

# Peripheral Arterial Disease in General and Diabetic Population

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### SUMMARY

Peripheral arterial disease (PAD) is stenosis or occlusion of peripheral arterial vessels by atherosclerotic plaque. It may present as intermittent claudication, rest pain and impotence. PAD of the lower limbs is the third most important site of atherosclerotic disease after coronary heart disease and cerebrovascular disease. Increasing age, family history, smoking, hypertension, dyslipidemia and more decisively diabetes are significant risk factors. PAD is a clinical condition that has often been neglected, underdiagnosed, undertreated and has a serious outcome. It may lead to nonhealing wounds, gangrene and amputation of the lower limbs. Hence, early identification of patients at risk of PAD and timely referral to the vascular surgeon in severe cases is crucial.

### KEY WORDS:

*Peripheral arterial disease, Intermittent claudication, Atherosclerotic plaque, Ischaemia, cerebrovascular disease*

### INTRODUCTION

Peripheral arterial disease (PAD) is stenosis or occlusion of peripheral arterial vessels by atherosclerotic plaque, which results in inadequate muscle perfusion and ischaemia<sup>1</sup>. It may present as intermittent claudication, rest pain and impotence<sup>2</sup>. It is one of a triad of vascular diseases caused by arteriosclerosis, the leading cause of death and disability in persons aged 50 years and above<sup>3</sup>. PAD of the lower limbs is the third most important site of atherosclerotic disease after coronary heart disease and cerebrovascular disease<sup>2</sup>. PAD is a clinical condition that has often been neglected, underdiagnosed, undertreated and has serious outcome<sup>3</sup>. Early identification of patients at risk of PAD, evaluating the disease progression with the use of appropriate tests, managing its complications and timely referral to the vascular surgeon in severe cases are important.

This review was prepared by searching the Proquest, Ovid full text and Medline with keywords PAD, PAD AND diabetes, PAD AND diagnosis AND management from year 1970-2004.

### Prevalence

The prevalence of PAD in the general population varies from 2% to 18% between the ages of 40 and 80 years<sup>2</sup>. In diabetic populations, the prevalence is higher and ranges from 10-42%<sup>4-6</sup>.

### Risk Factors

Epidemiological data among the general population have shown that male gender, ageing, family history, smoking,

diabetes mellitus, hypertension and dyslipidemia are significant risk factors for PAD,<sup>2</sup> and diabetes mellitus is a particularly important risk factor. PAD is commoner in males, especially atherosclerosis of the lower extremities in the elderly males,<sup>2</sup> but in diabetics, females have a similar prevalence<sup>5</sup>.

Hypertension is the most prevalent risk factor for atherosclerosis<sup>1</sup>. The Framingham data have documented a 2.5 fold increase in the risk of PAD in men with hypertension and 3.9 fold increase of the risk in women<sup>7</sup>.

PAD is more common among diabetics, and type 2 diabetics are 20 times more likely to develop PAD than non diabetics<sup>8</sup>. This is because PAD progresses more rapidly in diabetics and its disease pattern is more diffuse<sup>9</sup>. Diabetic patients are at greater risk of developing peripheral macroangiopathy and microangiopathy<sup>10</sup>. However, the detection of PAD in diabetics may be masked by the presence of peripheral neuropathy (PN) and calcification of medial arteries. In diabetic patients with PAD and PN, ischaemic symptoms are usually not felt due to reduced sensation and the ankle systolic pressure is not reduced while measuring ankle brachial pressure index (ABPI) due to calcification of medial arteries<sup>11</sup>. The American Diabetic Association has estimated that 40% to 50% of all DM related amputations are preventable<sup>8</sup>. Therefore early detection of PAD in the diabetic population is extremely important.

Dyslipidemia has been associated with an increased prevalence of PAD. Although some studies have documented total cholesterol concentration as an independent risk factor,<sup>12</sup> others have suggested that the ratio of high density to total cholesterol is perhaps a better predictor<sup>13</sup>. Hereditary disorders such as hypobetalipoproteinemia, type III hyperlipoproteinemia and lifestyle factors such as high fat diet and physical inactivity increase the severity of vascular disease<sup>1</sup>.

