.

The European Society of Vascular Surgeons defined CLI as a recurring ischaemic rest pain requiring analgesia for 2 weeks or ulceration or gangrene of foot or toes with ankle systolic pressure 50 mmHg or toe systolic pressure 30 mmHg (Fontaine’s III and IV). Fontaine’s classification, proposed in 1954, remains a popular way of staging PAD. It divides patients into groups according to their clinical presentation.

A similar clinical classification developed by Rutherford has the advantage of including haemodynamic data, helping to ensure that any rest pain or tissue loss is directly related to PAD [Table 2].

DIFFERENTIAL DIAGNOSIS: The differential diagnosis of pain in the lower limb when walking includes sciatica and spinal stenosis, deep vein thrombosis, entrapment syndromes and muscle/tendon injury [Table 3].

DIAGNOSIS: PAD can be easily and accurately diagnosed by calculating the ankle-brachial index (ABI).

The ABI is defined as the ratio of the systolic blood pressure in the ankle divided by the systolic blood pressure at the arm. The tools required to perform the ABI measurement include a hand-held 5–10 MHz Doppler probe and a blood pressure cuff.

The ABI is measured by placing the patient in a supine position for 5 min. 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 interpreted as follows:

- 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.
An ABI value >1.3 suggests poorly compressible arteries at the ankle level due to the presence of medial arterial calcification. This renders the diagnosis of PAD by ABI alone less reliable.

ABI ≤ 0.9 in symptomatic patients has 95% sensitivity in detecting PAD and almost 100% specificity in identifying healthy individuals. ABI can be falsely elevated in the presence of arterial calcification, and heavily calcified vessels may be incompressible the normal toe pressure is > 0.70. In this circumstance, the toe–brachial index is useful in diagnosing PAD as digital vessels are spared from calcification. Another method of assessing PAD when ABI measurements are unreliable is by evaluating the ischaemic angle (pole test). This is determined by the level at which a pedal Doppler signal disappears on elevating the foot.

Other methods of investigation include MR angiography and CT angiography. MR angiography may be offered prior to revascularization. Digital subtraction arteriography is not recommended as the primary imaging modality and is essentially a preoperative investigation. Its use is limited to an adjuvant of endovascular management, surgical planning or the management of an acute ischaemic limb.

MANAGEMENT: Most patients’ symptoms improve with optimal medical treatment and invasive intervention is often not required. Smoking cessation and exercise are considered the two most important treatments for PAD.

Approximately 20% will deteriorate and develop critical limb ischaemia.

LIFESTYLE MODIFICATION:
1. **Smoking Cessation:** Cigarette smoking is the single most important risk factor for the development and progression of PAD. A meta-analysis of 17 studies found a 2.2-fold greater prevalence of symptomatic PAD in smokers compared with nonsmokers. Although smoking cessation has not been shown to significantly improve overall walking distance, it does reduce the risk of cardiovascular events and slows the progression to CLI.

PAD patients who achieve abstinence from smoking have far higher survival rates than those who do not.

2. **Exercise Therapy:** The overall improvement in walking ability is found to be around 50–200%, with most of the studies recommending a thrice-weekly programme of 30-min walking sessions to near-maximal pain for a period of at least 6 months. Supervised exercise regimes are required to achieve best possible results. A recent randomized trial showed equivalent outcomes for supervised exercise, angioplasty or both, at 12 months.

MODIFICATION OF RISK FACTORS:
1. **Management of Diabetes Mellitus:** 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.

