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CONVENTIONAL AND NON-CONVENTIONAL RISK FACTORS FOR PERIPHERAL ARTERIAL DISEASE IN WOMEN

Igor Spinei^{1,2}, Dragoş-Alexandru Lubaş¹, Dumitru Casian^{1,2}

¹ "Nicolae Testemiţanu" State University of Medicine and Pharmacy, Chişinău, Republic of Moldova

² Department of Vascular Surgery, Institute of Emergency Medicine, Chişinău, Republic of Moldova

Summary

Objectives. To conduct a scoping review of the scientific literature summarizing current knowledge regarding gender-related differences in conventional and the impact of non-conventional risk factors for peripheral arterial disease (PAD) in women.

Methods. A comprehensive literature search was performed across PubMed, MEDLINE, SCOPUS and Google Scholar databases examining the risk factors for PAD. After initial identification of the most relevant articles, forward and backward citation tracking was performed for selection of additional publications. Finally, a total of 49 publications (45 original articles, 2 systematic reviews and 2 clinical practice guidelines) were included and analysed.

Results. Conventional factors for the development and progression of PAD have several sex-specific features in women: more significant impact of smoking and diabetes, less effective correction of dyslipidemia and hypertension, frequent association with obesity and osteoporosis. Furthermore, current evidence highlights the importance of non-conventional risk factors for PAD in females: sex-hormones disbalance, reproductive history and adverse obstetric events.

Conclusions. There are numerous gender-related peculiarities in the natural evolution of PAD in female patients which may influence the clinical presentation, diagnosis and outcomes of medical and interventional treatment. Further studies are required for a better understanding of sex-related vulnerability mechanisms and elaboration of individualized management.

Keywords: peripheral arterial disease, risk factors, reproductive history, women

Introduction

One of the most worrying health problems, burdening almost 200 million people worldwide, is peripheral arterial disease (PAD) [1, 2, 3, 4]. This pathology is characterized by progressive stenosis and occlusion of peripheral arteries and reduced blood flow to the lower extremities. The primary mechanisms of this process are endothelial dysfunction, reduced nitric oxide (NO) production and availability, vasoconstriction, and arterial stiffness. Proinflammatory mediators, oxidative stress, and metabolic disturbances play a vital role in the comprehension of the pathophysiology of the disease and the conduction of potential therapeutic strategies.

Untreated, PAD may cause complications such as foot ulcers and lead to lower limb amputations, thus increasing the number of major cardiovascular and cerebrovascular adverse events and ultimately elevating the mortality rates [1, 5, 6, 7]. Moreover, the conditions that often occur comorbidly with PAD, such as diabetes and hypertension, significantly increase the risk of acute cardiovascular and cerebrovascular events, further contributing to mortality. While PAD affects both men and women, misdiagnosis in women is more common, leading to delayed or improper treatment [8, 9]. Similarly, the risk factors associated with this disease are mostly studied among the male population. Life-course determinants such as diet, exercise, and smoking are the primary modulators of the development and progression of PAD. Risk factors can be divided into traditional and non-traditional categories for better understanding and management of PAD. Furthermore,

investigating non-traditional elements yields a more complex milieu than conventional risk factors.

The present study aim was to conduct a scoping review of the scientific literature summarizing current knowledge regarding gender-related differences in conventional and impact of non-conventional risk factors for PAD in women.

Materials and Methods

A comprehensive literature search was performed across PubMed, MEDLINE, SCOPUS and Google Scholar databases examining the following aspects of PAD: (1) prevalence of both traditional and non-traditional risk factors (e.g., smoking, diabetes, hypertension, chronic kidney disease, osteoporosis) with a specific focus on women; (2) sex-specific differences in the progression of PAD and its comorbidities; (3) impact of lifestyle factors such as physical inactivity, diet, and obesity on PAD development; (4) influence of reproductive history, hormone use, and adverse pregnancy outcomes on PAD risk; (5) assessment of the role of socioeconomic status and environmental factors in exacerbating PAD-related negative outcomes among women. After initial identification of the most relevant articles that align with the study aim, forward and backward citation tracking was performed for selection of additional publications. Consistent with the main research question and broad character of the narrative review, the search process was iterative, identifying some additional items with each subsequent search session. Inclusion of a publication in the review was debriefed and the decision was made by

consensus among authors. Finally, a total of 49 publications (45 original articles, 2 systematic reviews and 2 clinical practice guidelines) were included and analysed.

