

## Gender specific differences in peripheral artery disease and their impact on cardiovascular rehabilitation -the experience of a Romanian Rehabilitation Hospital

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### Abstract

**Introduction.** As the prevalence of peripheral artery disease (PAD) is increasing in developing countries, so are the healthcare and socio-economic costs it brings about. This particular form of atherosclerotic disease is very much age-dependent, and along with the increase in life-expectancy, the last decades have seen a sharp rise in PAD prevalence in women. Knowledge regarding gender-specific aspects of the disease are scarce. This has a negative effect on overall outcomes of female PAD patients. **Aim.** This research aimed to identify gender peculiarities of PAD and evaluate their impact on cardiovascular rehabilitation. **Material and methods.** This was a retrospective observational study of 104 PAD patients (73 men and 31 women) admitted in 2016 to the Cardiology department of the Rehabilitation Hospital Cluj-Napoca. Demographic, clinical and biological parameters were recorded, as well as the treatment/rehabilitation regimens prescribed. The subjects were divided into to groups according to gender. Statistical analysis was done using the student t-test for unequal variances, hi-square test and the stepwise method for multivariate analysis. **Results.** The female group had a higher prevalence of diabetes mellitus (45% vs 33%,  $p=ns$ ), but men were more likely smokers (74% vs 51% -  $p=0.017$ ). Women had higher median total cholesterol values ( $p=0.006$ ) and lower HDL-cholesterol levels ( $p=0.033$ ). More than half of the female patients were already experiencing symptoms of critical limb ischemia on admission (57%), while intermittent claudication was predominant with men (66%). Multivariate analysis identified female gender ( $p=0.028$ ) and ABI ( $p<0.0001$ ) as sole independent predictors for the severity of the disease. Revascularization using percutaneous techniques was the preferred option for women (35% vs 27%), while surgery was performed more often in men (38% vs 29%) -  $p=ns$ . Home-based exercise training was indicated on discharge for more than half of the male group while only 30% of women had physical rehabilitation as a first line of treatment. **Discussion.** Our research offered similar findings to older studies regarding the gender-specific profile of PAD women, showing they are less exposed to smoking but more likely to experience metabolic disorders. Women had higher rates of critical limb ischemia on admission, suggesting a more advanced disease. Because of a more stable disease in men, this category benefited to a greater extent from exercise training compared to women.

**Conclusion.** Peripheral artery disease has specific gender-related differences that in women have an important impact on both diagnosis and management, impeding rehabilitation and full social reintegration.

**Key words:** *peripheral artery disease, gender, cardiovascular rehabilitation*

### INTRODUCTION

The prevalence of peripheral artery disease (PAD) is increasing in developing countries. It comes along with socio-economic effects comparable to those of ischemic heart disease and stroke, both regarding healthcare costs and social reintegration. Although not so long ago it was considered almost an exclusively male disease, because of an increasingly ageing population literature data show a constant rise in PAD incidence in women over the last few decades [1]. PAD is strongly age-related, as there is an increase of more than 10% in prevalence over the age of 60 [2]. Unfortunately, women's suboptimal representation in PAD related clinical trials, along with sometimes atypical clinical symptoms, often lead to misdiagnosis and mismanagement of this illness in female patients [3]. This adds to the particular anatomical characteristics of women,

leading to an overall increase in morbidity and mortality compared to their male counterparts [4]. Not only are women more exposed to misdiagnoses and ill treatment of PAD, but often those exposing claudication-like symptoms are less likely to benefit from inclusion into a supervised exercise program, which in time will lead to the worsening of their symptomatic status and other disease-related complications [5,6]. Therefore, the aim of this study was to sketch the profile of women diagnosed with PAD in a Rehabilitation Hospital and compare it to that of age-matched men, taking into account specific risk factors, but also clinical and anatomical peculiarities. The research also concentrated on detecting any relevant differences regarding the treatment and rehabilitation regimens prescribed for the two groups.

## MATERIAL AND METHODS

This is a retrospective analysis of 104 subjects (73 men and 31 women) diagnosed with clinically manifest PAD (intermittent claudication or rest leg pain/trophic lesions) and an ankle-brachial index (ABI) lower than 0.9 or higher than 1.4, admitted during the year 2016 to the Cardiology department of The Rehabilitation Hospital in Cluj-Napoca, Romania. Patients diagnosed with acute limb ischemia requiring emergency reperfusion, the ones with non-atherosclerotic arterial disease, as well as those who had no imagistic documentation of the severity of the disease, were excluded from the study. Thus, anatomical data were available for analysis in all subjects. Demographic parameters, atherosclerotic risk factors and the treatment regimes prescribed were also obtained from the patients' medical records. Subjects were divided into two groups according to their gender. Statistical analysis was done using the student t-test for unequal variances, as well as the hi-square test. Multivariate analysis using the stepwise method was also performed. A p value of less than 0.05 was considered statistically significant.

