

Peripheral artery disease in women

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ABSTRACT

Peripheral artery disease (PAD) is a common disease among women and is expected to increase in the coming years. Diagnostic and therapeutic management of PAD in women is difficult due to their gender-related differences, comorbid factors, atypical symptoms, more functional disorders, the presence of advanced disease, being older age of the disease onset, smaller vessel diameter, and psychosocial factors. Especially due to the high prevalence of asymptomatic disease, late admission status and further disease on admission affect the success of the treatment negatively. By focusing more on PAD in women and more clinical studies, gender-specific differences can be identified. Hereby, there is a need to develop appropriate strategies to improve women's overall quality of life. In this review, we aimed to draw attention to the female gender with PAD, which is increasingly occurring.

Keywords: Peripheral artery disease, women, female gender, risk factor

Peripheral artery disease (PAD) occurs as the third most common result of systemic atherosclerosis after coronary artery disease and cerebrovascular disease. Lower limb PAD is estimated to affect about 8.5 million people in America and 202 million people worldwide over 40 years of age, which is increasingly leading to impaired functional disability and quality of life, and is a cardiovascular disease that is associated with myocardial infarction and stroke-related mortality [1]. It has been reported that major cardiovascular events, vascular interventions and re-hospital admissions are significantly higher in patients with PAD than in patients with coronary artery disease [2]. Patients with PAD have 5-6 times higher risk of morbidity or mortality than stroke and coronary artery disease [3].

The main risk factors for PAD are older people, smoking, hypertension, diabetes and dyslipidemia [4, 5]. However, gender-specific risk factors have not

been fully elucidated. In 2012, American Heart Association (AHA) highlighted that in the "Scientific Statement- A call the action: Women and Peripheral Artery Disease", the prevalence of PAD in adults over 40 years of age has increased and clinical awareness in women, focused treatment plans and research on PAD in women are needed [6]. Although it is stated that the prevalence of PAD is higher in men, recent evidence suggests that PAD is also common in women. Since PAD is an age-related disease, considering that women make up the majority of the elderly population, it can be said that PAD in women will increase rapidly in the near future. In addition, asymptomatic / subclinical disease rates are higher in women and most of them have atypical symptoms [7]. In addition, the psychological effects of the disease are more pronounced in women, and in a study, younger women under 65 years of age diagnosed with PAD have a 4-fold higher risk of depression than men [8]. Therefore, in this re-

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PREVALENCE OF PAD IN WOMEN

The prevalence of PAD in women has not been fully elucidated. Recently, there is no study in progress on a large population [6]. In the first studies on the prevalence of PAD, the disease was reported to be more common in men than in women and was accepted. However, these studies were conducted on symptomatic patients [9, 10]. In a review, the prevalence of PAD has been reported to be between 3% and 29% among women 45 to 93 years of age, as in the male gender [9]. A recent review related to population-based studies reported that the mean prevalence of PAD is 15.6% in women and 13.4% in men [11]. Similarly, Sigvant *et al.* [12] reported contradictory results in women with a prevalence of PAD, that is similar to or higher than men. Population studies have showed a prevalence of PAD of 19.2% and 16.5% in women and men, respectively, which is not statistically significant. However, there was a significant gender-based recognition for asymptomatic PAD with a higher prevalence in women than in men (13% vs. 9%; $p < 0.03$).

Compared to Western European countries, although total cholesterol levels are low in Turkey, risk factors such as increased smoking, increased frequency of obesity and metabolic syndrome, diabetes and hypertension are reported as important problems [13]. Although Turkey has a young population, the prevalence of atherosclerotic diseases and their associated mortality are highly observed. Therefore, although there is no large-scale study on PAH in Turkey, this rate is estimated to be higher [14].

