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Review article

Peripheral arterial disease in the Middle East: Underestimated predictor of worse outcome

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ABSTRACT

Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis and is associated with significant morbidity and mortality. The prevalence of PAD in the developed world is approximately 12% among adult population, which is age-dependent and with men being affected slightly more than women. Despite the strikingly high prevalence of PAD, the disease is underdiagnosed. Surprisingly, more than 70% of primary health care providers in the US were unaware of the presence of PAD in their patients. The clinical presentation of PAD may vary from asymptomatic to intermittent claudication, atypical leg pain, rest pain, ischemic ulcers, or gangrene. Claudication is the typical symptomatic expression of PAD. However, the disease may remains asymptomatic in up to 50% of all PAD patients. PAD has also been reported as a marker of poor outcome among patients with coronary artery disease. Despite the fact that the prevalence of atherosclerotic disease is increasing in the Middle East with increasing cardiovascular risk factors (tobacco use, diabetes mellitus and the metabolic syndrome), data regarding PAD incidence in the Middle East are scarce.

Keywords: Peripheral arterial disease, Middle East

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THE ANCIENT HISTORY OF ATHEROSCLEROSIS IN THE MIDDLE EAST

Atherosclerosis was first identified in ancient Egyptians.[1–3] In 1911, Sir Ruffer identified histologic evidence of atherosclerosis in the aorta and its large arteries on autopsies from 3,000-year-old Egyptian mummies.[2] Recently, Allam et al.[3] examined 52 ancient Egyptian mummies to identify cardiovascular structures and arterial calcifications. Forty-four of the 52 mummies had identifiable cardiovascular structures, and 20 of these had either definite atherosclerosis (defined as calcification within the wall of an identifiable artery) or probable atherosclerosis (defined as calcifications along the expected course of an artery). Calcifications were found in the aorta as well as in the coronary, carotid, iliac, femoral, and peripheral leg arteries. Definite coronary atherosclerosis was present in 2 mummies, including a princess who lived between 1550 and 1580 BCE. These findings represent the earliest documentation of coronary atherosclerosis in human beings.

PERIPHERAL ARTERIAL DISEASE (PAD)

PAD is a manifestation of systemic atherosclerosis; therefore, it shares its natural course of insidious and gradual progression.[4] PAD is an indicator of widespread atherosclerosis in other vascular territories, such as the cerebral and coronary circulations. There is also considerable overlap between PAD, cerebrovascular disease (CVD) and coronary artery disease (CAD), with the presence of PAD being associated with increased risk of CVD and CAD and their consequences.[5] Ethnicity has been shown to be an independent predictor of adverse cardiovascular outcomes in patients with atherothrombotic disease, including cardiovascular and all-cause mortality.[6] Ethnicity- related variations in the treatment of atherothrombotic disease have been reported even after adjustment for risk factor, variability in access to care, adherence to medical therapies, and other socioeconomic factors.[6] Prior epidemiologic reports have shown that blacks are disproportionately affected by PAD, with a two to three-fold increased risk compared to whites. On the other hand, Asians have similar to slightly lower PAD rates than whites. Though, major studies investigating associations between ethnicity and PAD have been confined to comparisons between blacks and whites.[6] Criqui et al.[7] considered black ethnicity a consistent and independent risk factor for PAD which is similar to other established risk factors. The predominance of PAD in certain ethnic groups could not be explained by the high incidence of diabetes mellitus (DM), hypertension, or increased susceptibility to other CVD risk factors. Therefore extensive studies are needed to investigate whether newer atherogenic, inflammatory, and prothrombotic markers, are associated with increased PAD incidence in a particular ethnic group.

