Gender is an independent risk factor for distribution pattern and lesion morphology in chronic critical limb ischemia

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Background: The aim of this study was to determine gender differences in atherosclerotic lesion morphology and distribution pattern of patients with critical limb ischemia (CLI).

Methods: In this prospective cohort study, 233 patients, including 134 men (58%) and 99 women (43%) presenting with critically ischemic limbs were consecutively enrolled. Lesions of the entire lower limb arterial tree were evaluated and grouped into iliac, femoropopliteal, and below-the-knee (BTK) arterial disease. To elucidate whether gender is an independent risk factor for distribution pattern, we performed multivariable logistic regression models adjusted for cardiovascular risk factors.

Results: At time of diagnosis, women with CLI presented with higher mean age (78 ±10 vs 74 ±10, P = .01), suffered more often from hypertension (83% vs 71%, P = .04), and fewer were current or former smokers (25% vs 70%, P < .001). After multivariate analysis, women with CLI showed a 2.5-fold higher risk for femoropopliteal lesions (odds ratio [OR], 2.53; 95% confidence interval [CI], 1.05-6.11, P = .04), with a threefold higher risk for occlusions compared with men (OR, 3.81; 95% CI, 1.45-10.0; P = .01). Moreover, in women a higher risk for multilevel disease was observed (OR, 3.81; 95% CI, 1.45-10.0; P = .01). In contrast, men presented more often with isolated BTK lesions compared with women (OR, 0.15; 95% CI, 0.05-0.70; P = .03).

Conclusions: The finding that female gender may be an independent predictor for pronounced femoropopliteal involvement and more severe and diffuse atherosclerotic disease in CLI may be of particular relevance for early detection and for choosing distinct treatment strategies in women compared with men. Further studies are warranted, especially on confounding risk factors that might be different in men and women and their possible association with lesion morphology in patients with critical limb ischemia. (J Vasc Surg 2012;55:98-104.)

Chronic critical limb ischemia (CLI), representing the most severe form of peripheral artery disease (PAD), is defined as the presence of rest pain, ulceration, or gangrene and the prognosis for potential limb salvage is dismal and even higher if left untreated.1 CLI is associated with increased mortality and patients are at an exceptionally high risk for other cardiovascular events.2 Cardiovascular diseases, including CLI, are responsible for the largest portion of health-care expenses and account for the highest rates of morbidity and mortality in women (42%), which even exceed the rates for men (35%).2 During the past decade, cardiovascular death, including death from CLI, has decreased among men, whereas women have experienced a continuous increase of cardiovascular mortality, despite improved diagnostic approaches and continuing advances in medical therapy.2,3

Based on numerous previous studies, it is anticipated that women with CLI have higher amputation rates and lower graft4 or stent patency5,6 rates as well as more wound complications7 after revascularization than men. Most of these differences in outcomes following revascularization have been attributed to delayed presentation, smaller vessel diameter, advanced age, and comorbidities.4,5,8,9 However, beyond these differences certain pathomorphologic gender differences have also been suggested since it seems that in women after menopause atherosclerotic disease is more rapidly progressing and more diffuse in women after menopause when compared with men.10,11 A position paper of the American Medical Women’s Association stated that only 25% of research studies were analyzed by gender.12 Yet, since the US National Institute of Health strongly recommended representative inclusion of women in clinical research, gender differences in cardiovascular disease have gained increased attention and evidence-based gender-specific treatment guidelines have already been released for coronary artery disease and cerebrovascular disease.13,14

Although the indications for immediate revascularization have been established for CLI,1 a more informative morphologic picture to describe the typical arterial involvement may be of value to design specific treatment

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guidelines for men and women suffering from CLI. To date, only very few studies investigating the impact of gender on CLI have been performed and data on lesion pathomorphology and distribution patterns in an unselected female CLI cohort investigating the entire lower leg arterial tree are missing. The aim of this cohort study of patients with CLI was therefore to analyze gender differences regarding morphology and distribution pattern of lower-limb lesions prospectively followed in “all-comers” patients treated in a large tertiary referral center. Moreover, we aimed to determine whether gender is an independent determinant of pathomorphologic differences by means of multivariate logistic regression analysis.

