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Pathophysiology of peripheral arterial disease and risk factors for its development

ABSTRACT

Peripheral arterial disease (PAD) is a systemic atherosclerotic process for which the major risk factors are similar to those for atherosclerosis in the carotid, coronary, and other vascular beds. Among the traditional risk factors for PAD, those with the strongest associations are advanced age, smoking, and diabetes mellitus. More recently, a number of nontraditional risk factors for PAD have also been recognized. This article briefly reviews the pathophysiology of PAD and the evidence supporting established and emerging risk factors for its development.

Peripheral arterial disease (PAD) refers to atherosclerotic and thromboembolic processes that affect the aorta, its visceral arterial branches, and arteries of the lower extremities.[1] PAD is a marker of systemic atherosclerosis and is found more frequently among persons with well-known cardiovascular risk factors (Table 1), especially older age, smoking, or diabetes mellitus, or those with atherosclerosis in other vascular beds. More recently, a number of "nontraditional" risk factors for PAD have also been recognized, including race/ethnicity, elevations in inflammatory markers, chronic kidney disease, genetics, hypercoagulable states, and an abnormal waist-to-hip ratio (Table 1).

Risk-factor identification is highly important, as PAD is associated with reductions in functional capacity and quality of life as well as increased cardiovascular morbidity and mortality, mainly from myocardial infarction and stroke. This article briefly reviews the pathophysiology of PAD and examines current data on the contributions of traditional and emerging risk factors for PAD.

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PATHOPHYSIOLOGY OF PAD

Atherosclerosis is a complex process that involves endothelial dysfunction, lipid disturbances, platelet activation, thrombosis, oxidative stress, vascular smooth muscle activation, altered matrix metabolism, remodeling, and genetic factors.[2] More recently, the role of inflammation in all stages of atherosclerosis development has been widely recognized.[3]

Atherosclerosis frequently develops at arterial bifurcations and branches where endogenous atheroprotective mechanisms are impaired as a result of the effects of disturbed flow on endothelial cells.[2] Risk factors such as increased age, diabetes mellitus, smoking, elevations in total and low-density lipoprotein (LDL) cholesterol, and hypertension play important roles in both the initiation and the acceleration of this process.[2]

The stages of atherosclerosis

Pathologically, the stages of atherosclerosis are divided into lesion initiation, formation of the fatty streak, fibroproliferative atheroma development, and advanced lesion development. Lesion initiation results from endothelial dysfunction, while the fatty streak is an inflammatory lesion that develops first, affects the intima of the artery, and leads to formation of the foam cell. The fatty streak consists largely of smooth muscle cells, monocytes, macrophages, and T and B cells.[4] The fibroproliferative atheroma originates from the fatty streak, containing larger numbers of smooth muscle cells filled with lipids. The advanced lesion results from continued accumulation of the cells that make up the fatty streak and fibroproliferative atheroma. The advanced lesion is highly cellular and contains intrinsic vascular wall cells (endothelial and smooth muscle) and inflammatory cells (monocytes, macrophages, and T lymphocytes) in addition to a lipid core covered by a fibrous cap.[2–5]

Arteries compensate—up to a point

Arteries initially compensate for atherosclerosis by remodeling, which causes blood vessels to increase in size. However, advanced lesions eventually intrude into the lumen, resulting in flow-limiting stenoses

and chronic ischemic syndromes.[4,5]

Acute arterial events occur if the fibrous cap is disrupted; the resulting exposure of the "prothrombotic" necrotic lipid core and subendothelial tissue leads to thrombus formation and flow occlusion.[2]

TRADITIONAL RISK FACTORS

Traditional risk factors for PAD are similar to those that lead to atherosclerosis in the carotid, coronary, and other vascular beds. In the Framingham Heart Study,[6] Cardiovascular Health Study,[7] PAD Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) program,[8] National Health and Nutrition Examination Survey (NHANES),[9] and Atherosclerosis Risk in Communities (ARIC) study,[10] major risk factors for PAD included advanced age, cigarette smoking, diabetes mellitus, dyslipidemia, and hypertension. Among these, cigarette smoking and diabetes mellitus are the modifiable risk factors that place patients at the greatest risk for PAD (Figure 1).[11,12]

Advanced age

The prevalence of PAD increases with age. In the Framingham Heart Study, subjects 65 years of age or older were at increased risk for development of PAD.[6] A strong association between advanced age (≥ 70 years) and PAD prevalence was also noted in the NHANES report: prevalence was 4.3% in subjects aged 40 years or older compared with 14.5% in those aged 70 years or older (Figure 2).[9]