PREVALENCE OF PAD

PAD has a variable yet relatively high prevalence in the western world.[8–11] Patients with PAD are at increased risk of coronary, carotid and cerebrovascular atherosclerosis disease and all-cause mortality.[12–15] These predictors are independent of the traditional risk factors of PAD.[15–17] PAD is not a static disease and its progression from intermittent claudication to rest pain or gangrene can occur.[14–17] The prevalence of PAD in the general population depends on the definition used and is substantially underestimated, if one considers only individuals who exhibit typical symptoms of claudication. Table 1 shows the clinical staging of PAD.[18] It is possible that the functional impairment in patients with PAD may keep them from ambulating to the point of having angina to the extent that those patients may present with much more advanced coronary atherosclerosis.[10] This risk increases with the severity of PAD.[14,15] Several studies have shown worse prognosis in both selected and unselected western population admitted with acute cardiovascular events or followed up in outpatient settings such as Global

Table 1. Clinical staging of PAD according to Fontaine and Rutherford classification.

	Fontaine classification	Rutherford classification		
Stage	Clinical finding	Grade	Category	Clinical finding
I	No symptom	0	0	No symptom
II	Intermittent claudication	I	1	Mild claudication
			2	Moderate claudication
			3	Severe claudication
III	Rest pain	II	4	Rest pain
IV	Ulcer or gangrene	III	5	Minor tissue loss
			6	Major tissue loss

Atherothrombosis Assessment study (AGATHA).[8,10,12,19–24] Data specifically addressing this important issue in the Middle East is lacking which needs urgent inception of a registry database. Moreover, the prevalence and the impact of PAD in patients from the Middle-Eastern countries were limited by small sample size, and retrospective nature of the studies including our earlier reports.[25–28] Table 2 shows review of population based studies investigating PAD in different ethnic groups including the Middle East.[29–41] The low incidence of PAD in our region is underestimating the true figures, which may be due the fact that our PAD patients were diagnosed at their presentation with acute coronary syndrome. Table 3 & 4 demonstrate risk factors associated with PAD in different studies.[7,39,42–63]

Table 2. Examples of population based studies investigating PAD in different ethnic groups.

Study	Country	Population	Age	PAD prevalence (%)
Fowkes et al.[29]	UK	1592	55–74	18.3
Meijer et al.[30]	Netherlands	6450	>55	19.1
Fabsitz et al.[31]	US	4549	45–74	5.3
Premalatha et al.[32]	South India	631	>20	3.2
Diehm et al.[33]	Germany	6821	≥65	18
He et al.[34]	China	2334	≥60	19.8
Al-Sheikh et al.[35]	Saudi Arabia	471	≥45	11.7
Garofolo et al.[36]	Brazil	1008	≥30	20.4
Sritara et al.[37]	Thailand	2305	52–73	5.2
Carbayo et al.[38]	Spain	784	≥40	10.5
Sigvant et al.[39]	Sweden	5080	60–90	18
Kumar et al.[40]	South Africa	542	>50	29.3
Tekin et al.[41]	Turkey	507	77	6
Gulf RACE[26]	Qatar, Bahrain, UAE, Oman, Yemen, and Kuwait	6705	65	3
Gulf-RACE-2[27]	Qatar, Bahrain, UAE, Oman, Yemen, and Saudi Arabia	7689	63	2

PAD defined as ABPI < 0.9. All studies include males and females. Gulf RACE = Gulf Registry of Acute Coronary Events

Table 3. Risk factors associated with peripheral arterial disease.

Reference	Risk factor	Association with PAD
Heliovaara et al.[42]	Smoking	As a sequale of atherosclerosis, smoking can result in a 7-fold increase in PAD
Premalatha et al.[43]		Smokers had 2.7 times higher risk for PAD
Newman et al.[44] Lucher et al.[45]	Diabetes mellitus	DM is associated with 2-4 fold increased risk of developing CAD and PAD
Creager et al.[46]		5-10% of PAD pts have type 1 and 90–95% have type 2 DM
Bennett et al.[5]		In DM, the risk of PAD increased by age, DM duration, DM control and neuropathy
Murabito et al.[47]		20% of symptomatic PAD pts had DM
Hirsch et al.[48]		Prevalence of PAD in DM is 20% in > 40 yrs old and 29% in people aged > 50 yrs.
Premalatha et al.[43]	Dyslipidemia	Limited data is available. Hypercholestrolimia and LDL-C are associated with development of PAD (OR 1.4 and 1.5 respectively)
Makin et al.[49]	Hypertension	PAD and hypertension are associated with 35–55% of patients with PAD having hypertension
Palumbo et al.[50]		The prevalence of PAD in DM increases with the presence of hypertension. If hypertension is controlled, the progression of PAD can be slowed
Liew et al.[51]	Chronic kidney disease (CKD)	CKD and PAD had higher mortality than patients with either CKD or PAD
Tzoulaki et al.[52]	Inflammation	IL-6, CRP and fibrinogen are associated with PAD, its progression and severity
Danesh et al.[53] Vene et al.[54]	Fibrinogen	Fibrinogen has been associated with PAD development and severity and in patients with intermittent claudication, fibrinogen has been shown to be an independent predictor of death
Tzoulaki et al.[52] Vainas et al.[55] Brevetti et al.[56]	CRP	CRP is be inversely associated with ABPI, endothelial dysfunction and PAD severity
Cheng et al.[57] Tseng et al.[58]	Lipoprotein (a) (Lp(a))	Lp(a) correlates with ABPI and severer forms of PAD. It increases steadily from absence of PAD to mild and severe PAD.