METHODS

Study design. Analysis was based on 233 patients with CLI referred to the Cardiovascular Center at the University Hospital of Berne between January 1999 and June 2004 by external general physicians, general hospitals, or the Department of Emergency Medicine of our institution. Recorded patient details comprised demographic characteristics, risk factors, clinical presentation, imaging studies, and treatment modality at initial diagnosis of CLI. Approval of the local ethics committee had been obtained before the beginning of the study. The study was carried out according to the Declaration of Helsinki. All patients had given informed consent prior to inclusion into this study.

The definition of CLI followed the Second European Consensus document, ie (1) presence of ischemic rest pain for more than 2 weeks or ischemic tissue loss associated with (2) an absolute ankle pressure <50 mm Hg or great toe pressure <30 mm Hg. Patients with acute limb ischemia due to an embolic etiology and onset of symptoms within 2 weeks before referral were excluded. All patients included in this study underwent digital subtraction angiography prior to treatment decision by a multidisciplinary vascular board. Angiographic findings of the preinterventional angiography were prospectively entered in a database. Double reading of the angiography was performed always by the same two vascular specialists.

All lesions of the arterial tree were grouped as iliac (common, external, and internal iliac artery), femoropopliteal (common, superficial and deep femoral arteries, popliteal artery) and below-the-knee (BTK: tibioperoneal trunk, anterior (common, superficial and deep femoral arteries, popliteal artery), external, and internal iliac artery), femoropopliteal or tibial occlusive disease (see below). In univariable analysis, or if the patient was taking antihypertensive medication. Dyslipidemia was defined by a total serum cholesterol level of >5 mmol/L, serum high-density lipoprotein cholesterol level of <1 mmol/L, or serum triglyceride level of >2 mmol/L. Diabetes mellitus was defined by fasting blood sugar levels >120 mg/dL, a hemoglobin A1c level >6%, or intake of antidiabetic drugs. Smoking habits were divided into either current or former smoking, or nonsmoking. Renal failure was defined as a serum creatinine level >130 μmol/L.

Statistical analysis. All analyses are based on patients with complete data sets. Continuous and normally distributed variables are presented as mean ± standard deviation, and asymmetrically distributed variables as median (interquartile range). Categorical variables are presented as numbers (percentages). Baseline characteristics were analyzed using Student t test or Mann-Whitney test for continuous and χ2 test for categorical data.

Associations between gender and morphologic characteristics of vascular lesions (lesion present, type of lesion and length of occlusion, tibial vessel patency, lesions treated, multilevel disease and localization of treated lesions) were determined using crude univariable and multivariable logistic regression models adjusted for age, smoking, presence of hypertension, dyslipidemia or statin use, and diabetes. Differences between gender and morphologic characteristics were tested using Wald tests for trend or interaction as appropriate. All P values and 95% confidence intervals were two-sided.

RESULTS

Cohort description and patient characteristics. Two hundred forty-nine patients with critically ischemic limbs were consecutively enrolled into the registry, 16 patients (6%, seven men and nine women) were excluded due to incomplete data. A total of 233 patients, including 134 men (58%) and 99 women (42%) with critically ischemic limbs were consecutively enrolled in our study and contributed to all analyses. Detailed demographic data and clinical characteristics of men and women at baseline are given in Table I. Compared with men, women presented with a higher mean age (78 ±10 vs 74 ±10, P = .01), suffered more often from hypertension (83% vs 71%, P = .04), and were less often current or former smokers than men at time of CLI diagnosis (25% vs 70%, P < .001).

Gender-specific differences of lesion morphology and distribution pattern of the iliac axis in patients with CLI. Arterial lesions of the iliac axis are shown in Table II. A minority of all lesions involved the iliac axis, namely 19% in men and 17% in women (P = .77). All lesions of the iliac axis were combined with lesions of other segments of the arterial tree (see below). In univariable analyses, no difference in lesion severity, in particular number of occlusions or occlusion length, was observed between men and women (P > .77, Table II). However, when adjusted for cardiovascular risk factors, we found a
tendency for a higher risk of more severe iliac lesions in women compared to men \( (P = .08) \).

