

Epidemiology, classification, and modifiable risk factors of peripheral arterial disease

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Abstract: Peripheral arterial disease (PAD) is part of a global vascular problem of diffuse atherosclerosis. PAD patients die mostly of cardiac and cerebrovascular-related events and much less frequently due to obstructive disease of the lower extremities. Aggressive risk factors modification is needed to reduce cardiac mortality in PAD patients. These include smoking cessation, reduction of blood pressure to current guidelines, aggressive low density lipoprotein lowering, losing weight, controlling diabetes and the use of oral antiplatelet drugs such as aspirin or clopidogrel. In addition to quitting smoking and exercise, cilostazol and statins have been shown to reduce claudication in patients with PAD. Patients with critical rest limb ischemia or severe progressive claudication need to be treated with revascularization to minimize the chance of limb loss, reduce symptoms, and improve quality of life.

Keywords: peripheral arterial disease, epidemiology, risk factors, classification

Epidemiology of peripheral arterial disease (PAD)

PAD affects 12%–14% of the general population and its prevalence increases with age affecting up to 20% of patients over the age of 75 (Hiatt et al 1995). Coexistent coronary artery disease (CAD) and cerebrovascular disease (CVD) are highly prevalent in patients with PAD particularly in the elderly population. Recent data from the Reduction of Atherothrombosis for Continued Health registry presented at the American College of Cardiology Annual Scientific Sessions (Bhatt 2005) showed that among 7013 patients with symptomatic PAD, polyvascular disease was present in 63%. Furthermore, patients over the age of 50 and with PAD in an academic, hospital-based geriatric practice have a 68% and 42% incidence of coexistent CAD and stroke respectively (Ness and Aronow 1999).

The PAD patients are at an exceptionally high risk for cardiovascular events and the majority will eventually die of a cardiac or cerebrovascular etiology. The more symptomatic and severe the PAD as objectively measured by the ankle-brachial index (ABI), the worse the overall prognosis of the patient. Criqui et al (1992) evaluated the association of large-vessel PAD with rates of mortality from all CVD and CAD. The relative risk of dying among subjects with large-vessel PAD versus none was 3.1 (95% CI 1.9–4.9) for deaths from all causes, and 5.9 (95% CI 3.0–11.4) for all deaths from cardiovascular disease. Mortality due to cardiovascular disease was 15-fold more among symptomatic subjects with severe large-vessel PAD. Finally, PAD has been classified as a coronary heart disease (CHD) risk equivalent, ie, carrying >20% risk of a coronary event in 10 years. The Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001) classified diabetes, multiple cardiac risk factors that confer a 10-year risk of >20%, and PAD including carotid disease and abdominal aortic aneurysm as a CHD risk equivalent.

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PAD is very thrombogenic and consists of a large percentage of diabetics, hyperlipidemics, and smokers conditions all associated with endothelial dysfunction and a hypercoagulable state (Shammas and Dippel 2005). Also, patients with PAD have a heightened inflammatory state similar to patients with unstable angina. In a study by Rossi et al (2002), 51 patients with symptomatic PAD were followed for 24 months. Of these patients 17 (34%) had fatal (11) or non-fatal (6) myocardial infarction (MI). Multivariate logistic regression analysis showed that only high C-reactive protein (CRP) values were significantly associated with MI ($p < 0.05$).

The natural history of PAD indicates that among patients with intermittent claudication, 7% will undergo lower extremity bypass surgery, 4% major amputations, and 16% worsening claudication. However, non-fatal cardiovascular events (MI, stroke) occur in approximately 20% over a 5-year period and the 5-year mortality rate is estimated to be 30% (versus 10% in controls), of which 75% were cardiovascular deaths (Weitz et al 1996).

Treatment of the PAD patient has the following goals: 1) reduce cardiovascular mortality in this high risk population, 2) improve quality of life in severe claudicants, and 3) lower the chance of amputation in patients with critical limb ischemia as manifested by rest limb pain or ulceration.