RISK FACTORS FOR PAD IN WOMEN

General risk factors for PAD are similar among men and women, including age, smoking, diabetes mellitus, hypertension, and dyslipidemia. In women with PAD, the disease manifests itself, on average, 10-20 years later than men [15]. PAD affects approximately 20-30% of women who are 70 years old or older [10, 16]. Female sex hormones, especially

estrogen, have been shown to protect women from cardiovascular disease until menopause [17]. Estrogen has been shown to participate in endothelial function, such as antioxidative defense, a reduction in cytokine-induced inflammation, and healing of vascular injury, including vasodilation and preservation of vascular tone [18]. The cardioprotective effects of estrogen can explain why women have cardiovascular disease 10-20 years after men. Pregnancy loss associated with low estrogen concentrations in postmenopausal women has been associated with a three-fold higher risk of cardiovascular disease. Additionally, inflammatory markers, which are predictors for PAD, are higher [19-21]. The difference in PAD prevalence between men and women closes with age. Postmenopausal women have similar or even higher PAD prevalence rates than men. The outcomes of hormone replacement therapy on PAD in postmenopausal women are not clear.

The Women's Health Initiative (WHI) and the Heart and Estrogen / progestin Replacement (HERS) studies found that hormone replacement therapy did not make any difference in terms of PAH and coronary artery disease [22-24]. In contrast, the Rotterdam study and another prospective cohort study reported that hormone replacement therapy was associated with a decrease in PAD prevalence [25, 26]. The Cardiovascular Health After Maternal Placental Syndrome (CHAMPS) study showed three-fold increased risk of PAD and two-fold increased risk of coronary artery and cerebrovascular disease in patients with maternal placental syndrome, including preeclampsia, gestational hypertension, placental abruption and placental infarction [27]. Although the possible cause is the underlying endothelial dysfunction, the mechanisms for this relationship are unclear.

Smoking is a greater risk factor for PAD in men, but diabetes and dysglycemia increase the risk of intermittent claudication in women 4 times [28, 29]. In patients with chronic renal failure, younger women (< 70 years; mean age 56.5) may have a higher PAD prevalence compared to paired men (1.53 times higher risk) [30]. Many studies have shown an association between obesity, C-reactive protein (CRP), osteopenia / osteoporosis and hypothyroidism, and PAD in women [31-35]. Risk factors specific to women are summarized in Table 1.

Table 1. Risk factors for female gender-specific PAD

Risk Factors	Comments
Menopause	Possible vasculoprotective effects
Oral contraceptives	Increased risk of venous and arterial thrombosis
Maternal placental syndrome	Preeclampsia, gestational hypertension, placental abruption and placental infarction
Depression	< Age of 65, 4 times higher risk than men
Elevated CRP	Higher levels of CRP than men
Osteopenia / Osteoporosis	Age-dependent
Hypothyroidism	This is controversial

PAD = Peripheral artery disease, CRP = C-reactive protein

SCREENING AND SYMPTOMS

The classic symptom of PAD is intermittent claudication, but not in all cases. Up to 40% of cases may not complain about leg symptoms and may occur with atypical symptoms. Women have higher subclinical, asymptomatic and atypical PAD rates [36, 37]. The American College of Cardiology / American Heart Association (ACC / AHA) guidelines recommend screening with the ankle-brachial index (ABI) for asymptomatic individuals over 65 and 50-64 years old with diabetes and smoking [37]. In the Women's Health and Aging Study (WHAS), 35% of 933 disabled women over 65 years were found to have ABI < 0.9 and were diagnosed with PAD. In their study, they showed that 63% of patients diagnosed with PAD did not have classical exercise pain [38]. Asymptomatic PAD is common among older women. Most patients with PAD are asymptomatic or have atypical symptoms, and only 10% of patients present with classical claudication [1]. Women may be more asymptomatic or present with atypical symptoms. Atypical symptoms in women can be misinterpreted as arthritis, neuropathy or spinal stenosis, which is also evident in this population. There is a similarity with PAD severity between the level of physical activity and the measured ABI value, but this may not apply to women [39]. In a study conducted at Northwestern University, it was found that women applying for PAD evaluation had more severe disease than men with ABI test [40]. Brevetti *et al.* [41] stated that women applying to the vascular laboratory are more likely to get Fontaine stage III or IV disease than men and have

less classic symptoms of claudication than men. In a cohort study, the Walking and Leg Circulation Study (WALCS), among 460 PAD patients without critical limb ischemia, they found that the presence of atypical stress symptoms, which sometimes began to rest in 187 female patients, was twice as high as in men [42].