Male-specific differences of lesion morphology and distribution pattern of the femoropopliteal axis in patients with CLI. Overall, 84% of all lesions involved the femoropopliteal axis. There was a trend toward more femoropopliteal lesions in women \( (P = .09) \), and when adjusted for risk factors, the risk for femoropopliteal lesions was 2.5-fold higher in women compared with men \( (P = .03, \text{Table III}) \). Of all femoropopliteal lesions, most were occlusions (58%), in particular 66% of all occlusions measured >10 cm in length (Table III). In general, a trend toward more severe femoropopliteal lesions in women compared with men was observed \( (P = .05) \), which became significant after adjusting for risk factors \( (P = .02) \). Therefore, women had an almost twofold increased risk for stenoses and a more than threefold increased risk for occlusions of the femoropopliteal axis as compared with men \( (P = .02) \).

Gender-specific differences of lesion morphology and distribution pattern of the BTK axis in patients with CLI. Almost all men and women with CLI presented with BTK lesions, only 1% of both genders showed patency of all three arteries in the BTK segment (Table IV). Concerning the number of patent vessels of BTK lesions, no difference was observed \( (P = .62) \), also when adjusted for cardiovascular risk factors \( (P = .50) \).

Gender differences of lesion localization and between single and multilevel disease in patients with CLI. Gender-specific differences in lesion localization and between single and multilevel disease are shown in Table V. We observed a 2.6-fold increase of the risk for involvement of multiple segments of the arterial tree in female patients compared with men \( (P = .03) \) which increased to almost fourfold after adjustment for risk factors \( (P = .01) \). The localization of lesion involvement was different between men and women \( (P \text{ for interaction } = .03 \text{ after multivariable adjustment}) \). In particular, women showed more involvement of the femoropopliteal or iliac axis combined with BTK lesions (92% vs 81%), whereas men presented with more isolated BTK lesions combined with women (18% vs 7%).

DISCUSSION

This prospective cohort study with 233 prospectively enrolled patients with CLI in a large tertiary vascular referral center is to the best of our knowledge the first study analyzing the entire arterial tree of an all comers...
CLI cohort and demonstrating that gender differences exist concerning lesion morphology and distribution patterns. We demonstrate that women with CLI after adjustment for risk factors still bear an increased risk for femoropopliteal lesions and specifically for occlusions. Moreover, female gender is associated with a higher risk for diffuse disease involving multiple segments of the arterial tree. In contrary, men presented with more lesions limited to the BTK axis. Since these differences are present when adjusted for cardiovascular risk factors, we conclude that female gender may be an independent risk factor for femoropopliteal involvement and a more severe and diffuse atherosclerotic disease pattern in CLI.

Table III. Characterization of arterial lesions of the femoropopliteal axis

<table>
<thead>
<tr>
<th>Femoropopliteal axis</th>
<th>Men</th>
<th>Women</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 134</td>
<td>n = 99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoropopliteal lesion present</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>26 (19%)</td>
<td>11 (11%)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>108 (81%)</td>
<td>88 (89%)</td>
<td>1.93 (0.90-4.11)</td>
<td>2.53 (1.05-6.11)</td>
</tr>
<tr>
<td>Type of lesion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>26 (19%)</td>
<td>11 (11%)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Stenosis</td>
<td>49 (37%)</td>
<td>34 (34%)</td>
<td>1.64 (0.72-3.76)</td>
<td>1.95 (0.75-5.10)</td>
</tr>
<tr>
<td>Occlusion</td>
<td>59 (44%)</td>
<td>54 (55%)</td>
<td>2.16 (0.98-4.79)</td>
<td>3.12 (1.22-7.97)</td>
</tr>
<tr>
<td>Length of occlusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10 cm</td>
<td>22 (37%)</td>
<td>16 (30%)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>37 (63%)</td>
<td>38 (70%)</td>
<td>1.41 (0.64-3.10)</td>
<td>1.41 (0.55-3.61)</td>
</tr>
</tbody>
</table>

95% CI, 95% Confidence interval; OR, odds ratio.

*Adjusted for age, smoking, presence of hypertension, hyperlipidemia, and diabetes.

Table IV. Characterization of arterial lesions below-the-knee

<table>
<thead>
<tr>
<th>Below-the-knee (BTK)</th>
<th>Men</th>
<th>Women</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 134</td>
<td>n = 99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tibial vessel patency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>46 (34%)</td>
<td>33 (33%)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>1 vessel</td>
<td>72 (54%)</td>
<td>51 (52%)</td>
<td>0.99 (0.56-1.75)</td>
<td>0.94 (0.48-1.82)</td>
</tr>
<tr>
<td>2 vessels</td>
<td>15 (11%)</td>
<td>14 (14%)</td>
<td>1.30 (0.55-3.06)</td>
<td>1.49 (0.55-4.06)</td>
</tr>
<tr>
<td>3 vessels</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>1.39 (0.08-33.1)</td>
<td>2.73 (0.09-83.0)</td>
</tr>
</tbody>
</table>

95% CI, 95% Confidence interval; OR, odds ratio.

