Gender variation in symptomatic peripheral arterial occlusive disease among type-2 diabetic patients

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Abstract

Purpose: Little is known about the existence of potential gender disparities in peripheral arterial occlusive disease. To our knowledge, this is the first study to analyze differences attributed to gender in type-2 diabetic patients with symptomatic peripheral arterial occlusive disease, with regard to clinical presentations, risk factors and anatomical distributions of atherosclerosis.

Patients and methods: This study was conducted at King Abdullah University Hospital, Jordan. Medical records of all diabetic (type-2) patients who presented with symptomatic peripheral arterial occlusive disease in the period from January 2012 and November 2017 were reviewed, data were collected retrospectively. In all, 364 patients (282 males and 82 females) were involved. Criteria for diagnosis include the following Ankle-Brachial Index $\leqslant 0.9$ and intermittent claudication or critical limb ischemia. Risk factors for atherosclerosis (age, smoking and hypertension) and computed tomography-angiogram findings were analyzed using Statistical Package for the Social Sciences. $p < 0.05$ was considered statistically significant.

Results: The mean age was higher in females than males (67.61 vs 62.61 years; $p = 0.001$). Females had greater prevalence of uncontrolled diabetes compared to males (HbA1c 9.07 in females vs 8.51 in males; $p = 0.03$). High density lipoprotein was higher in females than males (1.02 vs 0.935; $p = 0.009$). Females presented more with critical limb ischemia than intermittent claudication in comparison with males ($p = 0.017$). Involvement of superficial femoral artery, deep femoral artery and peroneal artery in hemodynamic relevant atherosclerotic lesion was significantly higher in females than males ($p < 0.05$). However, involvement of common iliac artery with hemodynamic relevant atherosclerotic lesion was significantly higher in males than females ($p = 0.003$).

Conclusions: Clinical presentation, risk factors and anatomical distributions of atherosclerosis among type-2 diabetic patients with symptomatic peripheral arterial occlusive disease are different between males and females. When compared to males, female patients presented more with critical limb ischemia than intermittent claudication. Females showed higher age at presentation, poor control of diabetes mellitus and higher level of high density lipoprotein. Involvement of superficial femoral artery, deep femoral artery and peroneal artery in hemodynamic relevant atherosclerotic lesion were significantly higher in females than males. In contrast, common iliac artery involvement with hemodynamic relevant atherosclerotic lesion was significantly higher in males than females.

Introduction

Peripheral arterial occlusive disease (PAOD) has become a global problem with significant impact on national health-care systems.[1] It affects over 202 million people worldwide.[2] It is the third most common cardiovascular cause of death, after coronary heart disease and stroke.[3] As a manifestation of atherosclerosis, PAOD is associated with lower extremity functional limitations, trophic complications, and a five- to sixfold increased risk of cardiovascular morbidity and death.[3,4]

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The traditional risk factors for development of PAD include diabetes mellitus, cigarette smoking, advanced age, dyslipidemia, and hypertension.[5] However, the sex difference in PAOD is not explained by these traditional cardiovascular risk factors.[6]

The population-based prevalence of PAOD in females has been incompletely evaluated.[7] Several community-based surveys reported higher rates of PAOD in females compared to males, even after adjusting for age.[4] On the contrary, not all studies have observed a greater prevalence of PAOD in females.[6] The traditional belief that the prevalence of PAOD is greater in males than in females does not take into account that females might have more asymptomatic disease.[8,9] Moreover, since females have a longer life expectancy than males, they are expected to be more disproportionately affected with PAOD in the future, as the population ages.[2] Yet, PAOD remains underdiagnosed in women, and women have been underrepresented in several PAOD revascularization trials.[5]

Diabetes mellitus is a potent risk factor for PAD and systemic atherosclerosis. About 20%–30% of PAD patients have diabetes.[10] The risk of developing PAD is proportional to the severity and duration of diabetes, it has been noted that it may increase the risk in women more than in men.[11]

