Peripheral Artery Disease in Women

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Abstract

Peripheral artery disease (PAD) represents an important cause of morbidity and mortality worldwide. In general, women are a particularly susceptible population for their sex differences with men in the development of the disease. The under-representation of women in existing PAD studies creates a gap of knowledge in the development of the disease, which is reflected as delayed diagnosis due to an asymptomatic or atypical presentation that increases their risk for unfavorable outcomes. The pathophysiology, risk factors, clinical presentation, diagnosis, management, outcomes, and quality of life of women with PAD are reviewed herein. Future areas of research should focus on women with PAD to fill the existing gap of knowledge and be able to inquire more about the natural history of disease and appropriate management for better outcomes and increased quality of life.

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Peripheral artery disease (PAD) is a progressive atherosclerotic condition characterized by stenosis or occlusion of large- and medium-sized arteries, decreasing blood flow and producing ischemia during walking.[1,2,3] It is a significant cause of morbidity and mortality, resulting in functional impairment, limb loss, and death all around the world.[4,5] In 2015, the global regional and national prevalence and risk factors for PAD indicated that the worldwide prevalence was more than 236 million cases and the majority (70%) live in low/middle-income regions of the world like Southeast Asia (55 million) and the Western Pacific Region (46 million).[1,6] The estimated occurrence of PAD in the United States is between 8.5 and 12 million cases, a number that will continue to rise as the population ages.[5,7]

Large studies have demonstrated that women have lower age-standardized cardiovascular disease incidence, prevalence, and death rates than men.[5,8] Women have a high rate of PAD, a circumstance that is not broadly recognized by clinicians or the public, probably because of the higher likelihood of asymptomatic or atypical clinical presentation in women compared with men.[4]

In general, women with cardiovascular disease are less likely to receive preventive management like lipid-lowering therapy, aspirin, and therapeutic lifestyle changes than men with the same condition.[9] Women also receive less care, less aggressive medical treatment options, and fewer investigations, are less likely to undergo revascularization than men, and are more likely to be under treated and have poorer outcomes after a coronary event.[4,8]

Biological variances between men and women are known as sex differences and are due to differences in the sex chromosomes and hormones resulting in sex-unique gene expression and function, giving variations in prevalence and presentation of cardiovascular conditions, including those associated with autonomic regulation, hypertension, diabetes, and vascular and cardiac remodeling. In contrast, gender differences arise from sociocultural practices (eg, behaviors, environment, lifestyle, and nutrition) and are characteristics unique to each human.[9]

Risk Factors

The traditional and strongest risk factors for PAD are advanced age, diabetes, smoking, arterial hypertension, hyperlipidemia, and chronic kidney disease (CKD)[2] as well as non-traditional risk factors. Women may present with less traditional risk factors associated with PAD.[10] A study that analyzed data from the National Health and Nutrition Examination Survey (NHANES) developed a PAD risk factor score and showed that a cumulative effect of the number of cardiovascular risk factors (3 or more) was associated with a higher prevalence in PAD and that women were particularly susceptible to this phenomenon.[11]

Sex and age. PAD prevalence increases with age, affecting 1% to 5% of adults aged 40 to 49 years and 15% to 20% of adults over 70 years. Although the prevalence of early-onset PAD (diagnosed age <50 years) is low, it is associated with significantly higher mortality and amputation rates.[12]

PAD has traditionally been identified as a predominantly male disease;[1,7] however, recent population studies on PAD have shown that women are affected at least as often as men.[1,7] Women

experience PAD up to twice the rate of men in lower-income countries.[6,7] Some studies showed that the prevalence of PAD in young women (<50 years) seems to be higher than in men, but for individuals aged 70-79 years, there is an equivalent prevalence of PAD among both sexes of approximately 11.5%.[1,7] Other authors indicate that its prevalence increases with age, being similar or greater in women than men at the advanced ages.[3] This can be a result of the loss of the vascular protective effects of estrogen, which has antioxidative effects and promotes vasodilation.[13] The prevalence of severe limb ischemia was found to be higher in women than men.[6,14]

Diabetes. The prevalence of PAD in women with diabetes increases with age. Some studies showed an increase in PAD in diabetic women at the age of 50 years compared with men who start at an earlier age.[15] Evidence shows that inflammation may have an important role in the pathogenesis of diabetes and atherothrombosis.[16,17] A study showed that patients greater than 65 years who developed diabetes had higher levels of C-reactive protein (CRP) at baseline compared with those who remained normoglycemic.[17]

