

PERIPHERAL ARTERIAL DISEASE

ALAA ALAHMAD, MD. MARWAN NASIF, MD.

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DEFINITION

Peripheral arterial disease (PAD), previously known as peripheral vascular disease (PVD) is the narrowing or blockage of the arteries in the legs which may lead to a decrease in blood supply to the lower extremities. The consequences of that is the development of pain and muscle weakness in the legs associated with exertion which leads to limited activity and poor life quality. Sometimes, PAD might lead to the development of foot ulcers, chronic pain, and occasionally amputation.

BACKGROUND

Peripheral arterial disease is a major national public health problem. PAD is associated with a profound impact in the quality of life and functional status, even for individuals who do not

report leg symptoms (1). Despite the high prevalence of PAD and the increased risk of mortality and morbidity of cardiovascular diseases in individuals with PAD, it is still underdiagnosed and undertreated because of lack of symptoms, subtle clinical findings, and lack of awareness. Three out of four people are not aware of PAD and few Americans know that having PAD significantly increases the risk for heart attack and stroke (2). Diagnosis of PAD is essential to improve life quality, prevent further functional impairment, and to reduce cardiovascular disease mortality and morbidity. This chapter will review the incidence, causes, risk factors, symptoms and clinical manifestation, complications, diagnosis, and management of PAD.

EPIDEMIOLOGY

The prevalence of PAD differs widely depending on the population, the diagnostic tool used, and the methods of the study. Based on the National Health and Nutrition Examination Survey (NHANES), approximately 8 to 10 million people in the United States had PAD in 1999-2000. The incidence of PAD increases substantially with age in both sexes at a rate of 1.5 to 2 fold for every 10 year increase in age. PAD affects 4 percent of people 40 years of age or older, however, the prevalence increases to 14.5 percent at age 70 (3). The prevalence of PAD is 25 to 30% among people with multiple risk factors in primary care settings (5). There is no substantial difference in PAD incidence between men and women, nevertheless, African-Americans have a 2.4 fold increase in prevalence than the non-Hispanic white population (3, 5). Individuals with PAD are at a 3 times increased risk for all cause mortality compared with the general population. Also, they are 6 times more likely to have a heart attack and 2 to 3 times more likely to have a stroke within the next 10 years (6). The cost of PAD-related treatment was 4.37 billion dollars in the Medicare population; however, this is not including the undiagnosed people (7).

RISK FACTORS

PAD shares the same risk factors related to coronary artery disease and stroke. Major risk factors include smoking, diabetes, hypertension, dyslipidemia (abnormal cholesterol levels), and obesity.

Smoking: Smoking is probably the most important risk factor for PAD. Cigarette smoking increases the risk of PAD by 7 fold. Smoking is associated with PAD more strongly than coronary artery disease (CAD) (8). In addition, current smokers appear to have higher rates of complications than non-smokers following invasive interventions. The incidence of limb amputation is 10 times higher in those who continue to smoke after developing arterial occlusion than in those who quit. Smoking cessation is essential in the management of PAD (9).

Diabetes: Diabetes is another major risk factor for PAD and its complications. PAD is twice more common among patients with diabetes than non-diabetic patients. Because it is accompanied with peripheral neuropathy (decreased sensation in the extremities especially legs and feet), the symptoms of PAD among patients with diabetes are often more subtle and the classic intermittent claudication (pain that occurs with walking and usually improves with rest) is less common. Foot ulcerations, infection, and gangrene may be the initial presentation of peripheral arterial disease among patients with diabetes. PAD in patients with diabetes are usually more diffuse and distal (10). Insulin resistance is also a risk factor for PAD even in individuals without diabetes (11).

Hypertension: Elevated blood pressure is associated with an approximate 2 fold increase in the risk of PAD. 2 to 5% of hypertensive patients have intermittent claudication, while 35 to 55% of patients with PAD at presentation have hypertension (12, 13). Although the large

epidemiological studies show a clear association between hypertension and PAD, the relative risk is stronger with coronary artery disease and stroke. This risk seems to increase with increased systolic blood pressure.

Dyslipidemia: Dyslipidemia (abnormal cholesterol) is also a significant risk factor for PAD. It is estimated that for every 10mg/dl increase in the total cholesterol concentration, the risk for developing PAD increases by approximately 10%. Different cholesterol molecules including low-density lipoprotein cholesterol (LDL-C), triglycerides, and lipoprotein (LPa) are independent predictive risk factor for developing PAD (14), whereas patients with relative elevation of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-1 are less likely to have PAD (15).