Since little is known about the existence of potential gender disparities in PAOD and the majority of data on gender-based differences has been derived from coronary artery disease (CAD),[12] differences between females and males in the etiology and clinical presentation of PAOD have also been suggested.[3] Females with PAOD are more likely to be older at presentation compared to their male counterparts and present with critical limb ischemia (CLI).[5]

A tendency to a distal distribution of PAOD has also been well characterized for certain subgroups such as patients with diabetes.[13] Many clinical and epidemiologic studies also have suggested that different segments of the leg may be affected by different factors such as smoking and diabetes mellitus.[14] The major risk factors seem to vary by anatomic location. Patients with distal crural disease resulting from diabetes mellitus had a greater risk of CLI than patients with proximal segmental disease related to smoking or older age.[14] No studies to date have assessed the distribution of PAOD in relation to patient gender in a specific group such as diabetic type-2 patients.

PAOD continues to be understudied in females. Females are under-represented in contemporary PAOD studies, contributing to significant gaps in knowledge about PAOD risk factors in females.[4] Awareness of these differences and similarities could help in better understanding of the disease pathophysiology and planning of the management.[1] This study was conducted to compare aspects of gender-specific differences concerning clinical presentation, risk factors and anatomical distribution of atherosclerosis.

Material and methods

Between January 2012 and November 2017, data were retrospectively collected on diabetic patients (type 2), admitted to King Abdullah University Hospital (KAUH; for interventional or surgical managements) with symptomatic PAOD, using computerized hospital records. The inclusion criteria involved diabetes mellitus type 2 with symptomatic PAOD. Diagnosis of PAOD was established based on Ankle-Brachial Index (ABI) $\leqslant 0.9$ along with intermittent claudication (IC) or CLI (rest foot pain, ulcers or gangrene). Patients managed as outpatients were excluded from the study due to insufficient data.

Data on clinical, laboratory and imaging variables including sex, age, clinical presentation (IC vs CLI), unilateral or bilateral symptoms, smoking, hypertension, hyperlipidemia, hemoglobin A1c (HbA1c), C-reactive protein (CRP), mean platelet volume (MPV) and computed tomography angiography (CTA) (for anatomical distributions of atherosclerosis) were collected.

The protocol for CTA for all patients was using 130 cc contrast material with arterial phase after 20–25 s by Philips (2008)-64, 0.9 slices. Hemodynamic relevant atherosclerotic lesion (HRAL) was defined as any atherosclerotic lesion causing greater than 50% stenosis or occlusion of any arterial segment.[14]

Data were analyzed using univariate and multivariate analyses by SPSS (version 22.0 for windows). Unpaired non-parametric student t-test was used to compare between the means. $p < 0.05$ was considered statistically significant. Continuous variables were reported as mean $\pm$ SD in the tables.

Results

The mean values of continuous variables were shown in Table 1. A total of 364 patients were studied. There were 82 females (22.5%) and 282 males (77.5%). The mean age was higher in females than males (67.61 vs 62.61 years; p = 0.001). Levels of HbA1c were higher in females compared to males (HbA1c 9.07 in females vs 8.51 in males; p = 0.03). high-density lipoprotein (HDL) was higher in females than males (1.02 vs 0.935; p = 0.009). However, other variables (total cholesterol, triglyceride, low-density lipoprotein (LDL), CRP and MPV) demonstrated no gender-related differences ($p > 0.05$).

In all, 63 female patients (76.8 %) presented with CLI compared to 19 patients (23.2%) who presented with IC. In contrast, 107 male patients (37.9%) presented with IC compared to 175 patients (62.1%) who presented with CLI (p=0.017). Other variables (unilateral or bilateral symptoms, hypertension, smoking, and previous cardiac disease) had shown no statistically significant gender differences ($p > 0.05$). See Table 2.

Involvement of superficial femoral artery (SFA), deep femoral artery (DFA) and peroneal artery (PA) in HRAL

were significantly higher in females than males (p < 0.05). However, the common iliac artery (CIA) involvement with HRAL was significantly higher in males than females (p = 0.003). Other arterial segments did not demonstrate statistically significant gender-related differences (p > 0.05). See Table 3.