Smoking is a major risk factor for atherosclerosis<sup>1</sup>. The risk of PAD was documented to be twice in smokers as compared to non-smokers in the Framingham study<sup>7</sup>. The increased risk seems to correlate with the number of cigarettes smoked, and cessation of smoking has been associated with a rapid decrease in the risk of intermittent claudication<sup>7</sup>. Smokers have an increased rate of PAD progression, higher amputation rates and lower success rates following vascular intervention<sup>14</sup>.

### Staging of Pad

Leriche and Fontaine have classified PAD into four stages<sup>2</sup>. In

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stage 1, patients are usually asymptomatic, and at this stage history may reveal paresthesia and cold extremities and objective examination will show normal, diminished or absent pulses or an ankle brachial pressure index (ABPI) of less than 0.9. In stage two patients may exhibit symptoms of intermittent claudication (IC). This stage may be further subdivided into Stage 2A and 2B. In stage 2A pain occurs when the walking distance (WD) is greater than 200m and in stage 2B pain occurs even if the WD is less than 200m. Stage 3 is characterized by rest pain (critical ischaemia), which usually gives trouble at night. In stage 4, ulceration ranging from trophic lesions to gangrene are apparent. Stages 3 and 4 of PAD have been defined as chronic critical leg ischaemia<sup>2</sup>.

### Symptoms of Pad

Most patients with PAD have no symptoms until late in the disease, as the disease is not clinically evident until approximately 70% of the vessel's lumen is occluded<sup>1</sup>. Symptomatic PAD ranges in severity from IC to critical limb ischaemia. Intermittent claudication presents with a characteristic history of pain in the muscle, typically in the calf, thigh or buttock, which is elicited by exertion and relieved within a few minutes of rest. The level and extent of PAD determines the location of the pain and also the amount of exercise needed to produce it. The distal lesions in the femoral, popliteal, or tibial arteries produces a cramping pain in the calf muscles, while proximal or aortoiliac occlusive lesions usually bring on an aching discomfort, often associated with a sensation of weakness in the hip, buttocks or thigh<sup>15</sup>. Thus the patient's level of activity will influence the symptoms of IC. Patients who are active commonly experience functional limitation earlier than those who are sedentary<sup>16</sup>.

On the other hand, critical limb ischaemia is manifested by pain at rest, nonhealing wounds and gangrene. Ischaemic rest pain is typically described as a burning pain in the arch or distal foot that occurs while the patient is recumbent but is relieved when the patient returns to a position in which the feet are dependent. Major amputation is eventually needed in more than one third of these patients once the threatening symptoms and signs occur. Mortality is closely related to critical limb ischaemia, with a one-year mortality rate of about 20% in several series<sup>17</sup>.

### Complications of Pad

PAD may lead to nonhealing wounds, gangrene and amputations. Nonhealing wounds are usually found in areas of foot trauma caused by improper fitting shoes or an injury<sup>17</sup>. Gangrene is usually found on the toes and it develops when the blood supply is so low that spontaneous necrosis occurs in the most poorly perfused tissues<sup>17</sup>. Amputation is indicated in cases where extensive tissue necrosis or life-threatening infection occurs and in cases where the lesions are not amenable to surgery<sup>17</sup>. Diabetic patients with lower extremities PAD are at increased risk of developing these complications such as foot ulcer, ischaemia, gangrene and amputation<sup>10</sup>. The development of foot ulcers in persons with diabetes mellitus (DM) is due to a combination of PAD and peripheral neuropathy<sup>8</sup>. The risk of lower extremity amputation has been estimated to be 15 times greater in diabetics than non-diabetics<sup>10</sup>. In patients who have already

had a leg amputation, 30% of them require an amputation of the remaining limb within three years<sup>8</sup>. The mortality rate in diabetic patients after lower extremity amputation has been estimated to be about 5-7 times higher than the general population<sup>8</sup>.

A retrospective study carried out in General Hospital Kuala Lumpur in 1972-79 on 132 patients revealed that diabetes mellitus was the cause in 43% of all lower limb amputation. Moreover, patients with diabetes mellitus and PAD have a higher failure rate for below knee amputations carried out for gangrene of the extremities<sup>18</sup>. Hence the American Diabetic Association recommends comprehensive foot screening for all patients with DM, which includes vascular, neurological, musculoskeletal, skin and soft tissue evaluations, and these should be performed annually<sup>8</sup>.

### Diagnosis of Pad

The diagnosis of PAD can be made on the basis of physical examination, symptoms of IC by the use of Rose Questionnaires or Edinburgh Claudication Questionnaires<sup>16</sup> and by measuring ABPI.