Classifying the PAD patient

Asymptomatic PAD

Asymptomatic PAD is typically suspected by clinical examination of the lower extremity pedal pulses. The ABI is a simple test that can be conducted in the office and typically would confirm the presence of disease. An ABI is calculated by dividing the ankle pressure over the highest brachial pressure. An ABI < 0.9 is abnormal and indicates PAD. An ABI between 0.7 and 0.9 is considered mild disease, 0.5 and 0.69 is moderate disease, and less than 0.5 is severe disease.

Intermittent claudication (IC)

IC is defined as discomfort in the calf muscles with exertion that resolves after a few minutes of rest. IC is present in 5% of men and 2.5% of women over the age of 60. In a study by Jernes et al (1986) the natural history of 257 patients with IC but no rest limb pain were followed for a mean of 6.5 years. Rest pain or gangrene of the worst affected leg was 7.5% in the first year after referral. Thereafter the rate was 2.2% a year.

Amputation is infrequent in claudicants and occurs in 5.8% of patients at a mean follow-up of 2.5 years (Imparato

et al 1975). There are many classifications for claudication and limb ischemia but a most utilized one is the Rutherford-Baker (R-B) classification (Rutherford et al 1997): R-B I indicates essentially asymptomatic patients or symptoms at very high level of activity, R-B II is symptoms at moderate level of activity, R-B III is symptoms at low level of activity, R-B IV is symptoms at rest, R-B V is ulceration, R-B VI is ulceration with tissue necrosis. Claudicants are considered in the R-B I-III. Typically, endovascular or surgical interventions are reserved for IC Class III and higher.

Chronic limb ischemia

Chronic limb ischemia (CLI) is pain in the lower extremity at rest or ulceration with and without tissue necrosis (R-B IV-VI). Aggressive treatment of CLI is needed, as progression to amputation is frequent. In patients with wound ulcers treated without revascularization, a high incidence of amputation has been reported particularly in patients with an ABI < 0.5 . Martson et al (2006) reported on the natural history of limb ulceration in 142 patients with 169 limbs having ischemic limb ulcerations and not surgical candidates because of comorbidities or lack of suitable targets for revascularization. All ulcers were treated with a protocol emphasizing pressure relief, debridement, infection control, and moist wound healing. The incidence of diabetes mellitus was 70.4% of limbs and chronic renal insufficiency 27.8%. Limb loss was more prevalent in patients with ABI < 0.5 with 28% and 34% experiencing limb loss at 6 and 12 months, respectively, compared with 10% and 15% of limbs in patients with an ABI > 0.5 ($p = 0.01$). Of all limbs included, 23% required amputation at 12 months. Overall the primary amputation rate in CLI patients is 10%–40% with a mortality rate of 20% at 1 year, 40%–70% at 5 years, and 80%–95% at 10 years (Dormandy et al 1999).

Acute limb ischemia (ALI)

ALI occurs within hours of presentation and is associated with rest limb pain and a pulseless, painful foot. The vessel is typically occluded with a thrombus that has occurred on top of mild to severe lesions. Collaterals are generally minimal or none. ALI occurs because of plaque rupture followed by in situ thrombosis or migration of a clot from a proximal location. The treatment of ALI is an emergency to save the limb.

Modifiable risk factors of PAD

Modifiable risk factors for PAD are not different from patients with coronary artery disease. Major risk factors include

smoking, hyperlipidemia, hypertension, diabetes, and the metabolic syndrome. PAD is also more prevalent in males and in the elderly.

Diabetes

Diabetes is one of the strongest predictors for PAD and its associated complications including higher mortality and amputation; the latter is predicted by the presence of neuropathy, retinopathy, low ABI, and male gender. In a cross-sectional analysis of a 4153 Greek adults (Athiros et al 2004) the odds ratio for vascular disease was 1.94 (95% CI 1.35–2.47) for patients with the metabolic syndrome, 3.04 (95% CI 1.98–4.11) for patients with the metabolic syndrome and diabetes, and 1.48 (95% CI 1.12–1.92) for patients with the metabolic syndrome but no diabetes. In this study, the presence of the metabolic syndrome and diabetes yielded a higher risk for PAD than either one alone. Hamalainen et al (1999) reported on 733 diabetic patients who were followed for 7 years after undergoing podiatric, circulatory, and neurophysiological examinations. Amputated patients were then compared with patients with no amputations. Using multivariate analysis, vibration perception threshold, low ABI, history of retinopathy, visual handicap, and male sex were independently associated with lower extremity amputation. Patient education is of paramount importance to reduce amputations in the diabetics secondary to foot ulceration.