Discussion

In the present study, differences and similarities between females and males were found in diabetic patients who were diagnosed with symptomatic PAOD. PAOD is a common manifestation of atherosclerosis and is said traditionally to be significantly more prevalent in males than females.[13] However, recent studies demonstrated a similar prevalence of PAOD between male and females.[15] In this study population, a total of 364 patients were analyzed. The

Table 1. Mean values of continuous variables.

Mean value of continuous risk variable (SD)	Gender		p-value
	Male	female	
Mean age (SD)	62.61 (10.54)	67.61 (10.62)	0.000*
HbA1c (SD)	8.51 (2.06)	9.07 (2.03)	0.03*
Total cholesterol (SD)	4.66 (1.13)	4.72 (1.15)	0.674
Triglyceride (SD)	2.35 (1.49)	2.25 (1.03)	0.592
LDL (SD)	3.01 (0.87)	3.06 (1.04)	0.713
HDL (SD)	0.935 (0.24)	1.02 (0.31)	0.009*
CRP (SD)	60.40 (60.39)	63.47 (41.39)	0.666
MPV (SD)	9.70 (1.22)	9.82 (1.12)	0.418

HbA1c: hemoglobin A1c; CRP: C-reactive protein; MPV: mean platelet volume; SD: standard deviation; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

prevalence was greater in males than in females (77.47% vs 22.52%).

Females were approximately 5 years older than males (67.61 vs 62.61 years), and they showed a higher rate of CLI when compared with males (76.8% vs 62.1%). This was consistent with previous studies which demonstrated that more females presented with CLI compared with males.[13] Others have postulated that females present with a more advanced state of PAOD and are older at the time of diagnosis.[5] Both males and females showed predominantly unilateral compared to bilateral symptoms (p = 0.187).

Risk factors for PAOD are the same in females and males.[15] However, the risk of death from cardiovascular disease (CVD) in females is lower than males.[1] This study showed that the traditional cardiovascular risk factors (hypertension, smoking and hyperlipidemia) were equal in males and females in diabetic patients with symptomatic PAOD despite age differences. However, HDL level did differ by gender which was greater in females. Diabetes, a risk factor with a high impact on atherosclerosis in females, increases the risk of CVD three to seven times among females and two to four times among males.[16] As long as all our patients in this study were diabetics, we found that females had greater prevalence of uncontrolled diabetes compared to males (HbA1c 67.61 in females vs 62.61 in males; p = 0.03).

CRP is an acute-phase protein that is elevated in individuals with PAOD, and higher CRP levels are associated with both risk and progression of PAOD. In addition, several population studies have demonstrated higher CRP levels in females compared to males. It is not known whether gender differences in CRP levels explain observed differences in the prevalence of PAOD in females compared to males.[2] In contrast to the previous studies, CRP mean values in this study were not elevated in females in comparison to males.

Table 2. Categorical risk factors in relation to gender.

Categorical CV risk variable	Gender		Total N	p-value	OR (95% CI)
	Male, n	Female, n			
Age ≤ 60 years	145	26	171	0.002	2.28 (1.36–3.84)
Age > 60 years	137	56	193		
HbA1c ≤ 7.5%	116	21	137	0.014	2.03 (1.17–3.52)
HbA1c < 7.5%	166	61	227		
Intermittent claudication	107	19	126	0.017	2.03 (1.15–3.57)
critical ischemia	175	63	238		
Unilateral symptoms	228	72	300	0.187	0.57 (0.28–1.21)
bilateral symptoms	54	10	64		
Arterial hypertension: no	110	31	141	0.898	1.05 (0.63–1.75)
arterial hypertension: yes	172	51	223		
Cardiac disease: no	172	55	227	0.365	0.77 (0.46–1.3)
yes	110	27	137		
Smoking: no	109	28	137	0.518	1.22 (0.73–2.04)
yes	173	54	227		

CV: cardiovascular; HbA1c: hemoglobin A1c.

Table 3. Arterial and segmental HRAL in relation to gender.

