Reviews

Peripheral Arterial Disease — What Do We Need to know?

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ABSTRACT

Peripheral artery disease (PAD) results from progressive narrowing of arteries secondary to atherosclerosis and is defined as an Ankle Brachial Index of <0.9. PAD is highly prevalent and is an increasing burden on both the economy and the patient, especially given the rapid shift in demographics in the United States. Despite its prevalence and association with cardiovascular disease, PAD is still underdiagnosed and undertreated. This may, in part, be related to lack of recognition from the physician's side or paucity of evidence from clinical trials. It has been shown that medical therapy approved for cardiovascular disease is effective in the treatment of PAD and decreases cardiovascular events. Various revascularization strategies are also available for improving symptoms and quality of life in these patients, yet they are underutilized. In an attempt to increase its recognition, PAD has been considered a coronary artery disease equivalent. This article reviews the diagnosis and management of PAD.

Introduction

Peripheral artery disease (PAD) is a general term used to describe progressive atherosclerotic narrowing of the peripheral arteries, most often used in reference to the arteries of the lower extremities. It is defined as an Ankle Brachial Index (ABI) of ≤0.9 in the lower extremities. With the growing elderly population in the United States, there is a significant increase in the burden of PAD. This disease affects 12% to 20% of Americans ≥65 years of age.[1,2] The prevalence of PAD in US adults is estimated to range from 8 to 12 million individuals, but there is a significant difference in the prevalence depending on the age, gender, or the diagnostic technique employed. PAD is considered a coronary disease equivalent as it confers equal risk of morbidity and mortality from cardiovascular disease regardless of whether coronary disease is known to be present or not. PAD is a strong predictor of myocardial infarction (MI), stroke, and death from vascular causes. Aggressive medical treatment of atherosclerotic risk factors has been shown to significantly decrease morbidity and mortality associated with PAD.[3] That being said, PAD is underdiagnosed and undertreated, with most patients not receiving optimal therapy that has been proven to reduce mortality.[4] This may be explained, in part, by lack of awareness on the physician's side and absence of effective screening tools for PAD. The purpose of this article is to review the importance of diagnosing PAD and its available therapeutic strategies.

Methods

A PUBMED search was performed with the terms "peripheral artery disease," "peripheral vascular disease," "endovascular therapy," and "percutaneous revascularization." High-quality randomized trials and retrospective studies addressing epidemiology, diagnosis, risk factors, and therapy of peripheral arterial disease were then included in this review. The citation lists from these articles were also examined for further relevant articles. When appropriate, some review articles were included in this review as they provided more comprehensive oversight on this subject.

Risk Factors and Pathophysiology of PAD

A review of the complete pathophysiology involved in the development and progression of PAD is outside the scope of this article, but understanding the basic etiologic factors is important in interpreting the advances in therapeutic strategies. PAD is similar to atherosclerosis elsewhere in the body; the initiating insult is endothelial injury, followed by inflammation and progressive atherosclerotic narrowing of the vessel. This leads to disruption of blood flow to the peripheral tissues resulting in ischemic

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injury. Compensatory mechanisms such as vasodilation, development of collateral vessels, and anaerobic metabolism in the tissues result from ischemia. However, as the disease progresses these compensatory mechanisms cannot keep up with the increasing oxygen demands of the ischemic tissue, with resultant tissue necrosis.

The risk factors for the development of PAD are the same as for other atherosclerotic diseases, including advancing age, male gender, family history, and black race. Modifiable risk factors for PAD include diabetes, smoking, hypertension, and hyperlipidemia.[5]

Clinical Presentation

Approximately 10% to 35% of patients with PAD present with intermittent claudication, defined as discomfort felt by the patient 1 level below the site of arterial occlusion and brought on by exercise and relieved with rest. However, 40% to 50% of patients can have atypical leg pain characterized by exertional lower extremity pain that does not occur with a consistent level of exertion and takes a longer time to resolve with rest. Only 1% to 2% of patients present with critical limb ischemia manifested as ulceration or gangrene. The majority of patients with PAD are asymptomatic.[6] Patients with PAD may also present with symptoms of coronary artery disease (CAD) or cerebrovascular disease (CVD) as these entities frequently coexist.