Smoking

Smoking is also a powerful risk factor for PAD promoting endothelial dysfunction, and altering lipid metabolism and coagulation (Lu and Creager 2004). Price et al (1999) followed 1592 men and women aged 55–74 years selected at random from 11 general practices in Edinburgh, Scotland for 5 years. The incidences of PAD and CAD were 5.1% and 11.1%, respectively. Cigarette smoking was a stronger risk factor for PAD than for CAD. Smoking was associated with an increase in coagulation and endothelial dysfunction markers. Current smoking of 25 or more cigarettes increased the odds ratio of PAD by 7.3 times (95% CI 4.2–12.8). Furthermore, current smokers seem to have a higher rate of procedural complications following percutaneous interventions. In one study (Shammas et al 2003) a total of 131 patients with PAD were evaluated for in-hospital predictors of complications following percutaneous peripheral intervention (PPI). Forty-five patients (34.4%) had recent onset of claudication and 15 (11.5%) had ulceration. Thrombus was angiographically visualized in 16.7% of patients. The best model associated

with emergent salvage revascularization included cigarette smoking within the past year, recent onset of claudication, and percutaneous transluminal angioplasty treatment below the knee. Smoking was a strong independent predictor of the risk for unplanned urgent revascularization of the lower extremities following initial successful treatment.

Dyslipidemia

Dyslipidemia is also significant risk factors for PAD. Familial hypercholesterolemia increases the prevalence of PAD from 5-fold to 10-fold compared with non-hypercholesterolemia subjects and its treatment with statins reduces the incidence of IC and increases walking duration. In a study by Ridker et al (2001), the predictive value of 11 lipid and non-lipid biomarkers as risk factors for development of PAD was compared. Of 14 916 initially healthy US male physicians, 40–84 years of age, 140 developed symptomatic PAD and were age- and smoking-matched to 140 men who remained free of vascular disease during an average 9-year follow-up. Multivariate analysis showed that the total cholesterol-HDL-C ratio (RR for those in the highest vs lowest quartile, 3.9; 95% CI 1.7–8.6) and CRP (RR for the highest vs lowest quartile, 2.8; 95% CI 1.3–5.9) were the strongest independent predictors for development of PAD. The addition of CRP to standard lipid screening significantly improved risk prediction models based on lipid screening alone ($p < 0.001$).

Obesity

Obesity is also a significant risk factor for atherosclerosis and PAD. In one study body fat was strongly associated with elevated inflammation markers including CRP and fibrinogen, which are predictors for active diffuse atherosclerotic disease. In a study by Gorter et al (2004) the prevalence of the metabolic syndrome in patients with atherosclerotic vascular disease was determined in 1117 patients, mean age 60 years. The prevalence of the metabolic syndrome in the study population was 46%: 58% in PAD patients, 41% in CHD patients, 43% in CVD patients, and 47% in abdominal aortic aneurysm patients. Also Planas et al (2001) have shown that the waist-to-hip ratio was independently associated with PAD. In a cross-sectional study of 708 men, aged 55–74, the relationships between total body fatness (assessed by body mass index (BMI)) and abdominal fat distribution (assessed by waist-to-hip ratio) was determined in patients with PAD (assessed by ABI). BMI did not correlate with PAD, whereas an increased waist-to-hip ratio over the median value doubled the prevalence of arterial disease. After controlling

for smoking, diabetes, hypertension, high-density lipoprotein cholesterol, and triglycerides, increased waist-to-hip ratio was independently associated with PAD (OR 1.68; 95% CI 1.05–2.70).