Table 4. PAD defined by ABI < 0.9 and traditional cardiovascular risk factors in multivariate analysis.

	Population	Age	Smoking (OR)	DM(OR)	HTN (OR)	Adjusted for
Meijer et al.[59]	6450	>55	2.64	1.9	1.32	Age, sex, alcohol, WBCs and homocysteine
Murabito et al.[60]	3313	≥40	2.0	NS	2.2	Age, fibrinogen, CAD
Cui et al.[61]	726	60–79	3.8	1.0	2.7	Age, alcohol, stroke, and CHD
Selvin et al.[62]	2174	>40	4.2	2.1	1.8	Age, sex, ethnicity, CVD history and GFR
Criqui et al.[7]	2343	29–91	1.63	6.9	1.9	Age, sex, ethnicity, education, lipid and antihypertensives and CVD
Allison et al.[63]	6653	45–84	3.4	2.1	1.63	Age, ethnicity, and education
Carbayo et al.[38]	784	>40	1.5	1.8	1.95	Age, CVD, and fibrenogen
Al Thani et al.[26]*	6705	65 ± 12	0.83	1.06	0.96	Age, sex, CAD, DM, hypertension, smoking, and renal failure

* = Renal failure and MI were independent predictors (OR 2.5 and 4.4 respectively)

ANKLE-BRACHIAL INDEX & PAD

Non-invasive screening tool is essential for diagnosing PAD as atherothrombosis is mostly asymptomatic, and often, the first sign of the disease involves a major life-threatening vascular event.[25,64] The ankle-brachial index (ABI) is a simple and useful assessment tool for measuring clinical bedside atherosclerotic burden and risk of future cardiovascular disease events.[16] In general, ABI test has a sensitivity above 90% and a specificity of 95% for the diagnosis of PAD (0.00-0.40: Severe PAD sufficient to cause resting pain or gangrene, 0.41-0.90: PAD sufficient to cause claudication, 0.91-1.30: normal vessels, and >1.30: non-compressible (severely calcified) vessel. However, depending on the symptoms, further tests may be performed such as computed tomography, catheter angiography, magnetic resonance imaging, or duplex ultrasound imaging.[65–66]

Nevertheless, the cut-offs for defining ABI risk differ from one study to another and remain controversial. The sensitivity and specificity associated with an ABI threshold of ≤0.90 ranged from a sensitivity of 79% to 95% and specificity of 96% to 100% compared with angiography.[67] McKenna et al.[68] found ABI as an independent predictor of mortality with a 5-year mortality of 50% and 30% in patients with an ABI of 0.40 and 0.70, respectively. Sikkink et al. also showed a 5-year mortality of 37% in patients with an ABI < 0.50, 29% for patients with an ABI between 0.50 and 0.69, and 9% for patients with an ABI between 0.70 and 0.89.[69] In another study, ABI < 0.90 had an all cause mortality of 1.69 and cardiovascular mortality of 2.52, while patients with an ABI of ≥1.40 had a all-cause mortality of 1.77 and cardiovascular mortality of 2.09.[70] Hence, similar association has been observed between high ABI and mortality versus low ABI and mortality.