*Adjusted for age, smoking, presence of hypertension, hyperlipidemia, and diabetes.

Table V. Characterization of arterial lesions according to anatomic level

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Men</th>
<th>Women</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 134</td>
<td>n = 99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilevel disease</td>
<td>25 (19%)</td>
<td>8 (8%)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Multilevel disease</td>
<td>109 (81%)</td>
<td>91 (92%)</td>
<td>2.61 (1.12-6.06)</td>
<td>3.81 (1.45-10.0)</td>
</tr>
<tr>
<td>Localization of lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iliac, femoropopliteal, and crural lesions</td>
<td>23 (17%)</td>
<td>13 (13%)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Iliac and crural lesions</td>
<td>2 (1%)</td>
<td>4 (4%)</td>
<td>3.54 (0.57-22.0)</td>
<td>3.43 (0.42-27.9)</td>
</tr>
<tr>
<td>Femoropopliteal and crural lesions</td>
<td>84 (63%)</td>
<td>74 (75%)</td>
<td>1.56 (0.74-3.29)</td>
<td>0.80 (0.32-1.96)</td>
</tr>
<tr>
<td>Femoropopliteal lesions only</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>1.77 (0.10-30.7)</td>
<td>1.81 (0.06-58.7)</td>
</tr>
<tr>
<td>Crural lesions only</td>
<td>24 (18%)</td>
<td>7 (7%)</td>
<td>0.52 (0.17-1.52)</td>
<td>0.19 (0.05-0.70)</td>
</tr>
</tbody>
</table>

95% CI, 95% Confidence interval; OR, odds ratio.

*Adjusted for age, smoking, presence of hypertension, hyperlipidemia, and diabetes.

bP value for interaction.
Although differences between men and women are now appreciated in cardiovascular research, gender differences in peripheral artery disease are still not completely understood. Surgical and endovascular revascularization trials have shown that women present with a higher complication rate and worse outcomes.\textsuperscript{4-7} Whether these worse outcomes in women are only due to disadvantageous preinterventional profile or whether gender-specific pathomorphologic determinants might play a role independently of cardiovascular risk factors is not clear.

Our study demonstrates that women present with a higher risk for lesions of the femoropopliteal segment, especially for more occlusions, when adjusted for risk factors. In patients with peripheral artery disease of all stages, gender-related effects on site selectivity of atherosclerotic lesions were shown in a cohort study of our group, including 1583 men and 1076 women.\textsuperscript{17} In line with our CLI data presented here, this study demonstrated that female gender is associated with pronounced femoropopliteal involvement, whereas men present with more BTK lesions.\textsuperscript{17} In accordance to our study, Hultgren and coworkers also have shown more BTK involvement in men compared with women with CLI, although no differentiation between single lesions and multilevel disease was performed.\textsuperscript{15} However, Hultgren et al considered only part of the atherosclerotic burden since only target lesions revascularized by surgical or endovascular means, independently of concomitant untreated lesions, were included in the analysis. Therefore, it is very likely that severe lesions, which were not feasible for revascularization, were not analyzed. Furthermore, we believe that the higher percentage of iliac lesions in women in that study might be due to the fact that more iliac revascularization procedures in women were performed to improve inflow. Importantly, no adjustment for cardiovascular risk factors was performed and no differentiation concerning severity of lesions as presented in our analysis were shown. Accordingly, the strength of the present study was that all lesions of the entire vascular tree were assessed prospectively from an unselected CLI population, and that adjustment for risk factors by multivariate analysis was performed. Importantly, the proportion of women in this study and the total proportion of lesion distribution of our patient cohort is similar to other CLI series.\textsuperscript{18,20}