Others have reported similar findings. Criqui et al reported the prevalence of PAD (defined by an abnormal ankle-brachial index [ABI]) to be 2% to 3% in individuals aged 50 years or less compared with 20% in those aged greater than 75 years.[13] Even higher PAD prevalence rates were observed in the Cardiovascular Health Study, which recruited older, Medicare-eligible adults (25% prevalence among subjects aged 80 to 84 years, and 30% among those 85 years or older),[7] and in the PARTNERS program (prevalence of 29%), which included individuals aged 70 years or older or aged 50 to 69 years with a history of smoking or diabetes.[8]

Although PAD may be present in younger individuals (≤ 50 years of age), such patients represent a very small percentage of cases. Younger patients with PAD tend to have poorer overall long-term outcomes, as well as a higher number of failed bypass surgeries leading to amputation, compared with their older counterparts.[14–16]

Smoking

Cigarette smoking is the single most important modifiable risk factor for the development of PAD and its complications: intermittent claudication and critical limb ischemia. Smoking increases the risk of PAD approximately fourfold and accelerates the onset of PAD symptoms (intermittent claudication) by nearly a decade, with an apparent dose-response relationship between the pack-year history and PAD risk.[7,17–19] Compared with their nonsmoking counterparts, smokers with PAD have poorer survival rates (death attributed to a major vascular event), are more likely to progress to critical limb ischemia, are twice as likely to progress to amputation, and have reduced arterial bypass graft patency rates.[6,20–22]

Although both former smokers and current smokers are at increased risk of PAD, individuals who are able to stop smoking are less likely to develop rest pain and have improved survival[20] (see also the article by Gornik and Creager beginning on page S30).

Notably, the association between smoking and PAD is about twice as strong as that between smoking and coronary artery disease (CAD).[19,23] The reason for this disparity is not clear.

Diabetes mellitus

Diabetes mellitus confers a 1.5-fold to 4-fold increase in the risk of developing symptomatic or asymptomatic PAD and is associated with an increased risk of cardiovascular events and early mortality among individuals with PAD.[24–26]

In the Framingham Heart Study, 20% of sympto-

TABLE 1
Risk factors for peripheral arterial disease

Traditional risk factors
Advanced age
Smoking
Diabetes mellitus
Hyperlipidemia
Hypertension
Nontraditional risk factors
Race/ethnicity
Elevated levels of inflammatory markers (C-reactive protein, fibrinogen, leukocytes, interleukin-6)
Chronic kidney disease
Genetics
Hypercoagulable states (altered levels of D-dimer, homocysteine, lipoprotein[a])
Abnormal waist-to-hip ratio

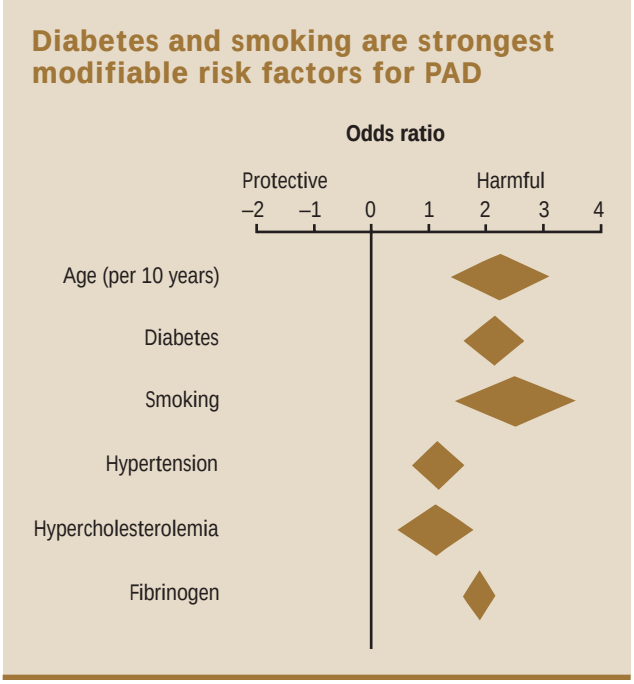

FIGURE 1. Range of odds ratios for developing symptomatic peripheral arterial disease (PAD) (ie, intermittent claudication) according to various risk factors. Adapted, with permission, from reference 11.

