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Review Article

Peripheral Arterial Disease and the Risk Factors: Short Review

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Summary

Peripheral Arterial Disease (PAD) is narrowing of peripheral arteries. It affects a large number of populations worldwide. Narrowing of the peripheral arteries are due to atherosclerosis of these arteries. Underlying reasons includes smoking, hypertension, dyslipidemia and many others. This review discusses all the risk factors for causation of PAD in short with review of relevant literature.

Background

PAD is a narrowing of the arteries other than those that supply the heart or the brain [1]. When narrowing occurs in the heart it is called coronary artery disease while in the brain it is called cerebrovascular disease. Peripheral artery disease most commonly affects the legs, but other arteries may also be involved [2]. The classic symptom is leg pain when walking which resolves with rest, known as intermittent claudication. Other symptoms including skin ulcers, bluish skin, cold skin, or poor nail and hair growth may occur in the affected leg. Complications may include an infection or tissue death which may require amputation; coronary artery disease, or stroke. Up to 50% of cases of PAD are without symptoms [3]. In 2015 about 155 million people had PAD worldwide. In the developed world it affects about 5.3% of 45 to 50 years olds and 18.6% of 85- to 90-year-olds. In the developing world it affects 4.6% of people between the ages of 45 to 50 and 15% of people between the ages of 85 to 90. In the developed world PAD is equally common among men and women while in the developing world women are more commonly affected [4]. In 2013 PAD resulted in about 41,000 deaths up from 16,000 deaths in 1990 [5].

Symptoms of PAD in the Legs and Feet are Generally Divided Into 2 Categories

Intermittent claudication

Pain in muscles when walking or using the affected muscles that is relieved by resting those muscles. This is due to the unmet oxygen demand in muscles with use in the setting of inadequate blood flow.

Critical limb ischemia

consisting of Rest pain, a pain in the soles of the feet, particularly when the feet are elevated, such as when in bed.

a. Tissue loss, consisting of arterial insufficiency ulcers, which are sores or wounds that heal slowly or not at all, and gangrene.

Medical signs of PAD in the legs, due to inadequate perfusion, include:

a. Noticeable change in color – blueness, or in temperature (coolness) when compared to the other limb.

b. Buerger's test can check for pallor on elevation of limb and redness (rubor) on a change to a sitting position, in an assessment of arterial sufficiency.

c. Diminished hair and nail growth on affected limb and digits

PAD in other parts of the body depends on the organ affected. Renal artery disease can cause renovascular hypertension. Carotid artery disease can cause strokes and transient ischemic attacks.

Risk Factors Contributing to PAD are the Same as Those for Atherosclerosis: [88,89].

Cigarette smoking

Smoking is one of the strongest risk factors for PAD in virtually all studies. Studies vary as to the measurement of smoking, often combining a categorical assessment of smoking status (current, past, or never) with some measures of current or historical volume of smoking, such as pack-years, with some estimates as high as a 4× greater risk among smokers than others. There are limited data on the association of passive smoking and PAD. In a Chinese study conducted with women who have never smoked, the hazard ratio (HR) for PAD (either IC or ABI<0.90) after second hand smoke exposure was significant at 1.67, with a significant dose–response relationship, both for the amount and the duration of exposure [6]. Similar relationships were reported from 2 studies of never smokers in Scotland. The first study used reported second hand smoke as the exposure variable, whereas the second used salivary cotinine measures [7,8]. Smoking seems to have an even more prominent role in PAD than in other atherosclerotic diseases. In a comparison of risk factors conducted in the same large cohort, Fowkes et al. [9]. found smoking to be associated with a significantly higher relative risk for PAD compared with other CVDs; smoking was the only traditional CVD risk factor for which the odds ratio differed significantly between PAD and other CVDs.

Diabetes mellitus

Diabetes mellitus is strongly associated with an elevated risk of PAD with odds ratios ranging from 1.89 to 4.05 [10]. However, the Framingham Offspring Study found such an association on an age- and sex-adjusted basis but not in multivariable models. Despite its strong association with PAD but because of its lower prevalence in populations when compared with other traditional risk factors, the population attributable fraction of type-2 diabetes mellitus for incident PAD was estimated at 14% in a longitudinal study on US professionals [11]. More severe or longstanding diabetes mellitus seems to be more strongly related to PAD. In the Hoorn Study, it was shown that known diabetes mellitus was associated with PAD in multivariable analysis, whereas newly diagnosed diabetes mellitus was only of borderline significance, and impaired glucose tolerance was not associated with PAD. However, one study in subjects aged >65 years reported a significant association between the homeostasis model assessment and incident PAD [12]. Studies conducted in patients with diabetes mellitus have shown that duration of diabetes mellitus, level of glycemic control assessed by glycated-hemoglobin, and use of insulin are associated with PAD [13].