Women with PAD have more inflammation than men with PAD. The inflammatory profile in diabetic women showed high levels of leptin and interleukin-8, while diabetic men showed higher levels of PEDF and insulin.[14] The increase of these inflammatory biomarkers in diabetes may partially explain why diabetes is a strong risk factor for PAD, and why hyperglycemia is associated with double the risk of developing PAD and higher risk of severe forms like chronic limb-threatening ischemia and amputation.[18] Diabetic women have higher hypercoagulable state, impaired endothelium-dependent vasodilation, worse atherogenic dyslipidemia, and more metabolic syndrome than diabetic men.[9] The evidence for sex-specific diabetes-related risk for PAD is unclear, but may be related to higher inflammatory state, increased age, and long history of diabetes, among other risk factors. Recent studies suggested relatively equal diabetes-related risk for PAD by sex.[18]

Smoking. Smoking is a predominant risk factor in individuals with symptomatic PAD. Men with PAD more frequently have a history of smoking than women with PAD.[8] Past and current women smokers had a greater risk for PAD compared with women who never smoked.[18] Women have a 25% increased risk for cardiovascular disease compared with men and the PAD-specific risk is similar if not higher in women.[8,9] The combination of smoking with oral contraceptive use increases the risk of cardiovascular complications.[9]

Hypertension. Hypertension is highly associated with the development of atherosclerosis in both women and men, which makes it an important risk factor for PAD.[6,18] Premenopausal women have greater blood pressure control due to the vasodilation produced by endogenous estrogen, developing hypertension about a decade after men.[9] Estrogen deficiency in postmenopausal women may explain their predisposition for endothelial dysfunction, resulting in an excess burden and multivessel predominance of PAD in women.[18] While some evidence shows that in patients with PAD hypertension is more common in women and the relationship with claudication symptoms is also more prominent in women than men,[9,18] other studies have shown that with more than 70% of the population having hypertension, claudication was less frequent in women.[1]

Chronic kidney disease. The CKD population has an increased frequency of PAD. Evidence from the National Health and Nutrition Examination survey showed that 24% of patients with severe CKD had PAD, but new studies have suggested an increasing risk even in mild to moderate CKD.[5,6] In patients with CKD under the age of 70 years, the incidence of PAD is 50% greater in women than men.[18] CKD was the principal contributor to PAD-related death in patients aged 40 to 59 years, particularly in women.[19]

Race and ethnic groups. In the United States, the highest prevalence of PAD is within the southern states. When stratified by ethnicity regardless of the geographic location, the African American population over the age of 70 years had the highest PAD prevalence, which can be explained due to socioeconomic inequities and fewer preventative treatment strategies utilized in this population.[7,13] The NHANES study found an increased prevalence of PAD for African Americans (men and women) and Hispanic American women compared with non-Hispanic White Americans (19.2% vs 19.3% vs 15.6%, respectively).[6]

Other risk factors. There are some non-traditional risk factors that are noted to increase the risk of PAD in women. Some studies indicated an association between women patients with PAD and depression, obesity, levels of C-reactive protein, hypothyroidism, osteopenia/osteoporosis (mostly in postmenopausal women), Turner syndrome (higher levels of low-density lipoprotein), history of pregnancy complications (hypertensive disorders of pregnancy), immune disease (rheumatoid arthritis), and hyperhomocysteinemia.[13,18,20] Worse outcomes in women with PAD were highly associated with lower socioeconomic status and lower education.[18]

Clinical Presentation

PAD can be asymptomatic or symptomatic. The main symptom is intermittent claudication, defined as pain, cramps, or tingling that occurs in the legs during walking and relieves with a short period of rest.[3] Symptomatic PAD ranges in severity from claudication to critical limb ischemia.[2,3] PAD is often diagnosed using the ankle-brachial index (ABI); most studies define PAD as an ABI <0.9.[1] In asymptomatic PAD, most patients do not have a clinical history of cardiovascular disease, but they have increased risk

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of a 10-year cardiovascular mortality of 18.7% in men and 12.6% in women with a low ABI.[1,8]

Prevalence of intermittent claudication is lower in women than in men.[1,8] Women tend to present with atypical leg symptoms or be asymptomatic.[1,13] Some of the atypical presentations in women can be attributed to a different etiology like spinal stenosis or additional comorbidities.[21]

The difference in presentation can be related to women being more sensitive to circulatory impairment and experiencing greater reduction in function at milder stages of PAD. Additionally, women can be less physically active and avoid activities that exacerbate their symptoms, and they may fail to report their symptoms or have an asymptomatic disease.[1,5,21] A study showed a linear relationship between severity of disease and presence of exertional leg symptoms among patients who walked more than 4 blocks per week and it was absent in women that were less physically active and walked less than 4 blocks per week.[21]

Women with PAD had poorer leg strength, faster functional decline, greater walking impairment, and poorer quality of life scores than men.[13,22]