Hypertension

Lastly, hypertension is also positively associated with PAD (Selvin and Erlinger 2004) as shown in the National Health and Nutrition Survey (NHANES) data. In this study, 2174 participants >40 years of age from the 1999–2000 National Health and Nutrition Examination Survey were included. PAD (ABI <0.9 in either leg) was prevalent in 4.3% of patients. Among those >70 years of age, the prevalence was 14.5%. Current smoking (OR 4.46, 95% CI 2.25–8.84), diabetes (OR 2.71, 95% CI 1.03–7.12), hypertension (OR 1.75, 95% CI 0.97–3.13), hypercholesterolemia (OR 1.68, 95% CI 1.09–2.57), and low kidney function (OR 2.00, 95% CI 1.08–3.70) were positively associated with prevalent PAD. In this study, PAD prevalence appears to disproportionately affect blacks (OR 2.83, 95% CI 1.48–5.42).

Treatment of patients with PAD

Medical therapies

The focus of PAD treatment is: 1) to reduce symptoms and improve quality of life, and 2) to reduce overall cardiovascular morbidity and mortality.

Smoking cessation

This an important step to reduce symptoms of claudication and the overall burden of cardiovascular complications of atherosclerosis (Weitz et al 1996). In a recent study current smoking and pack-years of smoking correlate with the presence of PAD and smoking cessation for 20 years or more was associated with a higher mean ABI and lower prevalence of lower ABI (<0.9) than current smokers (Cui et al 2006). Smoking cessation and exercise are considered the two most important treatments for PAD (Mukherjee and Yadav 2001).

Exercise

Exercise has also been shown to improve symptoms of claudication and prolong pain-free walking time and distance and improve peak oxygen consumption. Exercise needs to be performed regularly with benefit becomes noticeable in few months. The exact mechanism by which exercise contributes to improvement in walking distance is unclear. Exercise, however, reduced resting plasma short-chain acylcarnitine (associated with functional impairment of PAD patients) by

26% that correlated with improvement in peak walking time ($r = -0.78$, p less than 0.05) (Hiatt et al 1990). In a randomized study by Hiatt et al (1990) 19 patients with disabling claudication were randomized to exercise (supervised treadmill walking [1 hour/day, 3 days/week, for 12 weeks] with progressive increases in speed and grade as tolerated) and compared with a control group. Exercise subjects increased their peak walking time 123%, peak oxygen consumption 30%, and pain-free walking time 165% (all $p < 0.05$). Control subjects had no change in peak oxygen consumption, but after 12 weeks, peak walking time increased 20% ($p < 0.05$). Exercise is an important therapeutic recommendation to patients with PAD (Mukherjee and Yadav 2001).

Cilostazol

This pharmacological agent also has been shown to increase walking distance after 24 weeks of treatment by a mean 54% from baseline compared with placebo or pentoxifylline. In a double-blind, placebo-controlled, multicenter, randomized trial by Dawson et al (2000) to evaluate the relative efficacy and safety of cilostazol and pentoxifylline, 698 patients were randomly assigned to blinded treatment with either cilostazol (100 mg orally twice a day), pentoxifylline (400 mg orally 3 times a day), or placebo. The primary endpoint was walking distance with constant-speed, variable-grade treadmill testing at baseline and at 4, 8, 12, 16, 20, and 24 weeks. The improvement with pentoxifylline was similar ($p = 0.82$) to that in the placebo group whereas cilostazol increased walking distance by 54% from baseline. Cilostazol has multiple pharmacologic actions including reduction in platelet aggregation, vasodilatation and improving lipid profile (Schorr 2002)

Statins

Statins have also been shown to reduce claudication and increase walking distance by 24% at 6 months and 42% at 1 year compared with placebo. Statins are also essential to reduce cardiovascular events in patients with atherosclerotic disease irrespective of lipid levels. Aronow et al (2003) has found that simvastatin significantly increased treadmill exercise time until onset of claudication by 24% ($p < 0.0001$) at 6 months and 42% ($p < 0.0001$) at 1 year after treatment with no change in these parameters in the control group. Furthermore, in a study by Mondillo et al (2003), high-dose (40 mg/day) short-term therapy with simvastatin in 43 patients with symptomatic PAD and a total cholesterol >220 mg/dL improved walking performance (mean 126 m improvement in distance; 95% CI 101–151 m; $p < 0.001$), ankle-brachial

pressure indices (mean, 0.09; 95% CI 0.06–0.12; $p < 0.01$), and symptoms of claudication compared with a control group of 43 patients receiving placebo. Statins are important drugs to reduce cardiovascular events in patients with documented vascular disease and therefore a low threshold to use these drugs in patients with PAD is warranted.