Women with PAD have more functional disorders than men. McDermott *et al.* [42] measured walking speed and distance, daily physical activity and performance scores in 273 PAD patients. They stated that despite similar disease severity in both genders, women experienced more impairment in lower limb function and strength, women had lower walking speeds, and achieved much shorter distances than men in a 6-minute walk. In a recent study in which PAD patients were followed up to 4 years, it was found that women with PAD had higher mobility loss and functional decline rates than men with PAD [43]. In a prospective WHAS cohort study, 847 women with low ABI (< 0.6) were predicted to have greater walking-related disorders [44]. PAD impairs the functional state more in women and women have a lower quality of life compared to men.

DIAGNOSTIC METHODS

A complete vascular history, presence of existing risk factors, and physical examination and control of the pulses are crucial for the diagnosis of PAD. Non-invasive diagnostic tests and objective evaluations are very valuable in detecting PAD due to limitations in physical examination. The most common first

diagnostic test is resting ABI. ACC / AHA guidelines recommend screening with ABI for asymptomatic individuals over 65 and 50-64 years old with diabetes and smoking [37]. In a study of 1775 healthy individuals, ABI was found to be approximately 0.02 lower in women [45].

Physiological tests such as exercise ABI, toe-brachial index, transcutaneous oxygen pressure, or skin perfusion pressure can be performed according to the clinical picture and resting ABI result [46]. Duplex ultrasound, magnetic resonance angiography (MRA), computed tomographic angiography, or invasive angiography are useful in providing anatomical location and severity of the disease. Currently, there is no large gender difference in the diagnostic sensitivity or accuracy of these tests [46].

Difficulties in diagnosis and treatment of gender-specific women in PAD are summarized in Table 2.

TREATMENT OF PAD IN WOMEN

Cardiovascular risk factor modification, exercise and medical therapy

The aim of symptomatic and asymptomatic PAD treatment should be primarily to decrease the progression of ischemic vascular events and to increase the quality of life and physical functionality. 2016-AHA / ACC guidelines recommend exercise

program, smoking cessation, lipid lowering with statin therapy, blood pressure control with angiotensin receptor inhibitors, antiplatelet therapy, and aggressive diabetes management [1]. The main goals for both genders are to reduce cardiovascular morbidity and mortality and improve the quality of life of patients by improving limb-related symptoms. In addition to modification of risk factors, medical and revascularization therapy should be added to these targets for the treatment of claudication.

Although aggressive risk factor modification is the basis of treatment, the German REACH registry cohort study showed that patients with PAD alone were less likely to receive treatment with statins, angiotensin-converting enzyme inhibitors or antiplatelet agents compared to concomitant coronary artery disease patients [47]. In parallel with this study, the REACH (Reduction of Atherothrombosis for Continued Health) registry records showed that women with 8,322 PAD patients had significantly less optimal risk factor control than men [48]. This makes us think that the success of PAD treatment in women will be less than men, by taking the recommended risk factor control treatment of women with PAD less.