Treatment

PAD management consists of exercise therapy, pharmacological treatment, and lower-extremity revascularization.[13] Women are less likely to receive cardiovascular preventive therapy such as antiplatelet, lipid-lowering, and other cardiovascular medication, and are also less likely to receive a more aggressive therapeutic regimen than men.[13,23-25] Platelet reactivity (higher aggregation and lower inhibition) was higher in women even when compared with men on similar antiplatelet regimens.[10] Achievement of therapeutic goals for the control of risk factors was twice as likely for men than women.[10,13,23]

Exercise therapy increases the distance and time before claudication starts and overall walking distance. Women with PAD, especially diabetics, are less likely to respond to exercise therapy.[13] Improvement in absolute walking distance after 1 year of standard exercise therapy was less for women than men. Higher levels of oxidative stress, poorer leg strength, higher level of inflammation, lower hemoglobin saturation during ambulation, and insulin resistance may explain these disparities.[13,14]

Women are less likely to have good medical optimization at the time of procedures, which may put them at higher risk for postoperative complications.[23,25] They are less often offered surgical revascularization.[24] The American Heart Association/American College of Cardiology guidelines recommend for lifestyle-limiting claudication and chronic limb ischemia to first undertake an endovascular approach.[13,24] Women with older age and advanced disease were preferentially treated with endovascular procedures and they were less likely to undergo surgical bypass or open vascular surgery than men.[13,23,24] Factors that may contribute to the surgical options presented to women may be related to the later age of disease onset, comorbidities, advanced disease, smaller vessel size, surgical outcomes, and psychosocial factors.[13,24,25] Vein grafts are less frequently used in women due to their smaller vessel size, which results in less adequate venous conduit.[23]

Outcomes and Quality of Life

Delayed diagnosis of PAD in women and late referral for management results in unsatisfying outcomes of surgical procedures.[26] Evidence is controversial regarding the outcomes and procedure types. Overall, women with different stages of PAD undergoing endovascular, open procedures and amputations had higher mortality than men.[13,23,24] Women with PAD and preexisting cerebrovascular disease had higher mortality than men after open surgical procedures, associated with postoperative infections and bleeding.[25]

In the short term (30 days), women had higher rates of amputation, mortality, early graft thrombosis, embolization, vascular access-site complication, and cardiovascular and pulmonary event after revascularization. Long-term outcomes were similar between men and women.[25] Decreased artery caliber and smaller-diameter venous conduits and target vessels in women may contribute to some of their complications, increasing the risk of graft failure and resulting in a higher incidence of postoperative wound infections.[21,25]

Some studies about platelet reactivity have shown that women have greater platelet aggregation and less platelet inhibition than men who are in a similar antiplatelet therapy, which may increase their risks for complications and worse outcomes after intervention, including poor wound healing, higher rates of infections, major amputation, and mortality.[10]

Quality of life and functionality of PAD patients may vary depending on the disease severity and type of procedure. Even when amputation rates have declined in the last decades, there are reports of disparities related to the outcomes in patients with PAD. Studies showed that women had higher rates of transfemoral (above-the-knee) amputation over transtibial (below-the-knee) amputation compared with men, which has a significant physical and psychosocial impact on their recovery and quality of life as the level of amputation moves proximally and their knee joint is absent.[27] Women undergoing a below-the-knee amputation have an increased quality of life vs women with an above-the-knee amputation.[28]

Women with PAD have faster functional decline, lower functional status, greater loss of mobility over time, and compromised health at diagnosis and follow-up and it took them longer than men to recuperate after amputation; these results were associated with lack of social support and lower education level.[8,10,13,29] Other studies showed that women had a significantly

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higher average score than men in quality of life domains and functional independence measures, so they were more likely to cope and function with disability than men.[30]

Severe illness in an adult family member can affect the ability to fulfill family roles, maintain cohesive relationships, and adjust to new routines, which can impact family dynamics and socioeconomic status, more so if the family member that suffers the disease is the woman.[29,31] Spouses of chronically ill women have reported increased rates of depression and less ability to bond with other members.[28,31] All of these factors may negatively impact the family on a functional level.

Conclusion

Women are a high-risk population for the development of PAD, and this may be associated with different factors like age, anatomy, hormones, metabolism, inflammation, environment, psychologic and socioeconomic factors, less preventive care, and less modification of lifestyle. The few data available for women-specific disease are paradoxical due to the lack of traditional cardiovascular risk factors in this population. The under-representation of women in existing PAD studies creates a gap of knowledge in the development of the disease, reflected as delayed diagnosis due to an asymptomatic or atypical presentation that increases their risk for unfavorable outcomes.

This information is especially valuable for primary care providers, who are often the first point of contact for patients and can take an appropriate course of action and approach this population with a different perspective, contributing to an early diagnosis and favorable results in the management of PAD in women.

Future research should focus on women with PAD to fill the existing gap of knowledge and to investigate the natural history of disease and appropriate management for better outcomes and increased quality of life.

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