Diagnosis

Ankle Brachial Index

The Ankle Branchial Index (ABI) is a simple and noninvasive diagnostic test of choice when evaluating a patient for PAD. It involves the measurement of the ratio of blood pressure in the dorsalis pedis or posterior tibial artery to that in the brachial artery, with the help of a handheld continuous wave Doppler device. This test has been validated by comparison with angiographic confirmation of PAD and was found to be 95% sensitive and close to 100% specific.[7] The severity of PAD can be classified based on the ABI values as shown in Table 1. Epidemiologic studies have demonstrated that abnormal ABI values are independent predictors of cardiovascular events and mortality.[8] In patients with a normal resting ABI and a high clinical suspicion of PAD, it is recommended that exercise treadmill testing be combined with pre- and postexercise measurement of ABI. This technique has been shown to unmask clinically silent PAD as well as providing a functional assessment of the patient.

Table 1. Severity of Peripheral Artery Disease Based on Ankle Brachial Index Values

ABI (Ratio)	Interpretation
>1.3	Noncompressible
0.91–1.29	Normal
0.41–0.90	Mild–moderate PAD
<0.40	Severe PAD

Abbreviations: ABI, Ankle Brachial Index; PAD = peripheral artery disease.

Doppler Ultrasonography

Doppler ultrasonography (DU) is a simple, noninvasive test to determine the location of PAD and to delineate stenotic versus occlusive lesions, a difference important when considering revascularization. DU is one of the most commonly ordered tests to evaluate patients with suspected PAD because it is reasonably accurate and cost effective.[9] Color flow Doppler and pulsed wave Doppler allow one to estimate stenosis severity based on Doppler derived velocity criteria.[10] It can also be used for surveillance of patients following revascularization procedures to identify reocclusion. Although DU is an accurate test for PAD, it requires a high degree of technical expertise as well as expensive equipment that may be lacking in some centers.

Computed Tomography/Magnetic Resonance Imaging Angiography

Computed tomography angiography (CTA) provides detailed images of the vascular system with better spatial resolution of PAD lesions. It provides information on soft tissue integrity surrounding diseased vessels that can be helpful in evaluating complications of PAD such as aneurysms and tissue infarction.[11] Disadvantages of CTA include image interference from calcified arteries, radiation exposure, and the need for contrast material.

Magnetic resonance angiography (MRA), on the other hand, does not involve radiation or iodinated contrast and is 93% to 100% sensitive and 96% to 100% specific for the diagnosis of PAD.[12] However, the cost and time necessary for the study limits its routine use.

Catheter-Based Angiography

Catheter-based angiography (CBA) is the gold standard test for PAD, but it is limited to patients who might be revascularization candidates. Pressure gradient measurement and intravascular ultrasound can be performed during angiography. This is helpful in determining the hemodynamic significance of arterial lesions.

Classification of PAD

The most widely used clinical classifications for PAD include Fontaine's stages (Table 2) and Rutherford's categories (Table 3).

Women and PAD

The influence of gender on the prevalence of PAD is controversial, with some studies showing that PAD is

Table 2. Fontaine's Classification of Peripheral Artery Disease[21]

Stage	Clinical
I	Asymptomatic
IIa	Mild claudication
IIb	Moderate to severe claudication
III	Ischemic rest pain
IV	Ulceration or gangrene

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Table 3. Rutherford's Classification of Peripheral Artery Disease[21]

Grade	Category	Clinical
0	0	Asymptomatic
I	1	Mild claudication
I	2	Moderate claudication
I	3	Severe claudication
II	4	Ischemic rest pain
III	5	Minor tissue loss
III	6	Major tissue loss

slightly more common in males and others showing a more equitable distribution in both genders. However, only one half of women with PAD are symptomatic; the rest are either asymptomatic or present with atypical symptoms.[13] Regardless of whether PAD is symptomatic or asymptomatic in women, there is similar cardiovascular morbidity and mortality to that observed in men. Therefore, it is important to screen for PAD in women with risk factors for atherosclerotic vascular disease.