matic patients with PAD were reported to have diabetes, although this might have been an underestimate because diagnoses were based on inquiries about symptoms of intermittent claudication rather than objective testing.[6,24] In the NHANES report, which used the ABI to diagnose PAD, 26% of subjects with PAD were identified as having diabetes,[9] while in the Edinburgh Artery Study, which used a World Health Organization questionnaire or an ABI less than 0.90, the prevalence of PAD was higher in individuals with diabetes or impaired glucose tolerance (20.6%) than in those with normal glucose tolerance (12.5%).[25] More recently, the ARIC study found that a prior history of diabetes with insulin treatment was independently associated with a greater incidence of PAD,[10] while the Multi-Ethnic Study of Atherosclerosis (MESA) found that 26% of women and 27.5% of men with an ABI less than 0.90 had diabetes.[26]

In patients with diabetes, the prevalence and extent of PAD also appears to correlate with the age of the individual and the duration and severity of his or her diabetes.[27] Diabetes is a stronger risk factor for PAD in women than in men, and the prevalence of PAD is higher in African Americans and Hispanics with diabetes than in non-Hispanic whites with diabetes.[12,24,27]

The severity of diabetes also appears to play an important role in the development of PAD. There is a 28% increase in the risk of PAD for every percentage-point increase in hemoglobin (Hb) A_{1c}, and the seriousness of PAD appears to be related both to the duration of hyperglycemia and to glycemic control.[24,27,28] PAD prevalence is also increased in individuals with impaired glucose tolerance, and the risk of PAD is significantly increased with higher HbA_{1c} levels even among individuals with dysglycemia in the nondiabetic range ($HbA_{1c} \geq 5.3\%$).[27,29]

Diabetes is most strongly associated with occlusive disease in the tibial arteries.[27] Patients with PAD and diabetes are more likely to develop microangiopathy or neuropathy and to have impaired wound healing than those with PAD alone.[27] Because diabetic neuropathy may often mask PAD symptoms, PAD is more commonly asymptomatic in diabetics; as a result, PAD tends to present later in life and in a more severe and rapidly progressive form in diabetics than in nondiabetics.[27] PAD patients who have diabetes also have a higher risk for ischemic ulceration and gangrene, which is one reason why diabetes is the most common cause for amputation in the United States.[27]

Diabetes is believed to contribute to an increased risk of PAD for a number of reasons. Persons with diabetes are more likely than their nondiabetic counterparts to have additional risk factors for PAD, such as tobacco use, elevated blood pressure, and increased levels of triglycerides, cholesterol, and other blood lipids.[25] They also appear to have more vascular inflammation, endothelial cell dysfunction, and abnormalities in vascular smooth muscle cells compared with nondiabetics. In addition, diabetes is associated with increases in platelet aggregation and impaired fibrinolytic function.[27]

Hyperlipidemia

In the Framingham Heart Study, an elevated total cholesterol level was associated with a twofold increased risk for intermittent claudication.[24] In the NHANES report,[9] more than 60% of individuals with PAD had hypercholesterolemia, while in the PARTNERS program, the prevalence of hyperlipidemia in patients with known PAD was 77%.[8]

Hyperlipidemia increases the adjusted likelihood of developing PAD by 10% for every 10-mg/dL rise in total cholesterol.[30] It is now recognized that elevations in total cholesterol, LDL cholesterol, very low-density lipoprotein (VLDL) cholesterol, and triglycerides are all independent risk factors for PAD, whereas elevations in high-density lipoprotein (HDL) cholesterol and apolipoprotein A-I appear to be protec-

tive.[30] In 2001, the Third Report of the National Cholesterol Education Program Adult Treatment Panel designated PAD as a CAD risk equivalent.[31]

The form of dyslipidemia seen most frequently in patients with PAD is the combination of a reduced HDL cholesterol level and an elevated triglyceride level, as commonly seen in patients with the metabolic syndrome and diabetes.[23] In the Cardiovascular Health Study, both of these finding were reported in association with a decreased ABI;[7] however, in the ARIC study and the Edinburgh Artery Study, both of which involved patients with diabetes, only elevated triglyceride levels were associated with PAD.[10,25]

Hypertension

Almost every epidemiologic study has shown a strong association between hypertension and PAD, with hypertension being reported in as many as 50% to 92% of patients with PAD.[7–9,24,32,33] In the NHANES report and the PARTNERS program, PAD and hypertension were encountered together in 74% and 92% of enrolled subjects, respectively.[8,9] The Cardiovascular Health Study reported that 52% of patients with an ABI less than 0.90 had high blood pressure,[7] and the Framingham Study demonstrated a 2.5-fold to 4-fold increase in the risk of developing intermittent claudication among both men and women with hypertension.[24] In the Systolic Hypertension in the Elderly (SHEP) trial, 25.5% of participants had an ABI less than 0.90.[33] Taken together, these studies underscore the high prevalence of PAD in patients with hypertension.