Inaccurate ABI measurements may result from calcified or incompressible vessels (false high readings) and the presence of a subclavian-artery stenosis.[68] Some studies have reported ABI of 1.3 as an indicative of medial arterial calcinosis and noncompressible arteries.[44,71] Mild claudication or obstruction occurs with an ABI < 0.9–0.75. Moderate to severe claudication occurs with an ABI < 0.75–0.4. ABI value of < 0.50 was found to be correlated with the progression to critical leg ischemia during the follow-up of 6.5 years].[72] Arterial calcification (medial calcinosis) can make the ankle arteries incompressible resulted in artificially high values of the ABI, which is commonly seen in diabetic patients.[73] ABI value of 1.4 may be a good compromise.[74–75] Compared with normal legs, legs with low-normal (0.91 to 0.99) and high-normal (≥1.40) ABIs had increased rate of pain, suggesting borderline disease and vascular stiffness.[75] In more than 80% of cases with an ABI >1.40, concomitant occlusive disease could be identified using other diagnostic modalities.[76] This could explain the similar rates of intermittent claudication and association with subclinical disease in other vascular beds found in this ABI range, compared to an ABI <0.90.[74–75] With increasing prevalence of DM, metabolic syndrome and renal failure in the Middle East, particularly in the Gulf region there is a need to revise the ABI cutoff value for better management of the disease.[77–80]

PERIPHERAL ARTERIAL DISEASE IN THE MIDDLE EAST

Peripheral arterial disease among chronic stable diseases

Data on the prevalence and outcome of Middle-Eastern patients with PAD are limited. A cross-sectional hospital-based study (402 patients) from Saudi Arabia reported high prevalence of PAD (ABI < 0.9) in elderly high-risk patients with DM (61.4%), chronic renal failure (13.4%) or ischemic heart disease (21.4%) when compared to controls (4.1%).[81] Another cross-sectional study evaluated 1477 diabetic patients from Bahrain found foot ulcer in 5.9%, and PAD in 11.8% cases.[82] Between 2004 and 2005, we conducted a multicenter study (AGATHA-ME) in 5 neighboring countries (United Arab Emirates, Kuwait, Qatar, Bahrain, and Oman).[25] These countries are characterized by small populations and similar ethnic distribution. The study included 1341 patients who were recruited from the tertiary care settings and were divided into 2 groups; patients with or without atherosclerotic disease. Group with atherosclerotic disease included patients with history of prior vascular disease or with current symptoms: (*a*) prior cerebrovascular disease (CVD), that is, ischemic stroke, transient ischemic attack, or carotid angioplasty or endarterectomy; (*b*) prior coronary artery disease (CAD), i.e. unstable angina, MI, or coronary angioplasty or bypass graft; (*c*) PAD, that is, intermittent claudication, vascular lab diagnosis, or lower-limb arterial revascularization; (*d*) current cardiovascular symptoms, that is, angina pectoris or intermittent claudication. The second group constituted patients at risk of vascular disease (at-risk group) without history of prior disease or current symptoms, with age more than 55 years and with 2 or more of the following risk factors (RFs): DM; dyslipidemia; hypertension, obesity; or smoking history, (current or former smoker). The AGATHA-ME study confirms that atherothrombosis disease often occurs at more than one site and that ABI is related to the RF profile and to the site and extent of atherothrombosis. The studied populations have a higher prevalence of the traditional RFs in a unique fashion.[77] Also, we found that gender and DM are associated with the worst outcome.