Management of PAD

The goals of therapy in PAD include a reduction in cardiovascular events (MI, stroke, and death) and alleviation of claudication with improvement in the quality of life in these patients. Important therapeutic strategies are summarized in Table 4.

Medical Therapy

Tobacco Cessation

Smoking cessation is 1 of the key aspects of PAD therapy and has received a class I recommendation from the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for management of PAD. There is a strong link between smoking and prevalence of symptomatic PAD.[14] Smoking not only contributes to the incidence, but also is a significant predictor of progression of symptomatic PAD.[15] Smoking cessation may not reduce claudication symptoms but has been shown to reduce overall mortality and cardiovascular events.[16]

Table 4. Summary of Management Strategies in Peripheral Artery Disease

Smoking cessation
Cardiovascular risk factor management (diabetes/hypertension/ hyperlipidemia)
Monitored, symptom limited exercise program
Antiplatelet drugs (ASA/clopidogrel, usually not in combination)
Claudication therapy (cilostazol/pentoxifylline)
Revascularization therapy (for the "ideal" patient)

Abbreviation: ASA = aspirin.

Cardiovascular Risk Factor Management

Diabetes is a strong predictor of symptomatic PAD and is associated with progression of atherosclerosis. In the Diabetes Control and Complications Trial, it was shown that intensive insulin therapy in patients with type I diabetes resulted in a 22% risk reduction of lower extremity PAD events such as claudication, revascularization, or amputation.[17] Pending further prospective trials, the American Diabetes Association recommends aggressive diabetes control (hemoglobin A1c of <7%) in patients with PAD to reduce microvascular complications.[18] It should be reinforced that meticulous foot care is needed in this cohort of patients (class I recommendation).[19]

Hypertension is another well-established risk factor for PAD, but it is not clear if treatment alters the progression of PAD. β-blockers and diuretics are commonly used in PAD patients. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers have shown to decrease progression of symptoms and improve cardiovascular outcomes in PAD.[20]

Hyperlipidemia is associated with symptomatic PAD as well as other cardiovascular events in this patient group; therefore, aggressive management is recommended. The target low-density lipoprotein (LDL-C) level in PAD patients is <100 mg/dL. In patients with coexistent CAD or CVD, a lower LDL-C (<70 mg/dL) may be beneficial.[21] The Heart Protection Study concluded that statins reduce mortality and other major cardiovascular events.[22] PAD patients often have low high-density lipoprotein or high triglyceride levels, in which case niacin or fibrates can be used to decrease cardiovascular events.[23]

Exercise Therapy

An often-neglected treatment strategy in PAD patients, a supervised formal exercise-training program has been shown to be beneficial in multiple trials.[24] Exercise therapy improves claudication distance, as well as quality of life and functional capacity in patients with PAD.[25] A meta-analysis that included only randomized trials showed that exercise produced a significant increase in maximum walking time with this benefit being greater than with angioplasty or bypass surgery.[26] Exercise therapy has several limitations, including lack of motivation from both patients and physicians, lack of coverage by medical insurance, and failure to adhere to the exercise regimen with time.

Antiplatelet Therapy

It is well established that antiplatelet agents decrease mortality and events in patients with known atherosclerotic cardiovascular disease. However, the Antiplatelet Trialists' Collaboration concluded that there was only a nonsignificant reduction in cardiovascular events in PAD patients free of vascular diseases in other territories who were treated with aspirin (ASA).[27]

Clopidogrel, on the other hand, decreases the risk of MI, stroke, and vascular death in patients with symptomatic PAD and is US Food and Drug Administration (FDA) approved for prevention of ischemic events in PAD patients.[28] Dual antiplatelet therapy has not shown to be better than any agent (ASA or clopidogrel) alone in patients with PAD.[29]

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Drug Therapy for Claudication

Although there is a theoretical possibility that vasodilators are useful in PAD, this has not been shown in clinical trials.[30] The pathophysiologic explanation is that lower extremity vessels distal to the site of occlusion or stenosis are already dilated, and therefore vasodilators do not work on these vessels. Instead, vasodilators cause systemic vasodilation resulting in a "steal" phenomenon, with resultant decreased perfusion pressure and thus worsening ischemic symptoms.