Results

Conventional Risk Factors

Smoking

Observational studies have shown that active smoking worsens outcomes in patients with PAD, with continued smokers having approximately four-fold increased risk of death, myocardial infarction, vascular graft occlusion, and amputation compared with patients who have quit smoking [10, 11, 12]. A study performed by Ness et al. highlighted that smoking significantly increased the risk of symptomatic PAD in the geriatric population. The study found that smoking was a powerful predictor, raising the risk of disease 2,6 times in men and 4,6 times in women [13].

In the same context, „second-hand” smoke also is emerging as a risk factor for PAD, particularly among women. Brody et al. reported that from 2015 to 2018, 20,8% of non-smoking adults in the United States were exposed to „second-hand” smoke. Exposure was highest among younger adults and non-Hispanic Black adults (39,7%). Rates decreased with higher education and income levels, and „second-hand” smoke exposure declined from 27,7% in 2009 to 20,7% in 2018, likely due to reduced smoking rates and smoke-free policies [14]. The findings are also supported by research done by Baheiraei et al. in Tehran, which found that lower education levels and social class increased women’s risk of exposure to „second-hand” smoke in Iran’s capital. Specifically, women with only elementary education had higher exposure risk than those with high school or higher education [15].

Even though smoking rates have been on a downward trend since the 1970s, looking at the data for women, the rates have not been so impactful [10, 16]. In recent years, the statistics show that the number of young girls who smoke is almost as high as for boys, contrary to the difference seen between adults [10, 17]. Smoking has been demonstrated to continue impacting the probability of development of PAD for as long as 30 years following smoking cessation, with both the quantity and duration of tobacco use contributing to increased risk [9, 18].

Diabetes

Diabetes represents one of the most common risk factors when it comes to PAD, as it raises the incidence of vascular disease by two to four times, with a higher prevalence among women, especially in those with an abnormal ankle-brachial index (ABI) as was observed in the Rotterdam population study [10, 19]. Considering this, Meijer et al. reported a higher incidence of abnormal ABI in female diabetic patients than in males [19]. The evidence for specific diabetes-related risk for atherosclerosis in female patients is weak. Some authors suggested that sex dependent differences in risk for PAD could be more evident in the early course of diabetes and disappear with increase in atherosclerotic burden [9]. It is worth noting that diagnosis of PAD in female diabetic patients may be more problematic compared to males,

because peripheral neuropathy and medial artery calcinosis are more prevalent in this group. Due to the presence of these complications, evaluation of clinical symptoms characteristic for limb ischemia (intermittent claudication, rest pain) and determination of ABI are usually more challenging and less reliable [19].

Recent studies highlight specific risk factors that significantly affect the development of PAD in men and women with type 2 diabetes. According to Cardoso et al., traditional and novel ultrasound markers of arterial stiffness such as carotid intima-media thickness and carotid-femoral pulse wave velocity are related to an increased risk of PAD development and progression. In the study which enrolled 681 participants from a long-term diabetes cohort both parameters independently predicted the decrease in ABI during the follow-up, need for limb revascularization, amputation or patient death. These data suggest that vascular stiffness could play a vital role in the development of vascular complications in diabetics. Secondly, it also emerged that an increase of risk was associated with a longer duration of diabetes and higher HbA1c levels, which indicates a cumulative burden of poor glycaemic control on vascular health [20].