Peripheral arterial disease among hemodialysis (HD) patients

Prevalence of PAD defined by ABI < 0.90 in patients with end-stage renal disease is extremely high, estimated at 38% in a single-center study, to which should be added 14% of cases with incompressible ankle arteries.[83] Prevalence of PAD is high among HD patients in our population. Between 2007 and 2010 we analysed the presence of PAD among hemodialysis patients in a prospective study of 3 years follow-up.[28] Among 252 consecutive HD patients, PAD was diagnosed in 97(38.5%) patients. Three-year all-cause mortality was higher in PAD group [unadjusted and adjusted hazard ratios (HR) were 3.6 (95% CI 2.11-6.01) and 2.92 (95% CI 1.55-5.51), respectively]. Other predictors for mortality were age (HR 1.06; 95% CI1.04-1.10), number of vascular access (HR 2.3; 95% CI 1.04-5.01), and prior CAD (HR 1.8; 95% CI 1.05-3.49). Diabetic retinopathy was also found to be an independent predictor of PAD. Further, PAD and number of vascular access procedures were independently associated with long-term mortality. Hence, early detection of PAD is of utmost value in HD patients. Recently, we have also completed a 5-year follow-up of 252 HD patients. The observed 5-year mortality rate reached 72% in PAD vs 36% in no-PAD (unpublished data) in comparison to 40% vs 14% in the first 3-year follow-up. Table 5 shows different studies evaluating PAD in HD patients.[84–88]

Peripheral arterial disease among acute coronary syndrome

In 2007, we studied PAD in acute coronary events,[26] involving 6705 consecutive ACS patients collected from a 6-month prospective, multicenter study of the Gulf Registry of Acute Coronary Events (Gulf RACE) from 6 adjacent Middle Eastern Gulf countries(Bahrain, Kuwait, Qatar, Oman, United Arab Emirates and Yemen). Patients were recruited from 64 hospitals with the diagnosis of ACS including unstable angina (UA) and non-ST- and ST-elevation myocardial infarction (NSTEMI and STEMI). Out of the 6705 ACS patients, PAD was found in 177 (2.6%) patients. Our data were collected from an observational study, which is one of the limitations. Moreover, inconsistent cut-off points for ABI would potentially miss patients with milder PAD leading to potential outcome bias in different studies. The results of this study showed that patients with PAD and ACS are in high-risk group that require more attention for evaluation of risk factors and early detection. Certain traditional risk factors were also independently associated with PAD which necessitates aggressive preventive measures. PAD in patients with STEMI is an independent predictor for in-hospital death. Detection of PAD in ACS patients might be useful simple bedside tool for early risk-stratification. Table 6 shows risk factors and outcomes of PAD in patients presented with acute coronary syndrome in different studies in comparison to our previous

Table 5. Studies evaluate peripheral arterial disease in hemodialysis patients (adapted from [28]).

Country	Rajagopalan et al.[84] USA	Ono et al.[85] Japan	Chen et al.[86] Taiwan	Ogata et al.[87] Japan	Adragao et al.[88] Portugal	Al Thani study[28] Qatar
HD pts number	29,873	1010	225	315	219	252
Design	Retrospective, multinational	Prospective	Prospective	Cross-sectional cohort	Prospective	prospective
Age (mean)	66	65	67	61	69	57
Men (%)	58	63.5	43.5	67.3	60	50
DM	38%	34%	41%	31%	20%	57%
PAD %	25.3	16.5	15.5	23.8	41	38.5
% of PAD in diabetics	59%	62%	69%	59.5%	22%	71%
Follow-up (mean, months)	18	22.3	42	–	28.9	36
Diagnosis of PAD	History & clinically	ABI	ABI	ABI and BA pulse wave velocity	ABI and vascular calcification	ABI and clinical
PAD and All-cause mortality	HR (1.36, $P < 0.001$)	Adjusted HR (4.04, $P < 0.001$)	N/A	N/A	Adjusted HR (3.9, $P < 0.001$)	Adjusted HR (2.9, $P = 0.001$)

HD = hemodialysis, PAD = peripheral arterial disease, HR = hazard ratio, ABI = ankle-brachial index, BA = brachial-ankle, N/A = not available, DM = diabetes mellitus

Table 6. Risk factors and outcomes of peripheral arterial disease in patients presenting with acute coronary syndrome in different studies (adapted from [26]).