Obesity: Obesity is also an important risk factor for developing PAD. Increased waist to hip ratio of more than 0.966 (median value) was found to be independently associated with PAD. In studies, it found that body mass index (BMI) did not correlate with PAD after controlling for smoking, diabetes, hypertension, high-density lipoprotein cholesterol, and triglycerides (16). Obesity leads to worsening of intermittent claudication, physical function, and health-related quality of life in the individuals with PAD.

CLINICAL MANIFESTATIONS

SYMPTOMS: Most patients with PAD do not have symptoms. Asymptomatic PAD is typically detected only by a low ankle-brachial index (ABI) or incidentally on physical exam. An ABI is the ratio of blood pressure measured in lower extremities compared to the upper extremities to help detect blockages in the legs. Intermittent claudication (IC), the classical manifestation of PAD, occurs only in 10% of patients. Intermittent claudication is characterized

by muscle pain, aching, leg heaviness, or cramping pain in the feet, calf, thigh, or hip that is aggravated by walking or climbing stairs and resolving with rest. Chronic critical limb ischemia is manifested by pain at rest, nonhealing wounds, and gangrene. Ischemic rest pain is described as nocturnal burning pain that is located on the arch or distal foot. This pain is aggravated by leg elevation and relieved, paradoxically, by walking and placing the legs in a dependent position. Rest ischemic pain implies severe critical PAD. Gangrene may result and necessitate the amputation of toes or foot. PAD may present with acute leg ischemia in 1-2% of patients. The cardinal six signs of acute limb ischemia are pain, pallor (pale), paralysis, paresthesias (numbness/tingling), poikilothermia (cool), and pulselessness. The extent of tissue damage is determined by the duration and degree of ischemia and the sensitivity of the tissues to ischemia.

PHYSICAL FINDINGS: A routine complete cardiovascular examination should include palpation and auscultation of all the accessible arteries in the neck, upper extremities, abdomen, and pelvis, in addition to the lower extremity arteries. A complete lower extremity circulation evaluation includes palpation of arteries of the leg including femoral, popliteal, dorsalis pedis, and posterior tibial arteries for any weak or absent pulses. A thorough inspection of the lower extremities for any signs of chronic peripheral arterial disease such as hair loss, thickened and brittle toenails, shiny leg skin, pale or cyanotic (blue) feet, dependent rubor (redness developing in the area of foot when it hangs in a dependent position), skin fissures, ulcerations, and gangrene (death of tissue because of lack of blood supply). Ulceration and gangrene are sometimes the initial presenting symptoms of PAD.

DIAGNOSIS:

The diagnosis of peripheral disease is confirmed by a non-invasive test called the Ankle-Brachial Index (ABI). This test compares blood pressure measurements taken by a hand-held device, called a Doppler, in the lower leg with those taken in the arm. An ABI of 0.91 to 1.30 is normal. Meanwhile, an ABI <0.90 indicates peripheral arterial disease, and an ABI >1.30 suggests the presence of calcified vessels. Ultrasonography may also be used to evaluate the severity and the location of the narrowing. Other non-invasive diagnostic tools include magnetic resonance angiography (MRA) and Computed Tomography Angiography (CTA).

PERIPHERAL ARTERIAL DISEASE MANAGEMENT

The goals of peripheral arterial disease treatment include symptom relief, improvement in functional status, and preventing cardiovascular complications including heart attack, stroke, and cardiac death. The peripheral arterial management includes cardiovascular risk factor modification, exercise rehabilitation, and pharmacotherapy.

I-Cardiovascular Risk Factors Modification:

Smoking cessation: Smoking is associated with a marked increased of the risk for PAD; thus, smoking cessation is a cornerstone of PAD management. Smoking cessation primarily leads to the reduction of cardiovascular events, but also lowers the risk of amputation and improves the long term patency of graft after revascularization (17.18). Physicians should strongly advise all patients who smoke to quit smoking at every visit, provide referrals to group counseling and smoking cessation programs, as well as provide pharmacotherapy assistance to augment quitting to all motivated smokers. The medications used to help with smoking cessation include nicotine

replacement in many forms including gum or patches, antidepressant medications such as bupropion, or the most recent FDA approved medication for this cause, Chantix.