Dyslipidaemia

Hypercholesterolemia, an elevated level of triglycerides and impacted balance of low- and high-density lipoproteins are the fundamental pathogenetic mechanism of atherosclerotic PAD development. According to the „Practice Guidelines for the Management of Patients with Peripheral Arterial Disease” from 2005, each 10 mg/dL of increase in serum cholesterol adds 5 to 10% to the risk of developing PAD [10, 21]. Significant evidence was accumulated during these years supporting use of statins in patients with early and advanced atherosclerosis, aiming not only decrease the levels of cholesterol to the target level but also contributing to the improvement of symptoms (such as prolonging the pain-free walking distance in patients with intermittent claudication, outcomes of revascularization and overall survival [10, 22, 23, 24]). However, there are several specific issues related to the use of statins in female patients with PAD: (1) studies reported that women generally are less likely to receive statin-based therapy – nearly 1,5 times less for standard doses and nearly 3 times less in case of high-intensity regime; (2) women are more likely to present with specific side effects of these drugs like muscular aches and weakness; (3) differences in body composition (less muscle and more adipose tissue) and a higher rate of polypharmacy could impact the drug metabolism [10, 25, 26].

Hypertension

Hypertension represents a significant risk factor for the development of PAD, and the probability of PAD increases directly with the level of blood pressure elevation [9, 10, 27, 28, 29]. Hypertension is significantly more common in women than in men with PAD, perhaps related to gender-specific differences in vascular physiology. Data from the Framingham Heart Study indicate that intermittent claudication occurs up to 2.5 times more frequently in men who suffer with hypertension and up to four times more

frequently in women [10, 30]. To manage arterial pressure effectively, reducing it below 140/90 mmHg, angiotensin-converting enzyme inhibitors are commonly used as a first-line treatment. However, their use in women, particularly those of childbearing age, raises concerns due to the potential for adverse fetal outcomes and the increased incidence of side effects such as cough and angioedema. Thus, men are approximately 1,3 times more likely to receive treatment with an angiotensin-converting enzyme [10, 31].

Chronic Renal Disease

Chronic kidney disease significantly enhances the risk of developing PAD. Women aged below 70 years who suffer with disturbed renal function, have a significantly higher risk of arteriopathy, with a susceptibility of 1,5 times higher compared to men, which underlines the importance of proactive cardiovascular care in this group [32, 33]. When combined with diabetic nephropathy, the prognosis for PAD becomes even more severe. Currently, there are no clear evidence regarding sex-related differences in the impact of renal pathology upon the evolution of PAD in males and females. Biomarkers such as increased albuminuria and decreased estimated glomerular filtration rate are essential for evaluating kidney function in PAD patients and advancing research on cardiovascular conditions [21, 34].

Osteoporosis

The association of PAD with osteoporosis in older women was examined by von Mühlen et al. in the Rancho Bernardo Study [35]. As this study shows, PAD, defined as an ABI ≤ 0.90 , may be associated with lower bone mineral density and higher rates of osteoporosis in women, although this is highly age-dependent. The researchers studied 1332 participants, of whom – 15,4% of the women and 13,3% of men suffered with PAD. Women without PAD, as compared to those with PAD, demonstrated considerably higher values of bone mineral density and a lower prevalence of osteoporosis. During 4-year follow-up, presence of PAD was observed to contribute to progressive loss of bone density in females but not in males. The association of PAD and osteoporosis in women disappeared after age adjustment, indicating that age is a strong confounder of the PAD-osteoporosis relationship. Also, von Mühlen et al. found no independent association of PAD with fracture risk in women when adjusted for age and other factors. Even though a relation between PAD and osteoporosis was observed, the fact that this did not provide any predictive value for fractures in women with PAD points out that other factors, such as body mass index, physical activity, and general cardiovascular health, have pivotal importance in both conditions.