Hypertension and blood pressure

The association of hypertension with PAD has been demonstrated in most studies in which blood pressure was studied with reported odds ratio was 1.32 as reported in the Rotterdam Study; Most other large, population-based studies have also found a significant, independent association of hypertension or systolic blood pressures with PAD [9]. Where both systolic and diastolic pressures were considered, systolic pressure was usually found to be associated with PAD [10]. Although the relative risks associated with hypertension are modest in some studies, its high prevalence, particularly among older patients, makes it a significant contributor to the total burden of PAD in the population. In the Framingham Study, 30% of the risk of IC in the population was attributable to blood pressure in excess of 160/100 mm Hg. An even higher population risk attributable to hypertension, 41%, was recently reported in the HPFS.

Dyslipidemia

In recent studies, the recognition that the total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio is the best lipid measure of risk, [14] along with the increasing use of medication, has led to analyses that use both these variables in the same model [15] or combine the ratio with medication use in a single variable, for example, dyslipidemia [16]. Total cholesterol has been the most widely studied lipid measure as a potential risk factor for PAD. Total cholesterol was examined as a potential risk factor in 4 of the index studies, and it was significantly associated with PAD in multivariable analysis in 3; in the remaining study, total cholesterol was significant in univariate analysis but dropped out of multivariable models in which other lipid measures were considered [17]. Similarly, in other studies, total cholesterol has usually been found to be associated with PAD [18] with occasional null findings in multivariable analyses in which other lipid measures are considered. According to the HPFS, the population attributable fraction for PAD related to hypercholesterolemia is at 17%.

HDL-C has been shown to be protective against PAD in most studies where it was evaluated, usually in models that also considered total cholesterol. HDL-C was included among the potential risk factors in 3 of the 5 index studies and the total cholesterol/HDL-C ratio in the fourth, and it was significantly associated with PAD in multivariable analysis in all 4. In 2 studies, both HDL-C and total cholesterol were significant in multivariable analysis, whereas in 1 study, HDL-C (but not total cholesterol) was significant. Other studies have also shown a protective effect of HDL-C Bowlin et al. [19]. found that non–HDL-C (total cholesterol minus HDL-C) was significantly associated with incident IC in a large cohort of Israeli men; neither total cholesterol nor HDL-C were significantly associated with disease in models that included non–HDL-C. In a comparison of incident cases of IC with healthy controls in the Physician's Health Follow-up Study (PHFS), Ridker et al. [20] found that the ratio of total cholesterol/HDL-C was the lipid measure most strongly associated with disease, with patients in the highest quartile having 3.9× the IC risk of patients in the lowest quartile; screening for other lipid fractions was judged to have little clinical usefulness beyond measurement of this ratio. Previous case–control studies showed a consistent relationship between triglycerides and PAD, suggesting a uniquely strong relationship with PAD; however, large, population-based cohort studies using multivariable modeling later called this into question. Among the index studies, only 2 included triglycerides among the potential risk factors evaluated. In both cases, triglycerides were significant in univariate analysis but dropped out of multivariable models based on stepwise logistic regression [17]. Similarly, in the Edinburgh

Artery Study cohort and in a large study of geriatric patients in the United States, triglycerides were not significantly associated with PAD after adjustment for other lipid measures [20]. However, other studies have shown triglycerides to be significantly and independently associated with PAD in multivariable analysis [13]. There is also some evidence suggesting that elevated triglycerides may have a role in disease progression or more severe PAD.

Obesity

To date, the preponderance of evidence fails to support a consistent, independent positive association between obesity and PAD. In one of the few large studies with a positive finding, Bowlin et al. [21]. estimated an odds ratio of 1.24 (95% confidence interval, 1.05–1.46) for incident claudication related to a 5.0-kg/m2 difference in body mass index (BMI) in a study of 10 059 Israeli men. Three of the index studies and many other large, population-based studies have failed to find a significant association between obesity and PAD or claudication after multivariable adjustment [17]. There have also been many studies, including the other 2 index studies, in which higher relative weight or BMI was actually shown to be protective against PAD. In the Framingham Study, claudication was significantly inversely related to relative weight in men in multivariable analysis and seemed to have a U-shaped nonlinear relationship with relative weight in women. In an analysis from the Edinburgh Artery Study, BMI was significantly associated with less disease in preliminary multivariable analysis, although BMI was excluded from the article's final multivariable model because it "suggested a counterintuitive effect."[9]. The CHS found higher BMI to be significantly protective against PAD after multivariable adjustment in a large sample of Medicare beneficiaries. BMI was significantly protective against PAD (defined based on a combination of ABI, Doppler flow curves, and history of surgery) in the Hoorn Study [22]. Similarly, the odds of PAD among subjects in the highest quintile of BMI compared with the lowest quintile were found to be significantly reduced in a cross-sectional analysis of elderly Japanese American men. Subjects with higher BMI were again shown to be at significantly lower risk of PAD in a study of Taiwanese subjects with diabetes mellitus.[150] Finally, the multi-ethnic San Diego Population Study (SDPS) reported a significant inverse association of BMI and PAD. As in coronary artery disease epidemiology, there is some evidence to suggest that central adiposity may be more closely related to an increased risk of PAD. Vogt et al. [23]. found that, after adjustment for BMI, higher waist/hip ratio was associated with significantly higher risk of PAD. In a group of patients with diabetes mellitus, it was shown that waist/hip ratio, but not BMI or body fat percentage, was associated with PAD [24].