Segmental and arterial HRAL	Gender		Total N	p-value	OR (95% CI)
	Male N	Female N			
Aorto-iliac HRAL: no	170	57	227	0.154	0.67 (0.4–1.13)
yes	112	25	137		
Femoro-popliteal HRLA: no	115	26	141	0.157	1.48 (0.88–2.5)
yes	167	56	223		
Crural HRAL: no	122	33	155	0.704	1.13 (0.69–1.87)
yes	160	49	209		
Aortic HRAL: no	245	69	314	0.585	1.25 (0.63–2.48)
yes	37	13	50		
Common IA HRAL: no	208	73	281	0.003	0.35 (0.17–0.73)
yes	74	9	83		
External IA HRAL: No	234	67	301	0.868	1.09 (0.58–2.07)
Yes	48	15	63		
Common FA HRAL: No	254	72	326	0.542	1.26 (0.59–2.72)
Yes	28	10	38		
Superficial FA HRAL: No	163	36	199	0.032	1.75 (1.07–2.87)
Yes	119	46	165		
Deep F.A HRAL: No	267	70	337	0.008	3.05 (1.37–6.81)
Yes	15	12	27		
Popliteal A HRAL: No	211	57	268	0.393	1.30 (0.76–2.24)
Yes	71	25	96		
Anterior TA HRAL: No	156	47	203	0.801	0.92 (0.56–1.52)
Yes	126	35	161		
Posterior TA HRAL: No	168	39	207	0.058	1.63 (0.99–2.66)
Yes	114	43	157		
Peroneal A HRAL: no	204	49	253	0.04	1.76 (1.06–2.94)
yes	78	33	111		

HRAL: hemodynamic relevant arterial lesion; IA: internal iliac; FA: femoral artery; TA: tibial artery; A: artery; N: number.

Impairment of immune response in diabetic patient may be suggested as a possible explanation.

Previously published studies are conflicting regarding the anatomical distributions of atherosclerosis among males and females. Some studies displayed a significantly 2.5-times higher risk for female patients with CLI to present a lesion in the femoro-popliteal region.[1] Another study demonstrated that PAOD in males was more common at all anatomical locations than in females.[13] Our data demonstrated relevant differences in the anatomic distribution of atherosclerosis. Involvement of SFA, DFA and PA in HRAL were significantly higher in females than males ($p < 0.05$). However, the CIA involvement with HRAL was significantly higher in male than female ($p = 0.003$). This could explain why females more commonly presented with CLI as more distal disease distributions usually associated with CLI rather than IC. On the other hand, other arterial segments did not demonstrate statistically significant gender-related differences ($p > 0.05$).

There are several limitations to this study. First, it was a retrospective study. Second, it is a single center study which did not represent all Jordanian patients. Third, the vast majority of diabetic patients with symptomatic PAOD with mild and moderate IC were not included in the study because they were managed as outpatient and they were not investigated by CTA as there were no indications for interventions or surgeries. Finally, the disproportion of men and women numbers in this study with unequally distributed risk factors among them may impact the final results.

To our knowledge, this is the first study to assess the contribution of gender-related differences in diabetic patients presented with symptomatic PAOD. Further studies are needed to investigate the importance of gender-related differences that can explore the clinical significance between males and females regarding PAOD.

Conclusion

Clinical presentation, risk factors and anatomical distributions of atherosclerosis among type-2 diabetic patients with symptomatic PAOD are different between males and females. When compared to males, female patients presented more with CLI than IC. Females showed higher age at presentation, uncontrolled diabetes mellitus and higher level of HDL. Involvement of SFA, DFA and PA in HRAL were significantly higher in females than males. In contrast, CIA

involvement with HRAL was significantly higher in males than females.

Author contributions

Nawaf J Shatnawi: meets conditions 1, 2, 3, and 4. Nabil A Al-Zoubi: meets conditions 1, 2, 3, and 4.

Declaration of conflicting interests

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Ethical approval

Ethics approval to conduct this study was obtained by IRB at KAUH 2018/111

Informed consent

Written informed consent from all subjects or their legally authorized representatives was waived by the Institutional Review Board/Ethics Committee as it was a retrospective study from a computerized data.

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