Glucose Control: Despite the lack of evidence that aggressive blood sugar control might reduce the macrovascular (large vessel) complications of diabetes such as PAD, it is still essential in PAD management. For every 1% increase in hemoglobin A1C (a measurement of average blood sugar values over prolonged periods) there is a corresponding 26% increase in the incidence of PAD (19). The current American Diabetes Association recommends hemoglobin A1C of less than 7.0 as a target goal of glycemic control.

Blood Pressure Control: Hypertension is an important risk factor for PAD. The target goal for blood pressure control is less than 140/90 mmHg and less than 130/80 if the patient has diabetes or renal insufficiency. All blood pressure medications are effective in reducing the cardiovascular events. Some blood pressure medications may be better in certain situations. Thiazide diuretics are the preferable first line medication, especially for the African American population. ACE-Inhibitors are the drug of choice in patients with diabetes, chronic kidney disease, and congestive heart failure. ACE-Inhibitors may increase the perfusion function and walking distance in patients with PAD (20). Some patients, especially African Americans, might need multiple drugs to control blood pressure (21). Beta-adrenergic blocking drugs are not contraindicated in PAD as previously thought, and can be given to treat hypertension in patients with PAD, especially in those who have concomitant coronary artery disease (22).

Dyslipidemia Control: The targeted goal for lipids in patients with symptomatic or asymptomatic PAD is to achieve a level of LDL cholesterol of less than 100mg/dl and less than 70mg/dl in very high risk patients. Diet modification and exercise should be the first line

intervention to achieve the target goal. The Heart Protection Study (HPS) has shown strong evidence supporting the use of a class of cholesterol lowering medications called statins to lower LDL cholesterol in patients with PAD. Statins reduce all causes of death, cardiovascular mortality, cardiovascular events, and non-coronary revascularization in the individuals with PAD (23). In patients with elevated triglyceride (>140mg/dl) or low HDL cholesterol (HDL<40mg/dl), other cholesterol lowering medications including Niacin or Fibrates are recommended.

Weight reduction: Obesity is a major risk for cardiovascular disease including peripheral arterial disease. Obesity decreases the time to claudication in individuals with peripheral arterial disease and increases the time needed for recovery after exercise. The management of overweight and obesity requires a comprehensive plan including diet, regular exercise, and behavior changes.

II-Exercise Rehabilitation:

Physical activity is essential in the management of patients with claudication. Daily exercise increases the distance of pain-free walking. The American College of Cardiology/American Heart Association recommends supervised exercise training programs for a minimum of 30 to 45 minutes for at least 3 times/week. A Cochran meta-analysis showed that exercise results in significant improvements in walking time compared to angioplasty and anti-platelet medications (24). Limitations of exercise rehabilitation are lack of coverage by medical insurance, lack of motivation, and lack of availability.

III-Pharmacotherapy:

Antiplatelet treatment: Given the higher incidence of heart attack and stroke in patients with PAD plus the higher all cause and cardiovascular mortality compared to patients without PAD, the ACC/AHA guidelines recommend Aspirin for individuals with PAD, particularly in patients with coronary heart disease and history of stroke. Ticlopidine also has been shown to reduce the risk of myocardial infarction, stroke, and vascular death, but its use has declined substantially because of side effects, such as neutropenia (low white blood cell counts) and thrombocytopenia (low platelet counts). It has also been shown that Clopidogrel reduces the risk of heart attack, stroke and vascular death in individuals with PAD (25).

Cilostazol: A selective phosphodiesterase inhibitor that inhibits platelets aggregation, thrombin formation, and vascular smooth muscle proliferation. It is a direct arterial vasodilator. It is an FDA-approved medication to treat recurrent claudication. It is contraindicated in patients with congestive heart failure (CHF). Common side effects of Cilostazol include headache, diarrhea, gastric upset, and palpitations.

Pentoxifylline: A methylxantin derivative that improves blood flow through blood vessels. It has an anti-inflammatory property. It is also a FDA-approved medication for claudication treatment. Common side effects include nausea, constipation, loss of appetite, and blurred vision.