Antithrombotic therapy (aspirin or ADP-receptor antagonists clopidogrel or ticlopidine)

Antithrombotic therapy has not been shown to improve symptoms of claudication but is important to reduce cardiovascular complications associated with the presence of atherosclerosis and PAD. The Antithrombotic Trialist Collaboration (2002) showed that a low dose aspirin (75–150 mg) reduces vascular events by 32% in the high-risk patient including the subset of patients with PAD ($p = 0.004$). In this meta-analysis of 287 randomized trials involving 135 000 patients in comparisons of antiplatelet therapy versus control and 77 000 in comparisons of different antiplatelet regimens among each others in high risk patients (with acute or previous vascular disease or some other predisposing condition), “serious vascular event” including non-fatal MI, non-fatal stroke, or vascular death were reduced in the antiplatelet group. In addition, in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial (CAPRIE 1996), the long-term administration of clopidogrel to patients with atherosclerotic vascular disease (follow-up for 1–3 years) was more effective than aspirin in reducing the combined risk of ischemic stroke, MI, or vascular death (5.83% versus 5.32% for aspirin versus clopidogrel respectively, $p = 0.045$).

Ticlopidine also has protective effects probably similar to clopidogrel in the high-risk vascular patient but its adverse side-effects have limited its use. The long-term use of the clopidogrel-aspirin combination compared with aspirin alone was recently published in the Clopidogrel and Aspirin versus Aspirin alone for the Prevention of Atherothrombotic Events (CHARISMA) trial (Bhatt et al 2006). The CHARISMA trial has enrolled 15 603 patients with established CAD, CVD, or PAD, or at high risk of developing atherothrombosis due to multiple risk factors. These patients were randomized to receive either clopidogrel or placebo, in addition to low- to moderate-dose aspirin. The rate of the primary efficacy end point was 6.8% with clopidogrel plus aspirin and 7.3% with placebo plus aspirin (RR 0.93; 95% CI 0.83–1.05; $p = 0.22$). Clopidogrel added to aspirin was not significantly more

effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes. In the subgroup of patients with documented vascular disease, the rate was 6.9% with clopidogrel and 7.9% with placebo (RR 0.88; 95% CI 0.77–0.998; $p = 0.046$). There was a suggestion of benefit with clopidogrel treatment in patients with symptomatic atherosclerotic vascular disease and a suggestion of harm in patients with multiple risk factors but no documented atherosclerosis. Currently clopidogrel alone or aspirin alone are strongly recommended in patients with PAD. Patients, however, with a recent acute coronary syndrome will benefit from the combination of aspirin and clopidogrel for at least 1 year after the event (CURE 2001).

Revascularization therapies

Revascularization is indicated for the relief of ischemic symptoms, particularly when medical therapy fails or is insufficient. There are two primary goals of revascularization: first, to relieve symptom-limiting claudication or rest ischemic pain; second, to minimize tissue loss or limit the degree of amputation.

Over the past decade there has been an exponential rise in lower extremity PPI with a concomitant drop in surgical interventions (Anderson et al 2004). Most patients with advanced PAD have occult or symptomatic coronary/cerebral vascular disease, and thus the mortality of peripheral bypass surgery may exceed 10% in high-risk patients (Dormandy and Rutherford 2000).

Minimally invasive endovascular therapy offers inherent advantages over traditional surgical revascularization, such as lower morbidity, shorter hospital length of stay, and considerably less patient discomfort. As the field of endovascular therapy continues to grow, the need for traditional surgical therapies will be considerably reduced. The discussion of revascularization techniques is beyond the scope of this manuscript.

In summary, PAD is a part of a diffuse atherosclerotic problem and a marker of cardiac and cerebrovascular mortality. Initial therapy is preventive for all patients with a focus on aggressively controlling modifiable traditional risk factors for coronary artery disease and PAD. Smoking cessation, controlling elevated blood pressure and blood glucose, losing excess body fat, exercise, treating hyperlipidemia with statins, and the use of antiplatelets are crucial first steps in the management of the PAD patient. Revascularization is reserved for the very symptomatic patient or those with critical limb ischemia.

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