In a study investigating the effect of quitting smoking by Armstrong *et al.* [49], a five-year follow-up showed a marked reduction in all-cause mortality and amputation-free survival in both men and women. Sigvant *et al.* [50] reported that smoking for 10 years

Table 2. Difficulties in diagnosis and treatment for female gender-specific in PAD

Status	Comment
Asymptomatic and atypical symptom	Delay in diagnosis
Higher prevalence of orthopedic diseases	Arthritis and arthrosis Delay in diagnosis
Presence of progressive disease at diagnosis	Low treatment success
Diagnosis at an advanced age	Low treatment success
Insufficient aggressive risk factor modification	Lower usage of antiplatelet agents, statins, angiotensin converting enzyme inhibitors Low treatment success
Failure to benefit from exercise training	Low exercise tolerance Low treatment success
Small arterial diameter (< 7mm)	Low patency rates Low treatment success

PAD = Peripheral artery disease

in women is a risk factor for PAD, while it is 30 years in men. Ness *et al.* [51] described that smoking has a more detrimental effect on females than males in the presence of symptomatic PAD in older patients. In the light of these studies, we can say that smoking has a significantly more negative effect on PAH in women than men. In that case, stopping smoking seems to be an important element of PAH treatment compared to males.

Patients with PAD have limited exercise in their daily lives. There is evidence that a regular exercise training program is useful. It has been shown that lower limb exercise training increases the duration of claudication, increases the distance before claudication and increases the total walking distance [52]. In a meta-analysis examining 1200 people with stable leg pain, it was found that the maximum walking time improved significantly with exercise, with an overall improvement of 50% to 200% in walking ability [53]. In most randomized trials comparing supervised exercise training with pharmacological therapy or revascularization procedures, gender-specific analyzes were not performed, as female participants were less than 30% on average [6]. On the other hand, a study has shown that especially women with diabetic PAD have less responses to exercise rehabilitation programs, and this is partly due to further deterioration in calf muscle oxygen saturation during and after exercise. They also attributed this to lower leg strength, higher inflammation, higher oxidative stress level during ambulation, and lower hemoglobin saturation during insulin resistance [54].

Many studies have shown that the use of cholesterol-lowering therapy, especially statin, can not only improve symptoms of intermittent claudication but also increase walking distance from baseline [55, 56]. Although the proposal for statin use does not vary by gender, women with PAD are found to be less likely to receive statins.

Hypertension is an important risk factor for PAD and must be treated. Heart Outcomes Prevention Evaluation (HOPE) study [57] involving those with PAH and Ahimastos *et al.* [58] in their studies, they reported that in blood pressure control with ACE-I, cardiovascular mortality and morbidity decreased and painless walking distance improved. Therefore, ACE-I is recommended as the first-line treatment for

hypertensive patients with PAD. However, ACE-I use in women has some limitations such as fetal toxicity, multidrug-intolerance syndrome and breast cancer recurrence [59, 60].

Current guidelines recommend antiplatelet therapy in symptomatic PAD, but also recommend the use of antiplatelet therapy in patients with ABI < 0.9 and no symptoms. It can be administered with 75-325 mg of aspirin once a day or 75 mg of clopidogrel once daily as a safe and effective alternative [1]. This recommendation does not vary by gender.

Among the available drugs, cilostazol, a phosphodiesterase inhibitor that inhibits platelet aggregation and has arterial vasodilating properties, is the drug with the most accurate evidence as a first-line pharmacological treatment in symptomatic PAD, including intermittent claudication [7]. In randomized clinical studies, it was concluded that Cilostazol improved both painless and maximum treadmill walking distance compared to placebo at a dose of 100 mg twice daily [61]. There were no different results in the treatment of cilostazol by gender.

Surgical Revascularization

The guidelines recommend revascularization in the presence of intermittent claudication that limits function despite optimal medical therapy. But although they have similar comorbidities with men, women have less revascularization procedures [6]. In the article "Scientific Statement- A call the action: Women and Peripheral Artery Disease" published by AHA in 2012, it was stated that women constitute only 32% of the participants in the PAD revascularization studies, and this shows that making treatment decisions is mostly with the results obtained from men [6]. Although the treatment options for both genders are similar, it was emphasized that women were recommended less surgical revascularization due to smaller vessel diameter, presence of advanced disease in diagnosis, advanced age of onset of disease, psychosocial factors and worse surgical results [6, 62, 63]. In studies conducted, it was stated that the patency rates of the graft were lower in women in lower extremity surgical revascularization [6]. Although these reports suggest that there are low patency rates, especially in women treated with surgical bypass, no significant gender effects have been identified in patients treated with endovascular procedures, surgical