Recently, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure acknowledged that PAD is equivalent in risk to ischemic heart disease.[34]

Patients with hypertension and PAD are at greatly increased risk of stroke and myocardial infarction independent of other risk factors.[23,32] In the SHEP study of older adults with systolic hypertension, an ABI of 0.90 or less was associated with a twofold to threefold increase in total and cardiovascular mortality.[33]

NONTRADITIONAL RISK FACTORS

Race/ethnicity

Several studies have shown PAD to be disproportionately prevalent in black and Hispanic populations, even after adjustment for traditional risk factors.[7–9] Age- and gender-adjusted analysis of the NHANES data showed that non-Hispanic blacks were approximately three times as likely to have PAD as non-Hispanic whites.[9] In the Cardiovascular Health Study and the PARTNERS program, nonwhite subjects (predominantly black) were disproportionately affected by PAD.[7,8] In the Multi-Ethnic Study of Atherosclerosis, which was designed to include an ethnically diverse population, PAD prevalence was highest among black men and women and lowest among Hispanic women and Chinese men.[26]

A recent population-based study by Criqui et al concluded that the excess risk of PAD in blacks was unexplained and was not related to diabetes, hypertension, or body mass index.[35] In contrast to some other reports, these researchers also noted lower PAD rates among Hispanics, although the rates were not significantly different from those among non-Hispanic whites.[35]

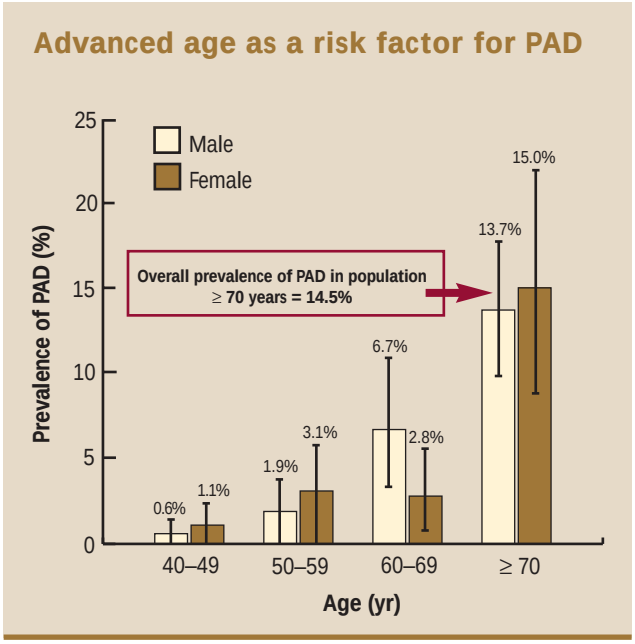

FIGURE 2. Prevalence of peripheral arterial disease (PAD) by age and gender, United States, 1999–2000 (N = 2,174). Error bars are 95% confidence intervals (for age groups 40–49 and 50–59, estimates have a relative standard error > 30%). Reprinted, with permission, from: Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. Circulation 2004; 110:738–743.

Inflammation

Elevated levels of the inflammatory markers C-reactive protein (CRP), fibrinogen, interleukin-6 (IL-6), and leukocytes have been observed in patients with atherosclerosis in other arterial beds; however, an association with PAD has not been established as clearly and only a few studies to date have looked at this relationship.[7,9,36]

Ridker and colleagues found in the Physicians' Health Study that elevated CRP levels predicted a future risk for development of PAD and greater extent of disease.[36] The NHANES report showed that elevated fibrinogen and CRP levels were associated with PAD,[9] and Wildman et al noted that elevated CRP or fibrinogen levels or an increased leukocyte count doubled the risk of developing PAD.[37] In the InCHIANTI study (*Invecchiare in Chianti*, "aging in the Chianti population"), McDermott et al found increased levels of fibrinogen, CRP, and IL-6 in men and women with PAD (compared with persons without PAD) in a community population in Italy.[38] In a separate study, McDermott et al demonstrated that higher baseline levels of inflammatory markers were associated with greater lower extremity functional decline among a group of 337 men and women with PAD.[39]

Chronic kidney disease

Until recently, very few epidemiologic studies recognized chronic kidney disease (reduced kidney function in a patient who is not receiving dialysis and is not a transplant recipient) as a risk factor for PAD.[40,41]