2. **Dyslipidemia Treatment:** Several reports have indicated that statins also improve pain-free walking distance and ambulatory activity in claudicants through a mechanism independent of their cholesterol-lowering properties.
More importantly, in the Heart Protection Study, simvastatin reduced vascular mortality by 17%, coronary artery events by 24% and strokes by 27% in a subgroup of patients with PAD at 5 years.\textsuperscript{13}

3. Hypertension Control: The Heart Outcomes Prevention Evaluation (HOPE) study showed blood pressure modification in patients with ABI 0.90 was twice as effective in preventing major adverse cardiovascular events compared with those with ABI0.90.\textsuperscript{14}

4. Antiplatelet Drugs: Antiplatelet therapy has not been shown to improve claudication but is important in reducing the risk of cardiovascular disease related to atherosclerosis and PAD.\textsuperscript{15} Currently, it is recommended that patients with symptomatic PAD should be on long-term low-dose aspirin or clopidogrel to minimize the rate of serious vascular events. \textsuperscript{15}

5. Peripheral Vasodilators: cilostazol has been shown to be of benefit in improving walking distance in people with intermittent claudication.\textsuperscript{3,16}

A dose of 100 mg twice daily (taken on an empty stomach at least ½ hour before or 2 hours after breakfast and dinner) is recommended to ensure effectiveness.

Cilostazol has multiple pharmacologic actions including reduction in platelet aggregation, vasodilatation and improving lipid profile.

SURGICAL: At present, the absolute indications for lower extremity revascularization are, critical limb ischemia (usually manifested as rest pain, non-healing lower extremity ulcers), and to relieve symptom-limiting claudication.

The two options are endovascular revascularization and surgery. Short stenotic (or occlusive) lesions can generally be successfully treated by endovascular intervention. Whereas, long lesions usually require surgical treatment.

1. Endovascular Interventions: Many centers now favor an endovascular approach, due to reduced morbidity and mortality, preserving the surgical option in case of failure. Percutaneous angioplasty carries a lower risk compared with surgical revascularization and can be performed on an outpatient basis. Proposed predictors of favorable long-term outcomes include the locations of treated lesions (better results with iliac artery angioplasty compared with femoropopliteal or infrapopliteal arteries).

The major drawback of endovascular interventions compared with surgery is the lower long-term patency. There is currently no established method, apart from inserting a stent, to improve at least the medium-term patency of angioplasty. The patency after angioplasty is greatest for lesions in the common iliac artery and decreases distally, and with increasing length, multiple and diffuse lesions, poor-quality run-off, diabetes and chronic kidney disease.\textsuperscript{17}

2. Surgical Procedures: Surgery is advocated for many patients presenting with critical limb ischemia. Occasionally, it is used for individuals with lifestyle-limiting claudication.

Endarterectomy and bypass grafting are the two most commonly used surgical techniques. Generally, endarterectomy is feasible and offers an excellent success rate when used for proximal
arterial segments (aorta, iliac, common femoral or profunda arteries) and bypass grafting is preferable for distal, long, or diffuse disease.

For infrainguinal bypass procedures, autogenous vein grafts have higher patency rates (70% to 80% at 5 years) compared with prosthetic grafts. Operative complications include myocardial infarction and stroke, wound or graft infection, peripheral embolization, and sexual dysfunction secondary to autonomic nervous system injury. The operative mortality rate ranges from 1% to 3% and success rates depend on the lesion site and severity, anastomotic site, and status of the outflow system.18

CONCLUSION: PAD is a systemic atherosclerotic process associated with high morbidity and mortality and significant impairment of quality of life, yet it remains under diagnosed and undertreated. Symptomatic PAD often impairs a patient’s quality of life and untreated disease can lead to limb loss. Aggressive management of atherosclerotic risk factors, a structured exercise program, use of antiplatelet agents and, when indicated, percutaneous or surgical revascularization is the keys for successful management