### Physical Examination

Physical examination of patients with PAD may reveal absent or decreased peripheral pulses<sup>19</sup>. However the dorsalis pedis artery is congenitally absent in 2% of population and post tibialis artery in 0.1%<sup>20</sup>. Physical signs that further support the diagnosis of PAD include decreased skin temperature, shiny, hairless skin over the lower extremities, dystrophic toenails, pallor on elevation of the extremity and rubor when the limb is dependent<sup>19</sup>.

### Intermittent Claudication Questionnaires

The clinical diagnosis of PAD may be made on the basis of an accurate history by using the WHO/ROSE IC questionnaires or the Edinburgh Claudication Questionnaires, an improved version of the WHO questionnaire<sup>21</sup>. The ECQ was found to be 91.3% sensitive and 99.3% specific in detecting IC among general population compared to the clinical diagnosis of PAD<sup>21</sup>.

### Ankle Brachial Pressure Index

PAD is common but often goes undiagnosed because nearly 90% of patients do not report classical symptoms of IC<sup>22</sup>. Using classic symptomatic IC as a marker tends to substantially underestimate the prevalence of PAD<sup>22</sup>. In fact if non-invasive tests such as APBI are used to identify such problems in both symptomatic and asymptomatic patients, significant PAD appears to be 2-7 times more common than the prevalence of IC would suggest<sup>23</sup>. Hence screening at risk patients using the ABPI can increase the detection rate of PAD<sup>23</sup>.

The ABPI is measured by placing the patient in a supine position for 5 minutes. Brachial systolic blood pressure (BP) is measured in both arms and is used as the denominator of the ABPI. Ankle systolic BP is measured in a resting position with a 12-cm wide occluding cuff placed just above the ankle with a Doppler device used as a distal sensor<sup>25</sup>. Ankle systolic BP is then measured in the dorsalis pedis and the post tibial arteries. The higher value of the dorsalis pedis and the post

tibial arteries is taken as the numerator of the ABPI in each limb. ABPI is then calculated by dividing the ankle systolic BP by the brachial systolic BP in each limb<sup>24</sup>.

Ankle Brachial Pressure Index is an effective way to detect PAD. An ABPI of less than 0.90 is considered diagnostic of PAD. Mild disease correlates with an ABPI of 0.70 to less than 0.90, moderate disease correlates with an ABPI of 0.40-0.70, and severe disease correlates with an ABPI of less than 0.40<sup>9</sup>. The sensitivity of ABPI is 90% and the specificity is 98% for an angiographically defined stenosis of 50% or more in a major leg artery<sup>4</sup>. ABPI is a significant predictive variable for disease severity<sup>9</sup>. Hence the American Heart Association has recommended screening high-risk patients in clinical setting for PAD with the ABPI<sup>24</sup>.

However an ABPI value of more than 1.3 suggests poorly compressible arteries at the ankle level, which is especially common among the diabetics due to the presence of medial arterial calcification. This renders the diagnosis of ABPI less reliable in these patients and toe pressure index has been used as an alternative diagnostic tool<sup>9</sup>.

Other modalities of investigations such as colour duplex imaging, duplex ultrasound, magnetic resonance imaging and magnetic resonance angiography are reserved for a minority of patients in whom invasive intervention are considered<sup>25</sup>.

### **Treatment**

The most important step in treating patients with PAD is lifestyle modifications and exercise. This follows by addressing patient's risk factors.

### **Exercise**

All patients with PAD should be advised to exercise regularly. Exercise has been shown to improve peak walking distance and pain free walking distance by 100% or greater<sup>25</sup>.

## **RISK FACTOR MODIFICATIONS**

### **Smoking Cessation**

Complete and permanent cessation of smoking is by far the single most important factor determining the outcome of patients with IC<sup>17</sup>. Unfortunately the rates of smoking cessation after simple oral or written advice from a doctor are as low as 13% at two years<sup>25</sup>. However RCTs have shown that nicotine replacement treatment and bupropion approximately doubles the cessation rate<sup>25</sup>.

### **Hyperglycemia**

Although good glycaemic control has been established to slow progression of microvascular disease, there is conflicting evidence about whether it affects the severity or progression of PAD<sup>11</sup>. Nonetheless the combination of DM and PAD results in a worse prognosis with regards to local progression and eventual amputation<sup>11</sup>. Therefore aggressive glycaemic control remains important in diabetic patients with PAD<sup>11</sup>.