## RESULTS

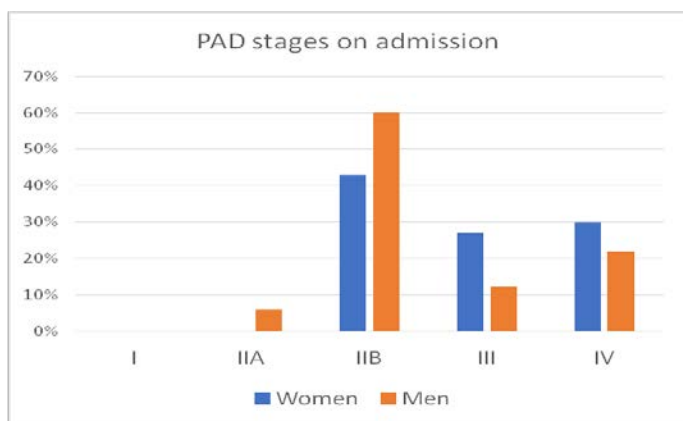
Of the total 104 subjects included in the final analysis, 30% were of female gender, with a mean age of  $69 \pm 11$  years. Women were more frequently diabetic (45% vs 33%,  $p=ns$ ), but men were more likely to have a history of smoking (74% vs 51% in women-  $p=0.017$ ). Prior arterial hypertension (90% for women vs 82% for men) or dyslipidemia (61% vs 53%) were common in both groups, but without significant differences between them. On the other hand, when studying the baseline values of different lipid fractions on admission, we found that the female group had significantly higher total cholesterol mean values compared to men ( $p=0.006$ ) with lower HDL-cholesterol levels ( $p=0.033$ ). This was despite the fact that there was no gender difference in the prior use of statins or other types of cholesterol-lowering medication. The general characteristics of the two groups are summarized in table 1.

Regarding other sites of associated atherosclerotic disease, we found no statistical difference in the rates of prior cerebrovascular or coronary ischemic events. When it comes to the severity of PAD on admission, there is a clear tendency for the female group to present with a more advanced disease. Thus, 57% of women were diagnosed with stages III or IV of the

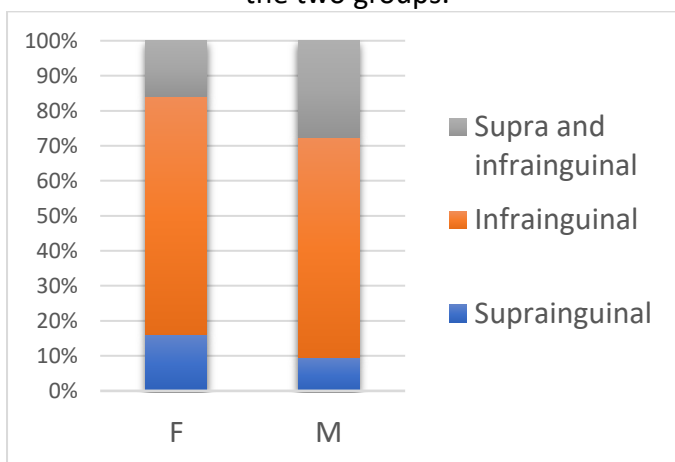
Lériche-Fontaine classification of PAD, meaning than more than half were already experiencing critical limb ischemia in need of immediate medical treatment and/or revascularization. On the other hand, men presented more often with a stable chronic disease, 66% of them complaining of intermittent claudication (stages IIA and IIB)- figure 1. In terms of the anatomical location of the arterial atherosclerotic lesions, we found no statistical significant difference between the two groups- figure 2. On multivariate analysis using the global stepwise method, we identified female gender ( $p=0.028$ ) and ABI ( $p<0.0001$ ) as independent predictors for the severity of the disease.

**Table 1.** General characteristics and CV risk factors for the two groups.

| Parameter              | Men                 | Women               | P value |
|------------------------|---------------------|---------------------|---------|
| Mean age               | 65.16 ± 8.23        | 69.09 ± 11.20       | ns      |
| Smokers                | 55 (75.3%)          | 16 (51.6%)          | 0.017   |
| Hypertension           | 60 (82.2%)          | 28 (90.3%)          | ns      |
| Diabetes mellitus      | 24 (32.9%)          | 14 (45.2%)          | ns      |
| Obesity                | 12 (16.4%)          | 7 (22.5%)           | ns      |
| Total cholesterol      | 174.85 ± 49.7 mg/dl | 205.31 ± 49.9 mg/dl | 0.006   |
| LDL-cholesterol        | 105.84 ± 41.0 mg/dl | 122.53 ± 45.5 mg/dl | 0.07    |
| HDL-cholesterol        | 41.90 ± 10.0 mg/dl  | 49.36 ± 17.3 mg/dl  | 0.033   |
| Blood glucose          | 108.37 ± 40.0 mg/dl | 107.1 ± 26.8 mg/dl  | ns      |
| Triglycerides          | 139.23 ± 66.5 mg/dl | 171.03 ± 118 mg/dl  | ns      |
| ABI                    | 0.51±0.16           | 0.49±0.17           | ns      |
| Ischemic heart disease | 20 (27.3%)          | 7 (22.5%)           | ns      |
| Stroke                 | 7 (9.5%)            | 2 (6.4%)            | ns      |