Obesity and Lack of Physical Activity

Oftentimes, obese patients present themselves with hypertension and diabetes, combining multiple risk factors that induce the development of PAD. Taking into account this bidirectional interplay between PAD and obesity, measures to help with metabolic disorders and weight management should be a priority. In the older population, the prevalence of hypertension is higher among women compared to men, probably due to the natural decline in the production of endogenous estrogens. It has been demonstrated that women

who are hospitalized for surgical interventions related to PAD are generally older and more likely to be obese, further implicating these factors as significant contributors to the risk for PAD. Variations in waist-to-thigh ratio and waist circumference have shown the role of body fat distribution in determining the risk of developing PAD [32, 36, 37].

Non-Conventional Risk Factors

Sex hormones and reproductive history

The impact of reproductive history on women's risk of PAD has been the subject of several recent studies. A study conducted by Cortés et al. assessed the relationship between pre-clinical PAD indicators, such as ABI and femoral artery intima-media thickness, and several reproductive history variables, including age at menarche, parity, and menopausal type. In this cross-sectional analysis, which included 707 women from the San Diego Population Study, reproductive variables and PAD markers had modest relationships, especially when examined by type of menopause. In women with natural menopause, ABI was slightly higher among those who had used oral contraceptives; this may indicate the protective vascular effects of hormone exposure. Estrogen has been shown to affect endothelial function and vascular tone, which may explain the observed differences in naturally menopausal women who have previously been exposed to hormones. However, there was no significant association between ABI values and surgical menopause, although this group of women did exhibit a generally more elevated cardiovascular risk profile [38].

In the RATIO study by Van Den Bosch et al., the association between oral contraceptive use and the risk of PAD in young women was investigated using a population-based case-control design. The study included 152 women aged 18-49 years with angiographically confirmed PAD and 925 control cases. The results demonstrated that women using any types of oral contraceptives were 3,8 times more likely to have PAD than those who did not. First-generation oral contraceptives were the most risky, with an odds ratio (OR) of 8,7, followed by third-generation contraceptives – OR 3,0 and second-generation contraceptives – OR 2,6. Although the overall incidence was low, higher levels of oestrogen ($\geq 50 \mu\text{g}$) in oral contraceptives were associated with a far higher incidence of PAD, with an OR of 19,8; compared with low-dose formulations, which had an OR of 2,4. The investigators also found a synergistic interaction between the use of oral contraceptives and traditional cardiovascular risk factors, including diabetes, smoking, high blood pressure, and high cholesterol. The OR for smokers using oral contraceptives raised dramatically up to 35,9 indicating a very significant increase in risk. There was no difference in the risk of PAD between oral contraceptives of the second and third generations containing $30 \mu\text{g}$ of ethinylestradiol. These findings indicate that thorough risk assessment should be performed in contraceptive counselling, as well as the strong association between oral contraceptive use and risk of developing PAD, especially in the presence of other concurrent cardiovascular risk factors [39].

The article by Ben-Ami et al., studied the association

of atherothrombotic occlusive vascular diseases in premenopausal women with adverse pregnancy outcomes. In this retrospective matched case-control study, 101 women below 50 years with cerebrovascular, coronary or peripheral arterial occlusions were matched for age and BMI with a group of healthy controls. The study investigated the classical risk factors for atherosclerotic arteriopathy such as smoking, hypertension, and diabetes, along with specific obstetric complications: preeclampsia, gestational diabetes, intrauterine growth restriction, and preterm delivery.

The study results indicated that the presence of adverse outcomes during pregnancy could be associated with a higher risk for the development of PAD in older age. Intrauterine growth restriction was mentioned to be independently connected to a risk for atherosclerotic arterial occlusions, with an OR of 8,41. Compared with controls, women with vascular diseases expectedly were more likely to smoke, to have hypertension, dyslipidemia, and type II diabetes. This group also demonstrated a higher frequency of adverse obstetric outcomes, including gestational diabetes, premature delivery, and preeclampsia [40].

