Peripheral Artery Disease
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Peripheral artery disease (PAD) is unfortunately infrequently recognized. The treatment of PAD continues to evolve but is fundamentally focused on control of risk factors in order to prevent the associated risk of heart attack, stroke, and premature cardiovascular death as well as improvement in exercise performance and limb preservation. The pathophysiology of progressive atherosclerotic plaque in the extremities is thought to involve plaque hemorrhage and rupture, but few data support this presumption. Clinical research is needed to develop agents designed to halt progression of atherosclerotic disease in the peripheral arterial system. Despite these current limitations in understanding and treating PAD, new lipid modifying agents and new antiplatelet treatment of risk factors and strategies to improve pain-free walking distance have emerged, including the use of emerging endovascular strategies. In addition, with the rapid evolution of technology to improve arterial perfusion with minimally invasive catheter-based strategies, options for revascularization of patients with advanced symptoms and signs of PAD are improving.

The primary objective of Peripheral Artery Disease is to provide the reader with the most current information on diagnosis and treatment of PAD.

We hope that this reference provides an easy-to-use resource for the practicing clinician, ultimately resulting in better care for our patients. In addition, we would like to dedicate this entire book to Alan T. Hirsch, MD, who died suddenly and unexpectedly in April 2017. It minimizes his impact on the field and all vascular specialists to discuss his publications, presentations, and advocacy. Alan was a tireless voice for patients around the World who suffered from PAD. It was through his efforts that exercise and guidelines-based medical therapies have become primary in the management of these patients. We will forever miss his enthusiasm, humor, expertise and care, but most importantly, the World is a bit smaller with his passing.
This chapter describes the epidemiology of peripheral artery disease (PAD). The definitions used to describe PAD and PAD syndromes are discussed. The prevalence and incidence, risk factors, progression and outcomes of PAD are summarized. Finally, the low awareness of PAD in the community is highlighted.

Definitions

Peripheral artery disease is an all-encompassing term used to describe disorders of the structure (including stenosis and aneurysms) and function of all non-coronary arteries [1]. Peripheral artery disorders include atherosclerosis, plaque rupture, abnormal vascular reactivity, vasospasm, inflammation, arterial wall dysplasia, and thrombus formation leading to occlusion. In the past, a range of other terms have been used, including peripheral vascular disease (PVD), peripheral artery occlusive disease (PAOD), lower extremity arterial disease (LEAD), and arteriosclerosis obliterans. The term “PVD” is not synonymous as it is less specific, potentially signify venous, arterial or lymphatic disease. PAD is preferred as it communicates the accurate anatomic disease site, is accepted in all current practice guidelines, and better communicates the disease site to patients and other health care professionals.

Lower extremity atherosclerotic PAD is a marker of systemic atherosclerosis which begins in childhood [2] as deposits of cholesterol and cholesterol esters called “fatty streaks” begin to line the intima of large and medium-sized arteries. At this stage, atherosclerosis is subclinical, but it can be quantified using arterial ultrasound imaging in other vascular beds (e.g., the extracranial carotid arteries) to measure carotid intima media thickness (cIMT). Various cohort
studies have demonstrated a higher prevalence of cardiovascular disease and increased incidence of poor cardiovascular outcomes in individuals with increased cIMT. This relationship of early atherosclerosis defined by cIMT measurements has been established in the Atherosclerosis in Communities (ARIC) study [3], the Osaka Follow-Up Study for Carotid Atherosclerosis 2 [4], the Cardiovascular Health Study (CHS) [5], the Rotterdam Study [6], the Tromsø study [7], and the Second Manifestations of ARTerial disease (SMART) study [8]. Progression of these fatty streaks by increased lipid accumulation, followed by development of a fibromuscular cap, lead to formation of a fibrous plaque. Risk factor exposure (e.g., smoking, diabetes, hypertension, diabetes, low high-density lipoprotein [HDL]-cholesterol concentrations, elevated non-HDL-cholesterol concentrations and obesity), lead to further progression of these atherosclerotic lesions and increase the risk of clinically manifest PAD and other atherosclerotic diseases [9]. Clinical PAD is detected when at least one infra-diaphragmatic stenosis leads to a measurable decrease in pedal systolic pressure measurements, with or without clinically recognized limb ischemic symptoms.

In this chapter, the term “PAD” is used exclusively to refer to partial or complete atherosclerotic obstruction of one or more lower extremity peripheral arteries.

**PAD Clinical Syndromes**

There are five recognized clinical syndromes of PAD that are characterized by distinct presentations. These syndromes are useful both in describing the epidemiology of PAD and in clinical care. They include:

- asymptomatic PAD
- classic claudication
- atypical leg pain
- acute limb ischemia (ALI)
- critical limb ischemia (CLI).

Approximately one-half of individuals with PAD may be asymptomatic, defined by the absence of self-reported leg symptoms [10–14], and this has important implications in estimating the accurate PAD prevalence. PAD in these individuals is defined by a low (≤0.9) ankle–brachial index (ABI). The diagnosis of PAD is discussed in detail in Chapter 2. Claudication, which is the hallmark symptom of PAD, occurs in 10–35% [10–13] of individuals with PAD, and refers to the discomfort, pain, ache or fatigue in limb muscles that reproducibly occurs with exercise (e.g., walking) and is consistently relieved by rest [15]. Atypical leg pain is defined in individuals with objective evidence of PAD and who experience any leg symptom that is not classic claudication [16–18]. Up to
30–50% of individuals with PAD present with atypical pain [13, 15, 16]. ALI is defined by the clinical symptoms that arise with a sudden decrease in limb perfusion and that threatens the viability of the limb. While ALI is presumed to be an immediate vascular emergency, “acute” has been variably defined as occurring within 2 weeks of the initial ischemic presentation. ALI is usually due to thrombosis or embolism [19] and is clinically recognized by the “six Ps”: pain, paresthesia, pallor, pulselessness, poikilothermia, and paralysis. It is estimated that 0.1–1% of PAD patients may experience an episode of ALI [20, 21]. CLI manifests as chronic (>2 weeks) ischemic rest pain, non-healing ulcer or gangrene in 1–2% of PAD patients [22].