### **Hypertension**

Hypertension has been shown to be linked with PAD<sup>4,5,26</sup>. The Heart Outcome Prevention (HOPE) trial has shown that

ramipril, an angiotensin converting enzyme inhibitor, reduces cardiovascular morbidity and mortality in patients with PAD by 25%<sup>26</sup>. The ABCD (Appropriate blood Pressure control in Diabetes) trial showed that patients with PAD and DM, intensive blood pressure lowering to a mean of 128/75 mmHg had resulted in a marked reduction in cardiovascular events<sup>27</sup>.

### **Hyperlipidemia**

Hyperlipidemia is a common feature in PAD and is an important risk factor for macrovascular disease<sup>11</sup>. The heart protection study had shown that lowering total cholesterol and low-density cholesterol by 25% with a statins reduced cardiovascular mortality and morbidity in patients with PAD by around a quarter irrespective of age, sex or baseline cholesterol concentration<sup>16</sup>. Furthermore reducing serum cholesterol levels has been associated with improved endothelial function in patients with PAD<sup>26</sup>.

## **MEDICAL MANAGEMENT**

### **Antiplatelet Agents**

The Antiplatelet Trialists Collaboration showed that aspirin reduces vascular death in patients with atherosclerotic disease by about 25% and that antiplatelet agents were equally effective in patients who present with CAD and PAD. Clopidogrel is at least as effective as and possibly more effective than aspirin in patients with PAD and has a better side effect profile<sup>23</sup>.

### **Referral**

Patient with critical limb ischaemia (rest pain, gangrene or ulceration) should be referred urgently to vascular surgeons. Other circumstances when referral to vascular surgeon is appropriate include: a second opinion is needed on diagnosis, the resources needed to institute and monitor medical treatment are lacking, there is concern that the symptoms may have an unusual cause, the patient has unacceptable symptoms despite a reasonable trial of and adherence to medical treatment, or the patient has weak or absent pulses<sup>25</sup>.

### **Surgical Management**

Surgical intervention has been reserved for rest pain, tissue loss and patient defined disabling claudication. Improvement in blood supply to the lower limbs involves vascular surgical treatment by endarterectomy and or bypass surgery<sup>28</sup>. However outcomes from these interventions in patients with DM tend to be poorer than the nondiabetic patients and revascularization is technically more difficult in diabetic patients<sup>11</sup>.

### **Radiological Intervention**

Recently there has been a dramatic increase in the use of interventional radiological procedures for the treatment of acute and chronic lower extremity arterial disease. The primary indications for an interventional procedure in patients with lower extremity arterial disease include incapacitating claudication interfering with work or lifestyle, limb salvage in patients with limb-threatening ischemia as manifested by pain at rest, nonhealing ulcers, and/or infection or gangrene; and vasculogenic impotence<sup>29</sup>. These interventional treatments include percutaneous transluminal

angioplasty (PTA), which accounts for approximately 30% of re-vascularization procedures, intravascular stents, and the more widespread use of intra-arterial thrombolysis for the treatment of peripheral arterial thrombosis<sup>29</sup>.

## CONCLUSION

More emphasis should be placed on preventive care, early detection and health promotion of such a common disease in an effort to improve quality of life and curb the rising health care costs associated with peripheral arterial disease.

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## Peripheral Arterial Disease in General and Diabetic Population

### MCQ'S:

1. Peripheral arterial disease may present as
  - A. Pain in calf muscles
  - B. Headache
  - C. Rest pain
  - D. Impotence
  - E. Weakness
  
2. Important risk factors for PAD are
  - A. Hypertension
  - B. Diabetes mellitus
  - C. Physical activity
  - D. Smoking
  - E. Male gender
  
3. In patients with diabetes PAD is
  - A. More common
  - B. Progress slowly
  - C. Localized
  - D. Associated with microangiopathy
  - E. Less symptomatic
  
4. Complications of PAD are
  - A. Ulceration
  - B. Numbness
  - C. Gangrene
  - D. Amputation
  - E. Ischaemia
  
5. The diagnosis of PAD can be made on the basis of
  - A. Absence of peripheral pulses
  - B. Symptoms of intermittent claudication
  - C. Ankle brachial pressure index  $>0.90$
  - D. Colour duplex imaging
  - E. CT scan