Alcohol consumption

Evidence for a protective effect of light-to-moderate alcohol consumption, as seen in coronary heart disease (CHD), is less consistent for PAD. Two of the 5 index studies considered alcohol intake; neither showed alcohol to be significantly associated with PAD in either age- and sex-adjusted or multivariable models [25]. However, in a later analysis of data from one of these studies, a significant protective effect was found in women but not in men [26]. Conversely, a protective effect of alcohol was seen in men but not in women in the Edinburgh Artery Study, but this association disappeared after adjustment for social class. In Native Americans, a protective effect of alcohol was seen in multivariable analysis, but in elderly Japanese American men, alcohol intake was found to increase rather than decrease the risk of incident PAD. In a large Chinese population study, low alcohol intake was associated with decreased prevalence of PAD in men but not in women. Data from the PHFS suggest that a protective effect related to moderate alcohol consumption may exist [27].In that study, there was no univariate association between alcohol and claudication incidence, but adjustment for cigarette smoking unmasked a significant protective association, reflecting the positive correlation of alcohol consumption with smoking, a strong risk factor for PAD.

Race and ethnicity

Data on the association of race with PAD are limited because many of the large studies of PAD have been conducted in NHW groups. Several studies suggest a higher risk of PAD among blacks. A study conducted in elderly native Africans in 2 cities in Central Africa found high rates of PAD, 15% and 32% [28]. The CHS, a study of 5084 Medicare beneficiaries in the United States, found that nonwhite (mostly black) race was associated with an odds ratio of 2.12 for PAD after adjustment for traditional risk factors. A study of 933 women aged ≥65 years found a higher percentage of black subjects among the PAD (36.3%) versus non-PAD (24.8%) groups. In the Atherosclerosis Risk in Communities (ARIC) study, Zheng et al. [29] found that PAD prevalence was higher in AA versus whites in both men (3.3% versus 2.3%) and women (4.0% versus 3.3%). The MESA reported a multivariable odds ratio of 1.67 for blacks versus NHW [30]. The SDPS reported an odds ratio of 2.34 for blacks versus NHW after adjustment for hypertension and diabetes mellitus, and additional analyses also showed no evidence of a greater sensitivity of blacks to traditional CVD risk factors. Finally, a synthesis of 3 studies addressing this question reported odds ratios of 2.3 to 3.1 for blacks versus NHW adjusted for age and sex; odds ratios of 1.7 to 2.9 after adjustment for traditional risk factors; and odds ratios of 1.5 to 2.0 after further adjustment for novel risk factors, including inflammatory risk factors [31]. Thus, this association is in part explained by traditional risk factors and in part by novel risk factors, but there is an unexplained residual difference. Interestingly, hospital-based studies suggest that the anatomic distribution of disease may differ in blacks, with a higher percentage of distal disease in black subjects, even after adjustment for diabetes mellitus and other cardiovascular risk factors.

Data on other races and ethnic groups are more limited. A study of Native Americans suggested PAD prevalence comparable with that in NHW. In a study in Honolulu, Hawaii, Asians were reported to have lower PAD prevalence than comparable NHW subjects [19]. Both the MESA and the SDPS data suggest somewhat lower rates of PAD in Asians and Hispanics compared with NHW [27]. In a community-dwelling population aged >40 years living in Japan, a low prevalence of PAD (1.4%) has been reported [32].

Homocysteine

The association of homocysteine with PAD has been examined in many studies, with conflicting results. A 1995 meta-analysis of early case–control studies conducted in the late 1980s and early 1990s suggested an odds ratio of 6.8 for a 5-µmol/L difference in fasting total homocysteine (tHcy). To put this in perspective, the differences between the 25th and 75th percentiles of tHcy among controls in the Physician's Health Study and a study of women in the Netherlands were between 3.5 and 4.0 mmol/L [33]. The 5-mmol/L difference noted above is, therefore, not unreasonable as the difference between low and high tHcy levels in the population. In that light, an odds ratio of 6.8 might make homocysteine the single most powerful risk factor for PAD. Interestingly, the odds ratio for PAD in the meta-analysis was strikingly higher than the odds ratios for coronary artery disease and cerebrovascular disease that were <2 in the same study Smoking – tobacco use in any form is the single most important modifiable cause of PAD internationally. Smokers have up to a tenfold increase in relative risk for PAD in a dose-response relationship.[90] Exposure to second-hand smoke from environmental exposure has also been shown to promote changes in blood vessel lining (endothelium) which is a precursor to atherosclerosis. Smokers are 2 to 3 times more likely to have lower extremity peripheral arterial disease than coronary artery disease. More than 80%-90% of patients with lower extremity peripheral arterial disease are current or former smokers. The risk of PAD increases with the number of cigarettes smoked per day and the number of years smoked. Other risk factors which are being studied include levels of various inflammatory mediators such as C-reactive protein, fibrinogen, hyper viscosity, hypercoagulable state.

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