Another study researched the association between prenatal hypertensive disorders and the risk of later-life development of PAD using data from the Genetic Epidemiology Network of Arteriopathy (GENOA study). Researchers analysed results of ABI measurements in 1,697 women. The prevalence of PAD, defined as an ABI ≤ 0.9 , was higher in women with a history of hypertension during pregnancy than in those with normotensive pregnancies, even after adjusting for conventional cardiovascular risk factors. The risk of PAD was similar for women with normal blood pressure during pregnancy and nulliparous women. The results of the study show that a history of hypertension during pregnancy is independently associated (OR 1,6) with the development of PAD some decades later and, therefore, helps identify women with increased cardiovascular risk. More than this, it points out the necessity for long-term vascular care in such patients [41].

Socioeconomic Status

Socioeconomic status frequently correlates with certain lifestyle choices, such as smoking and dietary patterns that may lead to metabolic disorders and cardiovascular diseases. However, it also determines access to medical care and the presence of chronic stress. According to recent studies, socioeconomic status and environmental factors contribute to the risk and outcomes of PAD, especially among women. Lower socioeconomic status, which is more frequently seen among women in many countries, relates to the higher prevalence of PAD and poor health outcomes [9, 42, 43, 44]. Consequently, environmental pollutants, including industrial air pollution and second-hand smoke, are also risk factors for enhanced cardiovascular diseases among women, which include a higher rate of PAD-related mortality. Residential proximity to busy roads with long-term exposure to traffic pollutants is known to be associated with an increased prevalence of PAD in women but not in men. The role of pollutants points to a potential of action on the quality of the environment as one of the ways to reduce health disparities,

particularly for females who are more vulnerable against PAD [45, 46, 47, 48].

Nutrition

It is well established that nutrition plays a role in the development of PAD. Dietary behaviors involving the consumption of high amounts of saturated fats, trans fats, and sugar lead to inflammation and metabolic dysregulation [49]. Fan et al. used the dietary inflammatory index (DII) to assess the inflammatory properties of dietary intake and risk of PAD. This study involved 5,840 participants from the NHANES (National Health and Nutrition Examination Survey) database and demonstrated direct association of high DII score with the prevalence of PAD. Chronic inflammation is one mechanism known to be a contributor to the progression of PAD, and it could be exacerbated by a pro-inflammatory diet. Higher C-reactive protein levels and other inflammatory markers were associated with higher DII scores, indicating a possible link between dietary patterns and systemic inflammation. According to Fan et al., those whose DII score exceeded 2,5 exhibited particular risk, suggesting a threshold beyond which pro-inflammatory diets markedly enhance the risk of PAD. It is worth noting that even though the confounding variables were controlled for in the highest DII quartile, women had a significantly higher risk for developing PAD than men with an OR of 1,54. Another finding in this study supports the important role of socioeconomic factors and lifestyle – women with a low level of physical activity, from low socioeconomic status, and with poor education have higher DII scores, indicating an increased risk for PAD. The results focus on the issues of dietary guidelines that specifically address cardiovascular health in female populations considered to be at high risk [1].

Conclusion

Along with the well-known significant burden of PAD worldwide, it should be recognized that women are affected at least as commonly as men or even more frequently due to the additive effects of conventional and non-conventional risk factors. The findings of this review emphasize that while well-recognized risk factors for the development of PAD such as smoking, diabetes, dyslipidemia and hypertension have distinctive features in the female population and act in combination with risk factors related to reproductive history and socioeconomic status. These gender-specific factors not only relate to the differences in pathophysiology but also can contribute to atypical clinical manifestation of PAD in women, disparities in diagnosis and outcomes of treatment and, finally, to higher burden of complications.

The challenges associated with early identification and management of conventional and emerging risk factors will require a multi-component approach. It will mainly require specifically targeted lifestyle modification and proactively engaged comorbid management or gender-sensitive health strategies for outcomes to begin improving from PAD. It will be critically required to bring sex-specific knowledge down to bedside practices after researching them to achieve reduced morbidity and mortality of PAD.

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Corresponding author: Igor Spinei, e-mail: igor41spinei41@gmail.com

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