Contemporary Medical Management of Peripheral Arterial Disease

A Focus on Risk Reduction and Symptom Relief for Intermittent Claudication

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KEYWORDS

• Peripheral arterial disease • Intermittent claudication • Supervised exercise therapy • Cilostazol • Pentoxifylline • Atherosclerotic risk factors • Ankle-brachial index

KEY POINTS

- Peripheral arterial disease (PAD) due to lower limb atherosclerosis is a common problem that is often asymptomatic but associated with a high risk of adverse cardiovascular events and mortality.
- The classic symptom due to PAD is exertional leg discomfort or intermittent claudication, but most patients are asymptomatic or experience atypical leg symptoms.
- Diagnostic testing should include measurement of the ankle-brachial index in all patients plus physiologic testing and/or advanced imaging as needed to determine disease severity and location, and revascularization options.
- Treatment of modifiable risk factors, including smoking cessation, lipid-lowering therapy, antihypertensive therapy, and antiplatelet therapies, is essential to delay disease progression and prevent ischemic events.
- Symptomatic relief for intermittent claudication should focus on supervised exercise training and pharmacologic therapy (most notably with cilostazol in North America).

INTRODUCTION

Peripheral arterial disease (PAD) most commonly refers to disease affecting the lower extremities that is primarily caused by progressive atherosclerosis. The spectrum of disease manifestations encompasses asymptomatic individuals with impaired resting flow, those with *intermittent claudication (IC)* or leg symptoms during exertion, those progressing to advanced manifestations of rest pain and tissue loss, or *critical limb ischemia* (CLI), and those with sudden inadequate limb perfusion to jeopardize viability in *acute limb ischemia*. IC results from an arterial oxygen supply and demand mismatch, usually as a result of arterial obstruction causing inadequate blood flow to the muscles during activity.

Approaching the patient with suspected PAD often presents a formidable challenge to the clinician. Given the myriad manifestations of disease that often present in an atypical fashion, a low index of suspicion and thorough yet focused history

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and physical examination are critical. Although the term PAD may include stenosis, occlusion, or aneurysmal changes of the upper or lower extremities or other noncoronary vascular territories,[1] this review focuses on lower extremity arterial obstructive disease. There are various nonatherosclerotic etiologies of PAD, including trauma, vasculitis, and emboli (**Table 1**); however, atherosclerosis comprises the vast majority of PAD presentations and has the greatest epidemiologic impact.

The epidemiology, clinical presentation, workup, and medical management of PAD are reviewed here with a focus on IC. Key advances in the recognition of cardiovascular risk in asymptomatic individuals with mildly abnormal ankle-brachial index (ABI), newer reflections on exercise therapy, including the incremental value of home-based, nonsupervised programs and results from direct randomized comparisons to invasive management techniques, and a review of established and investigational agents for the treatment of PAD, such as cilostazol, statins, and angiotensin-converting enzyme (ACE) inhibitors, are also highlighted. With a limited role for medical management, the use of adjunct, noninvasive therapies for CLI is outside the scope of this review but the promise of angiogenesis is briefly discussed.

EPIDEMIOLOGY

PAD is highly prevalent, with estimates of disease burden in the United States alone at 8 million adults.[2] There is an expected increase in prevalence with aging, with an estimated 10% of adults 65 years or older affected by the spectrum of disease, and approximately 30% affected at 80 years or older,[3] which mirrors data in the diabetic and smoking cohorts from the PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program more than a decade ago.[4] There is a startling prevalence of PAD in patients newly diagnosed with coronary artery disease (CAD) or cerebrovascular disease (CVD); the diagnosis of concomitant PAD is a significant negative prognosticator for cardiovascular events.[5] Although the overlap between these comorbid conditions (PAD and CVD, PAD and CAD, and CAD and CVD) is well-recognized, patients often remain undertreated (**Fig. 1**).[6] In addition, analysis of the National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2004 revealed an ethnic disparity disfavoring those of African American and Mexican American heritage, showcasing the need for maintaining a low index of suspicion in these groups.[3] Furthermore, despite controlling for traditional risk factors, PAD affects African Americans twofold more than it does others, as seen in the Multi-Ethnic Study of Atherosclerosis (MESA) study,[7] which suggests a need for greater screening efforts on a population-wide basis, but also perhaps the need for enhanced risk factor analysis and optimization, beyond traditional factors applied to the general population.

Risk Factors

Traditionally recognized risk factors for atherosclerosis play an important role in the risk of PAD onset, accelerated development, and overall disease severity. Among the myriad causative factors, smoking, diabetes mellitus (DM),

Table 1
Differential diagnoses in the patient with suspected PAD

Nonvascular Causes of PAD-like Symptoms	Vascular Causes
Orthopedic causes (joint disease, Baker cyst, bursitis)	Peripheral atherosclerosis
Compartment syndrome (from fracture or crush injury)	Thromboembolism (cardiogenic, related to aortoiliac aneurysm, or in situ thrombosis)
Peripheral neuropathy	Connective tissue disorders (Marfan syndrome or Ehlers-Danlos [type IV] syndrome)
Venous claudication (after iliofemoral DVT, such as in May-Thurner syndrome)	Fibromuscular dysplasia
Spinal stenosis or cauda equina pseudoclaudication	Buerger disease
	Heritable thrombophilias (Factor V Leiden, prothrombin gene mutation, antithrombin III deficiency, and protein C and S deficiency)
	Vasculitides (giant cell arteritis, polyarteritis nodosa, systemic lupus erythematosus)
	Entrapment syndromes (popliteal)

Abbreviation: DVT, deep vein thrombosis; PAD, peripheral arterial disease.