	SPRINT[8] 1994			GRACE[22] 2007			PAMISCA[23] 2008			MASCARA[19] 2009			Gulf RACE[26] 2009		
Patients n.	4258			32,735			1410			6745			6705		
PAD Prevalence	6.3%			7.6%			39.8%			8.8%			2.4%		
	PAD	No PAD	P value	PAD	No PAD	P value	PAD	No PAD	P value	PAD	No PAD	P value	PAD	No PAD	P value
Age (years)	66 ± 10	62 ± 11	0.01	71	64	0.001	69 ± 11.3	64 ± 11	0.001	70 ± 10	67 ± 10	0.001	65 ± 11	56 ± 12	0.001
Diabetes mellitus	25	20	0.01	38	22	0.001	41.5	30.6	0.001	49.4	28.1	0.001	70	40	0.001
Hypertension	47	39	0.01	72	58	0.001	84.1	76.1	0.001	71.9	58.3	0.001			
Dyslipidemia	–	–	–	58	46	0.001	85.7	83	NS	57	46.4	0.001	66	31	0.001
Smoking	35	36	NS	69	59	0.001	29.9	31.6	NS	21.6	28.3	0.001	32	38	0.001
Hospital outcome															
Death	24	13	0.001	7.2	4.5	0.001	2	0.2	0.001	9.1	4.8	0.001	8	4	0.002
CHF	23	19	NS	–	–	–	15.9	8.4	0.001	–	–	–	31	16	0.001
Re-ischemia	–	–	–	7.7	8.3	NS	13.7	7.8	0.001	–	–	–	14	10	0.03

SPRINT = Secondary Prevention Study Reinfaction Israeli Nifedipine Trial, GRACE = Global Registry of Acute Coronary Events, PAMISCA = Prevalencia de Afectacio'n de Miembros Inferiores en el paciente con Si'ndrome Coronario Agudo, MASCARA = Manejo del Sindrome Coronario Agudo. Registro Actualizado, Gulf RACE = Gulf Register of Acute Coronary Events, CHF = congestive heart failure.

findings in the Gulf region (8,19,22,23). The analysis showed PAD patients from the Arab Gulf region were relatively younger with higher prevalence of diabetes mellitus.

Polyvascular disease

Polyvascular disease (PolyVD) is defined as presence of more than one affected vascular bed i.e., any combination of the following: coronary artery disease (CAD), peripheral arterial disease (PAD) and cerebrovascular disease (CVD).[10,12,19,21,22] Interestingly, we published the first study from the Middle East addressing the incidence and impact of PolyVD in ACS patients.[27] This study included 428 patients of PolyVD comprised of ACS plus PAD (110 patients), ACS plus CVD (284 patients) and ACS plus PAD and CVD (34 patients). The limitation of this retrospective analysis is the diagnosis of PAD based on the clinical history and not on a standard measurement of ankle-brachial index (ABI) or angiography. This limitation could be explained in part by facts that clinical variables used were insensitive to identify PAD, as approximately half of subjects with ABI $<$ 0.90 were asymptomatic. Moreover, only few cases had classic intermittent claudication in the symptomatic group. The presence of PolyVD is underdiagnosed in our daily practice which may underestimate its true prevalence and impact on the outcome. Although PolyVD patients represent a high-risk population in the setting of ACS, they received less aggressive therapy. Apart from major bleedings, PolyVD is an independent predictor for adverse hospital outcomes and short and long-term mortality. Great efforts should be directed to primary and secondary prevention. In ACS patients, assessment of the other affected vascular bed will add important step in risk stratification and management. We also observed that PolyVD is an independent predictor for the risk of strokes. Table 7 shows risk factors and in-hospital mortality in patients with versus without ÿ PolyVD presented with ACS in different clinical studies in comparison to our findings.[10,19,22] Though the prevalence of PolyVD was lower in our region, the mortality rate was higher in comparison to other western studies. Moreover, the mortality in patients who had PAD and ACS was higher in the Gulf region in comparison to other regions.