The overall prevalence of PAD in the National Institutes of Health's United States Renal Data System in 1999 was 15%, determined using the following clinical parameters: prior diagnosis of PAD, history of amputation, previous revascularization procedure, intermittent claudication, tissue gangrene, or a decrease in peripheral pulses on physical examination.[41] Based on data from the NHANES report, 24% of the population aged 40 years or older with renal insufficiency (estimated creatinine clearance < 60 mL/min/1.73 m^2) was estimated to have PAD (ABI < 0.90), compared with 3.7% of those whose creatinine clearance was greater than 60 mL/min/1.73 m^2.[42] In the Cardiovascular Health Study, 12% of individuals with renal insufficiency (defined as serum creatinine ≥ 1.3 mg/dL in women and ≥ 1.5 mg/dL in men) had an ABI of less than 0.90, compared with 7% of subjects with normal renal function.[43] In the ARIC study, a low ABI (< 0.90) was associated with an increase in serum creatinine levels over time.[44]

An association with PAD also appears to apply to more severe renal disease. The prevalence of an abnormal ABI (< 0.90) is much higher in patients with end-stage renal disease (ie, requiring hemodialysis) than in those with chronic kidney disease, ranging between 30% and 38%.[40] PAD patients with chronic kidney disease are at increased risk for critical limb ischemia, while those with end-stage renal disease are at increased risk for amputation.[40] Several studies have reported an increased risk of cardiovascular and all-cause mortality in hemodialysis patients, although this issue has not been examined as well among patients with milder chronic kidney disease.

The association between chronic kidney disease and PAD is independent of diabetes, hypertension, ethnicity, and age, and although the exact reason for this association is not known, it may relate to the increased vascular inflammation and markedly elevated plasma homocysteine levels seen in chronic kidney disease.

Genetics

Genetic predisposition to PAD is supported by observations of increased rates of cardiovascular disease (including PAD) in "healthy" relatives of patients with intermittent claudication. Although the relative contributions of genes and environment to the pathogenesis of premature PAD are difficult to separate, one study found that one in four siblings of patients with premature PAD will have a vascular event before age 55 years, and up to half of asymptomatic siblings will develop occult disease at a young age (< 50 years).[45]

To date, no major gene for PAD has been detected, but an ongoing National Institutes of Health–sponsored study in more than 2,000 subjects called "Genetic Determinants of Peripheral Arterial Disease" should help to clarify the role of genetics in PAD.

Hypercoagulable states

Hypercoagulable states, or thrombophilia, represent an uncommon risk factor for PAD. However, in select patients—younger individuals who lack traditional risk factors, patients with a strong family history of premature atherosclerosis, and individuals in whom arterial revascularization fails for no apparent technical reason—evaluation for an underlying hypercoagulable condition should be considered.

Several recent studies have suggested an independent association between PAD and altered levels of hemostatic factors, including lipoprotein(a), homocysteine, antiphospholipid antibodies, and D-dimer.[38,39,46,47] In particular, D-dimer levels appear to be inversely related to the ABI and have been associated with a greater decline in walking and poorer physical function scores.[39]

Evaluation for elevated homocysteine and lipoprotein(a) levels appears to be important in individuals with diffuse PAD who lack traditional risk factors. Hyperhomocysteinemia is associated with premature atherosclerosis and appears to be a stronger risk factor for PAD than for CAD.[48,49] It has also been implicated in PAD progression and as a risk factor for failure of

peripheral interventions, although not all studies have shown such a relationship.[49,50]

Several studies have reported an increased prevalence of elevated lipoprotein(a) in patients with PAD. Although there are conflicting data on the role of lipoprotein(a) as an independent risk factor for atherosclerosis, it may also be useful for screening individuals with premature PAD.[10,46]

Abnormal waist-to-hip ratio

Although it is unclear whether any association exists between PAD and body mass index (BMI), an association between abdominal obesity and PAD has been reported. Planas et al demonstrated that an increased waist-to-hip ratio (> 0.966) was associated with a 1.7-fold increase in the risk of PAD after adjustment for covariates.[51]

One explanation for the lack of association with BMI is the tendency of smokers (who are at increased risk for PAD) to have lower BMIs than nonsmokers. Moreover, many of the individuals at risk for PAD are elderly males, who typically have lower BMIs as well.[52]

CONCLUSIONS

PAD is a systemic atherosclerotic process associated with high morbidity and mortality and significant impairment of quality of life, yet it remains underdiagnosed and undertreated. Advanced age, smoking, and diabetes are clearly the most important risk factors for PAD. The association with diabetes is particularly concerning, given the exponential growth in diabetes prevalence in recent years. Recognizing these and other traditional risk factors for PAD (hyperlipidemia and hypertension), as well as the nontraditional factors reviewed above, is important to the management of PAD. Nevertheless, even if clinicians focus largely on smoking and diabetes as risk factors, significant gains can be made in detecting PAD earlier and treating it more successfully.

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