Pentoxifylline improves the pliability of red blood cells and has some antiplatelet activity. Evidence is split regarding the benefits of pentoxifylline in PAD with 1 randomized trial showing improved lower extremity symptoms with increased claudication distance.[31] However, a more recent study showed that this agent was no more effective than placebo in increasing maximal treadmill walking distance or improving quality of life.[32] A meta-analysis of all pentoxifylline studies concluded that the drug may have a small effect on walking ability, but the data is insufficient to support its widespread use.[33]

Cilostazol is a phosphodiesterase-3 inhibitor with antiplatelet activity that is FDA approved for the treatment of claudication. The mechanism of action is unclear, but multiple randomized controlled trials have shown that cilostazol did improve both pain-free and maximal walking distance, thereby improving physical functioning and quality of life.[34]

Revascularization

Revascularization therapy is increasingly being performed for the treatment of PAD; however, careful selection of patients is extremely important. Table 5 summarizes the common indications for revascularization in PAD. Endovascular therapy consists of angioplasty and stenting. Significant advances in catheter and balloon design, and the development of intravascular stents have resulted in an increase in the number of percutaneous procedures performed. A randomized clinical study comparing percutaneous transluminal angioplasty and bypass surgery for iliac or femoropopliteal disease with claudication or rest ischemia, concluded that there was no significant difference in outcome after a median of 4 years regardless of the revascularization strategy.[35] Surgical revascularization is performed for lesions not amenable to angioplasty and when long segments of the vessel are involved. Bypass can be performed using autologous (saphenous vein graft) or synthetic grafts (dacron and polytetrafluroethylene).

Table 5. Indications for Revascularization in Peripheral Artery Disease[35]

Symptoms refractory to exercise and claudication drug therapy
Presence of severe disability or serious impairment of functional status
Anticipated natural history of progression of the disease
Absence of other comorbidities (such as angina or respiratory disease) that would explain limitation of functional status
Lesion amenable to revascularization with high probability of success

Controversies in PAD

Even though hypertension is a well-established risk factor for CAD, its association with PAD has been questionable.[36,37] However, follow-up data from the Framingham study showed a 2.5 to 4-fold increase in risk of PAD in patients with hypertension.[38] The ACC/AHA practice guidelines for management of PAD recommend a target systolic blood pressure (SBP) of <140 and diastolic blood pressure (DBP) <90 mm Hg in nondiabetics and SBP <130 and DBP <80 mm Hg in diabetic patients.[19] However, a recent study by Bavry et al showed fewer cardiovascular outcomes with an SBP of 135 to 145 mm Hg and a J-shaped relationship between PAD patients and SBP.[39] Therefore, the target blood pressure is still debatable in patients with PAD. Controversy persists in the choice of antihypertensive agents that can be safely used in patients with PAD, as some of these medications (β-blockers) decrease lower limb perfusion pressures thereby worsening ischemia. However, a meta-analysis of 11 placebo-controlled trials in patients with intermittent claudication showed that β-blockers did not adversely affect walking capacity, therefore demonstrating its safety in PAD patients.[40] Patients referred for revascularization therapies also seem to have a differential benefit for many reasons. At this time, revascularization therapy should be offered to patients who satisfy the following criteria: severe disability from the disease, absence of other exercise limiting diseases, lack of response to drugs and exercise, and a lesion that is amenable for revascularization.[19]

Conclusion

Peripheral artery disease is a marker for systemic atherosclerosis and is increasingly prevalent in the United States given the rapid shift in demographics. PAD is associated with coronary and cerebrovascular disease, and is a strong predictor of cardiovascular outcomes and death. Therefore, it becomes important to screen for PAD in patients with multiple risk factors for vascular disease. Medical therapy decreases cardiovascular events in patients with PAD, and if symptoms are refractory to medical therapy, revascularization should be considered.

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