GENDER AND PERIPHERAL ARTERIAL SYNDROME

Gender differences for the incidence and prevalence of PAD are inconsistent compared to other cardiovascular diseases.[89] Prior reports showed that 12% of men and women in the community and 16% to 19% of the elderly population were affected with PAD.[89–91] Intermittent claudication is the most common presenting symptom of PAD; however, it alone is an insufficient diagnostic indicator for PAD in women.[92] Moreover, women with PAD were found to be more functionally impaired than men and had lower rates of revascularization of the lower extremity.[93–94] Also, women who do undergo revascularization procedures had more adverse outcomes than men.[95] However, PAD related mortality rates were comparable among both genders.[96]

Data based on American and European populations have consistently demonstrated a sharp increase in PAD prevalence with age and higher rates in men than in women.[7] Although women are less likely to be diagnosed on the basis of symptoms, they do have clinically significant PAD when tested.[97–99] Since, symptomatic PAD predominates in men, many reports of surgical therapy do not analyze gender-specific outcomes. Reasons that may in part explain late diagnosis of PAD include economic considerations; women might focus more on seeking medical care for their families than for themselves, and are more likely to ignore mild-to-moderate symptoms.[89,99]

Figure 1 – 3 shows the prevalence of PAD in women and men in different epidemiological studies.[38,44,59,100–105] In contrast to western literature, our previous studies showed that women had higher prevalence of PAD in comparison to men.[26,28]

Figure 4 shows the presence of PAD among hemodialysis patients stratified by gender and age in Qatar. Prevalence of PAD patient undergoing HD was higher in women aged between 41 and 50, otherwise it predominates in men.

Table 8 shows Men and Women in AGATHA-ME study in the Gulf region (GCC). It showed that women had the worse presentation and morbidity in comparison to men.[25]

OUTCOME IN PATIENTS WITH PAD

The main cause of death in PAD patients is related to the coronary and/or cerebrovacular events, rather than complications related to PAD itself, as PAD is mostly a powerful indicator of progressive, systemic atherosclerotic disease. In a meta-analysis including nine studies, the likelihood of a low ABI

Table 7. Risk factors and in-hospital mortality in patients with versus without polyvascular disease presenting with acute coronary syndrome in different clinical studies (adapted from [27]).

	GRACE(n = 32,735)				MASCARA(n = 6745)				GULFRACE-2(n = 7689)				ALLIANCE(n = 8904)			
		PolyVD (15.6%)				PolyVD (16.6%)				PolyVD (5.6%)				PolyVD (13%)		
	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
Patients %	84	7	6	2	83	9	6	2	94	1	4	0.6	87	8	4	1
Age (mean yrs)	64	71	73	73	67	70	73	72	56	63	65	66	65	72		
Smoking	59	69	53	68	36/28*	61/22*	44/16*	60/21*	54	54	39	62	59	63		
Diabetes mellitus	22	38	34	42	28	49	43	52	38	77	61	82	19	34		
Hypertension	58	72	78	82	58	72	76	69	45	72	79	82	48	66		
Dyslipidemia	46	58	52	65	46	57	50	53	36	55	53	67	43	47		
Renal failure	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3	20	10	30	3	12		
Mortality	4.5	7.2	8.9	9.2	4.8	9.1	9.2	16	4	12	7	15	5.7	9.8	14	13

A = acute coronary syndrome (ACS) alone, B = ACS plus peripheral arterial disease (PAD), C = ACS plus cerebrovascular disease (CVD), D = ACS plus PAD plus CVD, PolyVD = polyvascular disease, all categorical variables represents in percentage(%), DM = diabetes mellitus, N/A = data not available, * = prior/current smoking.