**Prevalence and Incidence**

There are an estimated 202 million people living with PAD globally, with almost 70% of them residing in low- and middle-income countries. Current data suggest that the global prevalence of PAD may be increasing, from 164 million individuals in the decade beginning in 2000–2010, representing an overall 23.5% rise in PAD prevalence (28.7% in low- to medium-income countries [LMICs] and 13.1% in high-income countries [HICs]) [23]. PAD affects most adult populations worldwide irrespective of socioeconomic or national developmental status [24, 25]. Fowkes et al. [23] recently collated the global prevalence of PAD using data from 34 studies (12 from LMICs and 22 from HICs). In women aged 45–89 years old, PAD prevalence ranged from 2.7% to 24.2% in HICs, and from 3.96% to 18.65% in LMICs. In men aged 45–89 years old, PAD prevalence ranged from 2.76% to 24.77% in HICs, and from 1.21% to 21.5% in LMICs.

Overall, PAD incidence and prevalence rates are similar in high- and low- to middle-income countries. PAD is as much a problem in HICs as it is in LMICs. Although the rates are similar, due to the greater population of people that live in LMICs compared with HICs, the number of individuals with PAD in LMICs exceed that in HICs (140.8 vs. 61.2 million people) (Figure 1.1). PAD is much more prevalent than common cardiovascular diseases, such as heart failure and atrial fibrillation [23, 26, 27] (Figure 1.2). Various studies have estimated the prevalence of PAD using the presence of claudication, identification of low ABI in asymptomatic individuals, or evidence of advanced forms of PAD (ALI or CLI). It is important to note that the prevalence of PAD in a given population depends on the characteristics of the population studied (i.e., age, ethnicity, socioeconomic status, and risk factors) and the method of diagnosis. In 2007, Allison et al. [28] summarized race- and ethnicity-specific estimates of PAD prevalence. They used data from seven community-based studies (the Cardiovascular Health Study, Honolulu Heart Program, Multiethnic Study of Atherosclerosis, US National Health and Nutrition Examination Survey, San
Diego PAD, San Diego Population Study and the Strong Heart Study). They found that with increasing age, the prevalence rates of PAD in men lay in the range 1.4–22.6% in non-Hispanic whites, 1.2–59% in blacks, 0.2–22.5% in Hispanics, 1.2–21.5% in Asians, and 2.6–28.7% in American Indians. PAD prevalence rates in women were in the range 1.9–18.2% in non-Hispanic whites, 3.0–65.1% in blacks, 0.3–18.2% in Hispanics, 0–18.2% in Asians, and 3.2–33.8% in American Indians. Eraso et al. [29] performed a multivariable age-, gender- and race/ethnicity-adjusted stratified analysis in this population, where the effect of each additional risk factor on the prevalence of PAD was

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**Figure 1.1** Prevalence of peripheral artery disease by age in men and women in high-income countries (HICs) and low- to middle-income countries (LMICs). Source: adapted from Fowkes et al. [23].
measured. Non-Hispanic blacks (odds ratio [OR] = 14.7, 95% CI: 2.1–104.1) and women (OR = 18.6, 95% CI: 7.1–48.7) had the highest odds of PAD as a result of this cumulative effect (Figure 1.3).

Due to the time and resources required to periodically retest study subjects for incident disease, fewer studies have evaluated the incidence of PAD. In 1970, Kannel et al. [30] assessed claudication incidence in the Framingham study. They reported the age-specific annual incidence of claudication for ages 30 to 44 years as 6/10 000 in men and 3/10 000 in women. The incidence increased among those aged 65–74 years to 61/10 000 in men and 54/10 000 in women. In 1988, the Edinburgh Artery Study used detection of claudication determined by the World Health Organization (WHO) questionnaire, the ABI, and a hyperemia test, among individuals aged 55–74 years, and reported an incidence of 15.5/1000 person-years. Hooi et al. [31] studied the incidence of asymptomatic PAD among 2327 Dutch subjects defined by an ABI < 0.9. After 7.2 years, the overall incidence rate for asymptomatic PAD was 9.9/1000 person-years. More recently, using data from CHS, Kennedy et al. [32] found that during 6 years of follow-up, incident PAD was detected in 9.5% of the cohort as defined by an ABI decrease of > 0.15 to a level of ≤ 0.90. Table 1.1 summarizes the available data on the age- and sex-specific incidences of PAD.

There have been significant methodological challenges relating to measuring the sex-based incidence of PAD. The male:female ratio of incident PAD is higher when measured based on claudication alone, with one study reporting a ratio as high as 1.97. However, in studies that have used an ABI definition of PAD, the incidence rates are lower for men (0.8) or similar between men and women (Table 1.1). Prevalent claudication is also more common in men than in women, with male:female ratio ranging from 1.2 to 2.38. However, when ABI