REFERENCES:
1. Fowkes et al. Lancet 2013; 382( 9901): 1329-1340.
2. Peach G, Griffin M, Jones KG, et al; Diagnosis and management of peripheral arterial disease. BMJ. 2012 Aug 14; 345.
3. Norgren L, Hiatt WR, Dormandy JA et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg 2007; 45 (Suppl. S): S5–67
4. Becker F, Robert-Ebadi H, Ricco J-B et al. Management of critical limb ischaemia and diabetic foot. Clinical practice guidelines of the European Society for Vascular Surgery. Chapter 1: definitions, epidemiology, clinical presentation and prognosis. Eur J Vasc Endovasc Surg 2011; 42 (S2): S4–12.
5. Criqui MH: Peripheral arterial disease: epidemiological aspects. Vascular Medicine 6 (Suppl. 1) : 3–7, 2001.
6. Ubbink DT. Toe blood pressure measurements in patients suspected in leg ischaemia: a new laser Doppler device compared with photo-plethysmography. Eur J Vasc Endovasc Surg 2004; 27:629–34.
7. Agarwal S. The association of active and passive smoking with peripheral arterial disease: results from NHANES 1999–2004 Angiology, 60 (2009), pp. 335–345.
8. Willigendael E.M, J.A.W. Teijink, M.L. Bartelink, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease J Vasc Surg, 40 (2004), pp. 1158–1165.
9. Rowlands TE, Donnelly R. Medical therapy for intermittent claudication (review). Eur J Vasc Endovasc Surg 2007; 34: 314–21.
10. Chi U.W., Jaff M.R.; Optimal risk factor modification and medical management of the patient with peripheral arterial disease. Catheter Cardiovasc Interv. 71 2008:475-489.
11. Shalhoub J, Qureshi M, Davies A. Supervised exercise in intermittent claudication: a sedentary notion? Vascular 2009; 17: 66–73.
12. Mazari FAK, Khan JA, Carradice D et al. Randomized clinical trial of percutaneous transluminal angioplasty, supervised exercise and combined treatment for intermittent claudication due to femoropopliteal arterial disease. Br J Surg 2012; 99: 39–48.

13. Orgren L, Hiatt WR, Dormandy JA et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg 2007; 45 (Suppl. S): S5–67.

14. Yusuf S, Sleight P, Pogue J et al. 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 2000; 342: 145–53.

15. Hammas NW. Epidemiology, classification, and modifiable risk factors of peripheral arterial disease. Vasc Health Risk Manag 2007; 3: 229–34.

16. Mangiafico RA, Fiore CE; Current management of intermittent claudication: the role of pharmacological and Curr Vasc Pharmacol. 2009 Jul; 7 (3): 394-413.

17. Diagnosis and Treatment of Peripheral Artery Diseases, European Society of Cardiology (2011)

18. Thrombolysis in the management of lower limb peripheral arterial occlusion—a consensus document. Working party on thrombolysis in the management of limb ischemia. Am J Cardiol. 81: 1998; 207-218.

Table 1: Non-atherosclerotic causes of PAD

| Fontaine’s                          | Rutherford’s                          |
|------------------------------------|---------------------------------------|
| **Stage**                          | **Clinical presentation**              |
| I. Asymptomatic                    | 0. Asymptomatic                       |
| II. Intermittent claudication      | 1. Mild claudication                  |
| IIA: on walking >200 metres        | 2. Moderate claudication              |
| IIB: on walking <200 metres        | 3. Severe claudication                |
| III. Rest pain                     | 4. Rest pain                          |
| IV. Ulceration or gangrene         | 5. Minor ischaemic ulceration         |
|                                   | Severe ischaemic ulcers or frank gangrene |

Table 2: Fontaine’s and Rutherford’s classification of PAD
Table 3: Differential Diagnosis

| Clinical Condition     | Location of Pain | Association with Exercise | Relieved by                                      |
|------------------------|------------------|----------------------------|--------------------------------------------------|
| Intermittent Claudication | Calf, hip, buttock or thigh | Always                     | Stopping                                         |
| Lumbar Spinal Stenosis  | Calf, hip, buttock or thigh | Yes and also when standing | Flexing or moving the spine                      |
| Herniated disc         | Radiates down leg | Varies                     | Varies, Aspirin or inflammation drugs            |
| Osteoarthritis         | Hips, knees, ankles | Varies, Not always reproducible | Varies, Aspirin or inflammation drugs            |