Large epidemiologic and autopsy-based studies have shown that distribution, extent, and progression of atherosclerosis are influenced by cardiovascular risk factors.\textsuperscript{17,21,22} Therefore, associations between anatomic lesions and gender might be confounded by traditional cardiovascular risk factors. Indeed, in our series, adjustments for these potential confounders unravel the effect of gender on lesion morphology and distribution pattern in patients with CLI, which became significant for femoropopliteal lesions and specifically for occlusions. The higher mean age observed in women is well in accordance with previous studies,\textsuperscript{4,5,8,15,23} and might be due to a later onset of disease, possibly resulting from the protective effects of endogenous estrogens before menopause.\textsuperscript{11}

Moreover, women tend to present at later stages of disease due to misdiagnosis and ignoring of symptoms of both the patient and the physician. They are also more fearful and skeptical towards health care providers and are often caregivers for others, which altogether may also account for the higher mean age of women compared with men.\textsuperscript{24-28} The higher prevalence of hypertension and the lower rate of smokers among women with CLI was also previously reported.\textsuperscript{15} Since the cardiovascular risk burden plays a pivotal role for extent and progression of atherosclerotic lesions, adjustment for risk factors unmasks the role of gender in these patients with CLI.

Of note, our finding that women present more often with more severe and more multilevel disease than men might be explained by the more rapidly progressing and more diffuse atherosclerotic disease process observed in women after menopause, when the protective effects of estrogens are lost.\textsuperscript{10,29} Hypotheses explaining female gender as an independent risk factor for pathomorphologic determinants of atherosclerotic lesions in CLI include hemodynamic changes related to arterial morphology and cellular or biochemical variations in the arterial wall.\textsuperscript{30} Therefore, differences in vascular anatomy, including increased arterial stiffness and a smaller lumen diameter in women leading to regional disturbances of blood flow, might be contributory reasons for the gender differences in the pathomorphologic pattern demonstrated.\textsuperscript{9-11,29} Moreover, the special role of oxidative stress indicated by increased levels of biomarkers,\textsuperscript{31} and local changes in the arterial wall leading to endothelial and smooth muscle cell dysfunction shown in women might also play a role.\textsuperscript{11,32,33}

**Limitations.** The following limitations of our study have to be discussed. First, we have corrected the data for different cardiovascular risk factors known to influence outcome in vascular interventions. However, these factors represent only a small number of possible confounding factors. Accordingly, we cannot exclude residual confounding that might have biased our estimates in any direction. Second, we are aware that grouping the treated vessels into three categories might be an over-simplification, and we might have overlooked some details of interest. However, a more differentiated analysis of vascular territories most likely would not have changed the main findings of the present study. Further, possible hormone replacement therapy, which might have influenced lesion patterns, was not assessed, and all patients with a first time CLI diagnosis were enrolled irrespective of any past history of revascularization. Therefore, lesions considered in this study may represent recurrent, not de novo lesions. However, this does not affect the pathomorphologic features in men and women with CLI.

**CONCLUSIONS**

The finding that female gender may be an independent predictor for severe and diffuse atherosclerotic disease, particularly of the femoropopliteal axis, may be of
particular relevance for early detection and prevention of lesions and for choosing distinct treatment strategies in women compared to men with CLI. It is known that female patients with CLI exhibit an increased risk of limb loss, which can be reduced after successful revascularization. Since the aim of revascularization is to improve peripheral tissue perfusion, knowledge of extension and characteristics of vascular lesions is of major importance. Based on our data, it becomes evident that in women, endovascular specialists and vascular surgeons have to be aware that they will encounter more severe disease of femoropopliteal arteries and diffuse atherosclerotic lesions of the femorocrural axis. The common multilevel disease accompanied with more occlusions in women with CLI also means that, in case of endovascular treatment, different techniques and devices may be used during a revascularization procedure. Importantly, with a substantial aging population and increasing prevalence of CLI in women, the treatment of atherosclerosis in this patient group will remain an important challenge for vascular specialists in the future. Therefore, further studies are warranted, especially on confounding risk factors, which might be different in men and women and their possible association with lesion morphology in patients with critical limb ischemia.

AUTHOR CONTRIBUTIONS
Conception and design: JO, IB, ND, Analysis and interpretation: JO, TT, IB
Data collection: ND, JO
Writing the article: JO
Critical revision of the article: IB, TT, EN, ND
Final approval of the article: JO, EN, ND, TT, IB
Statistical analysis: EN, JO
Obtained funding: JO, TT
Overall responsibility: JO

REFERENCES


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