PERIPHERAL ARTERIAL DISEASE IN WOMEN

According to National Health and Nutrition Examination Surveys (NHANES), the prevalence of peripheral arterial disease has increased from 4.1 percent in 1999-2000 to 6.3 percent in 2003-2004. This may be explained by the increasing prevalence of obesity in women (26). According to the survey, only

28% of women know about the disease. Women with peripheral arterial disease are 2 to 4 times more likely to suffer from coronary heart disease or stroke than women without PAD, and 2 to 3 times more likely to die from cardiovascular disease comparing to women without PAD. Hirsch et al. found that only 27% of women are familiar with the risk of developing a heart attack and stroke associated with PAD, and only 14% are aware of increased risk of mortality related PAD (27). Increasing awareness among women about PAD is an essential first step to improve life quality, reduce rate of amputation, and decrease mortality.

PERIPHERAL ARTERIAL DISEASE AND METALS

Exposure to metals such as lead and cadmium may promote atherosclerosis. In the National Health and Nutrition Examination Survey (NHANES), blood cadmium and lead at levels well below the current safety standards were associated with peripheral arterial disease (PAD) (28). Urinary cadmium levels, in another study, were associated with PAD more strongly than cadmium blood level in a sample of the US general population. This association was not found for other metals like cobalt, barium, cesium, and thallium (29).

PUBLIC HEALTH POLICY

Peripheral arterial disease is a major public health problem. The public health burden of PAD is vast. PAD-related treatment costs in the United States are substantial. It was reported to be around 4.37 billion for the Medicare population. Treatment of PAD was provided to a total of 6.8% of the elderly Medicare population (30). It is expected that the cost of PAD treatment will increase with age, as prevalence of PAD increases with age. Despite the high prevalence of PAD and high risk of mortality and morbidity of cardiovascular diseases in individuals with PAD, it is

still underdiagnosed and undertreated. Early recognition by physicians and patients will lead to improvement in life quality, prevention of functional impairment, reduction of cardiovascular disease mortality and morbidity, and eventually limit national health care costs. Prevention of Atherothrombotic Disease Network is an international multidisciplinary group that outlined a campaign called “**A Call to Action**” in order to promote awareness, detection, and treatment of PAD. The first item of “a call to action” is increasing awareness of PAD and its consequences (myocardial infarction, stroke, vascular death) including an educational initiative for physicians and patients. Second and third items are improving the identification of patients with symptoms of PAD through public campaign awareness and initiating screening for patients at high risk for PAD especially smokers, people with diabetes, people with a history of myocardial infarction and/or stroke including an ABI assessment. The last items include improving treatment rates among patients who have been diagnosed with PAD and increasing the rate of early detection among the high-risk population with asymptomatic PAD. The group also recommends treating risk factors associates with PAD such as smoking, diabetes, dyslipidemia, and hypertension (31).

PREVENTION PROGRAMS FOR PERIPHERAL ARTERIAL DISEASE IN CLEVELAND:

1- Evaluation and Prevention Center in University Hospitals Heart & Vascular Institute:

The Evaluation and Prevention Center at Case Western University Hospitals is specialized in the precise diagnosis of existing heart disorders and/or potential risk factors fro heart disease. This program offers multidisciplinary approach; collaboration and clinical expertise from different professional staffs from several departments to prevent and treat heart diseases including peripheral arterial disease (PAD). This is the website for this program

<http://www.uhhospitals.org/OurServices/MedicalInstitutes/HeartVascularInstitute/EvaluationandPreventionCenter/tabid/3085/Default.aspx>

2- Heart and Vascular Health & Prevention in Cleveland Clinic Heart & Vascular Institute:

The Preventive Cardiology Program in Cleveland Clinic is multidisciplinary program. It consists of two programs that treat patients who are at risk for cardiovascular disease and those who have had a cardiovascular event. These programs promote optimal life-style changes and medical management for cardiovascular disease including peripheral arterial disease. This is the website for this program <http://my.clevelandclinic.org/heart/prevention/pcrp.aspx> .

BENEFICIAL WEBSITES TO BE USED AS REFERENCE:

National Heart, Lung, and Blood Institute

<http://www.nhlbi.nih.gov>

Vascular Disease Foundation

<http://www.vdf.org>

Peripheral Arterial Disease Coalition

<http://padcoalition.org>

Society for Vascular Medicine

<http://www.symb.org>

Society for Vascular Surgery

<http://www.vascsurg.org>

Peripheral Vascular Surgery Society

<http://www.pvss.org>

American Heart Association

<http://www.americanheart.org>

Society of Interventional Radiology

www.sirweb.org

FOOTNOTES

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