**Figure 1.** Leriche-Fontaine stages on admission for the two groups.



**Figure 2.** Lesion localization for both sexes

Treatment-wise, no significant differences were determined on statistical analysis between sexes, both groups receiving antiplatelet agents and statins in more than 90% of the cases. Aspirin was used in 73% of subjects, while the remainder were prescribed Clopidogrel. Subjects with intermittent claudication from both groups were given adjuvant vasodilator therapy. Concerning the revascularization techniques used, although there was a clear tendency to utilise percutaneous techniques more often in women (35% vs 27%), with surgical therapy more prevalent in men (38% vs 29%), it did not reach statistical significance. This might be probably due to the reduced overall number of female subjects in our study.

Subjects with non-debilitating intermittent claudication from both groups were instructed, alongside drug therapy, to undergo a home-based exercise program consisting of at least 3 hours of maximal/submaximal walking per week, for at least three months. Due to the higher number of women presenting with critical limb ischemia, this exercise therapy was more frequently indicated in the male group (51.5% vs 31.5%,  $p < 0.05$ ).

## DISCUSSION

There is an obvious lack in knowledge concerning the specific epidemiologic data and risk factors for peripheral artery disease in women. This is coupled with reduced sensitivity and specificity of current diagnostic tests in detecting PAD for this population group, leading to under-diagnosis and treatment delay [3,4]. The current study wants to give a small glimpse regarding demographic, risk factor and treatment characteristics of women with PAD by comparison with men, for which literature data is more abundant.

Hiramoto et al found in a voluntary screening population that men were more likely to be current smokers, have diabetes or coronary artery disease. On the other hand, women had a lower ABI and higher median C-reactive protein levels compared to men [7]. Our research offered similar findings regarding smoking, but the women in our group were more exposed to having a history of diabetes mellitus compared to men, although it did not reach statistical significance.

Older studies have shown that women with PAD tend to be older and have dyslipidemias more often than men [8,9]. In our cohort this was true regarding total cholesterol values, which were significantly higher on admission than those of men, whereas HDL-cholesterol was lower. All of these point to a particular cardiovascular risk profile, with women being less exposed to smoking but more likely to experience metabolic disorders.

When it comes to clinical presentation, the female group had higher rates of critical limb ischemia on admission (pain at rest with or without trophic lesions), suggesting a more advanced disease, although there was no difference concerning the location or severity of lesions compared to men. This is in line with the findings of a large study by Lo and collaborators, which showed women presented in more advanced stages of the disease and therefore, there was a preference towards performing endovascular over surgical revascularization [10]. The same was true for our group, with women being treated percutaneously in a higher proportion.

Owing to the nature of a more stable presentation in men, this category benefited to a greater extent from exercise training compared to women. Evidence shows that home-based exercise improves pain-free walking distance by up to 180 m compared to no exercise [11,12]. This is the reason why current practice guidelines recommend exercise training

(supervised or home-based) as the first line of treatment in patients with intermittent claudication, superseding vasodilator drugs [13]. However, even patients undergoing revascularization procedures should be referred for inclusion in cardiovascular rehabilitation programmes, especially following surgical treatment. This will shorten convalescence and facilitate speedy social reintegration. A study by Jakubsevičienė et al proved that enrolment in such programmes yielded significant increases in walking distance and quality of life in the rehabilitation group compared to controls [14]. Unfortunately, in our case only half of the subjects from the male group and about a third of women were initially advised to undertake a home-based exercise program, mostly due to the advanced stages of the disease upon presentation.

New technology might be of great help when it comes to home-based exercise programmes, as a research by Cornelis et al. found that PAD patients show significant interest in technology-delivered exercise [15]. This should be perfected in the future to widen the spectrum of patients benefitting from a form of inexpensive, customised rehabilitation schemes. Other rehabilitation strategies, like the use of carbonated mineral water, might yield promising results, improving the quality of life and self-dependence of patients if employed on a case to case basis [16].

## CONCLUSION

Peripheral artery disease has specific gender-related differences that should be taken into consideration in order to optimise its management. In the real world setting female patients tend to have a particular cardiovascular profile, which often leads to delayed diagnosis and treatment, thus hindering their rehabilitation and full social reintegration.

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