bypass or a combination of these [64]. Similarly, another study reported that there were no gender differences in graft patency rates [65]. However, studies have found that female gender is an independent risk factor for postoperative wound complications (odds ratio: 1.376, 95% CI: 1.076-1.757; $p = 0.01$). It has also been noted that wound complications increase the risk of limb loss, mortality, increased hospital stay, and decreased quality of life [66]. However, it has been suggested that women with lower extremity bypass are more likely to have hematoma, seroma and infection than men [67]. Despite the gender-related differences noted, the idea that revascularization option should be considered as a priority in women is strengthened because the amputation-free survival is similar in women and men [6].

Endovascular Therapy

It is likely that women are less likely to benefit from revascularization due to anatomical, comorbidity, advanced disease, age of onset of the disease, etc. In addition, it has been shown by studies that wound complications are more common in women. All these reasons raise the question of what is the place of endovascular treatments (stent, balloon angioplasty, atherectomy) in women.

According to the TransAtlantic Inter-Society Consensus (TASC), in iliac obstructive lesions for both men and women, endovascular approach with angioplasty and/or stenting is recommended as the first treatment option today, not only for patients with TASC A and B lesions, but also for patients with TASC C and D lesions, who are particularly poor candidates for open surgical repair [6].

As with surgical revascularization, caution should be exercised in endovascular therapy due to the presence of more aggressive atherosclerotic disease and smaller arterial diameter in the female sex. In several published studies [68-70], the results of iliac artery stents have been published, especially in women, but the results were insufficient as only bare metal stents were used. Piazza *et al.* [71] in their study investigating the effect of gender on endovascular treatment for iliac lesions, they reported that primary and secondary patency rates were significantly lower in women in the long-term follow-up, although they showed similar results in men and women in the early

period. They determined that this was due to the fact that women had smaller arterial diameters and that the stent diameter was less than < 7 mm as a negative predictor. In the same study, it was emphasized that open surgery may still be a viable option in female patients with a target artery diameter of < 7 mm [71]. In another large patient-scale study, Ramkumar *et al.* [72] investigated the role of gender in determining the type of intervention in endovascular therapy. In this study, they found that women were less likely to undergo stenting or atherectomy than men, while they found higher rates of occlusion and re-intervention in women, especially in femoropopliteal arteries. Again in this study, they emphasized the effect of artery diameter on gender inequality in endovascular treatment.

As mentioned before, women with PAD are at an advanced age and more advanced disease stages, so any treatment in women is difficult. Matsi and Manninen [73] noted significantly higher bleeding complications (15% vs. 6%) in women undergoing percutaneous lower extremity angioplasty. In three state studies involving open surgery and endovascular treatments, a total of 372,692 patients, approximately 45% of whom were women, Vouyouka *et al.* [74] reported that women had higher mortality and morbidity rates than men after any type of vascular intervention.

CONCLUSION

The scarcity of research studies also prevents us from fully evaluating PAD results in female gender. Diagnosis and treatment management of PAD in women is difficult due to their gender-related differences. Especially due to the high prevalence of asymptomatic disease, late admission status and further disease on admission affect the success of the treatment negatively. As a result, the risk of mortality and morbidity increases in women. By focusing more on PAD in women and more clinical studies, gender-specific differences can be identified. Hereby, there is a need to develop appropriate strategies to improve women's overall quality of life.

Authorship contributions

Concept-Design: KKÖ, ŞY; Data collection:

KKÖ, USS, FT; Analysis: KKÖ, FT, ŞY; Literature search: KKÖ, USS, FT; Writing: KKÖ, USS, ŞY; Critical review: ŞY.

Conflict of interest

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