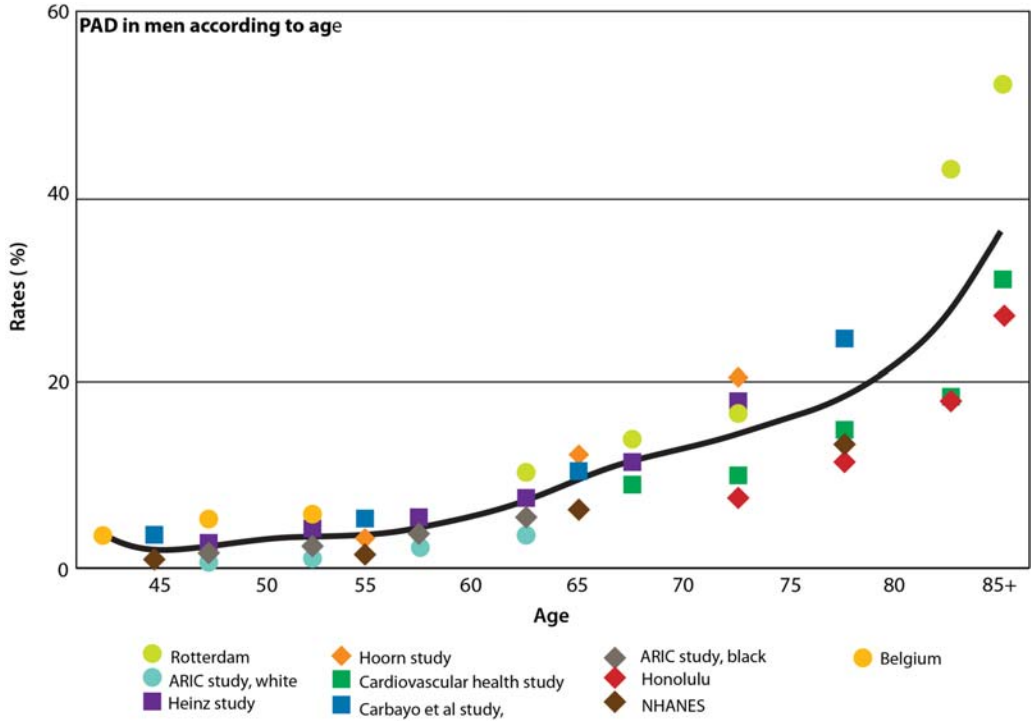

Figure 1. PAD in men according to age (adapted from [89]).

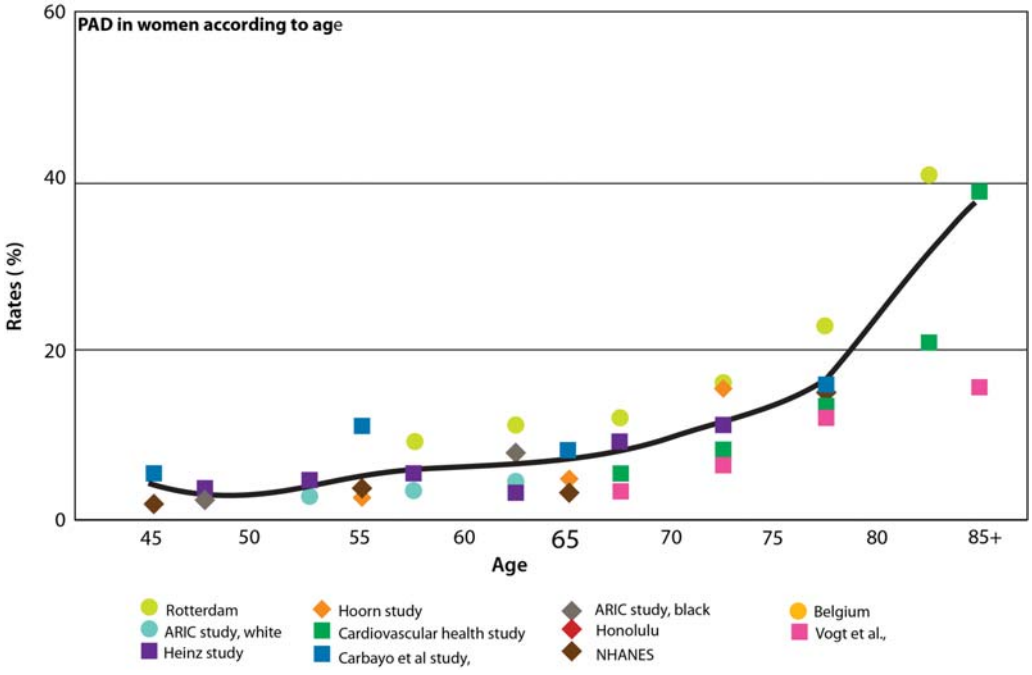

Figure 2. PAD in women according to age (adapted from [89]).

(between 0.80 and 0.90) to predict all-cause mortality was 4, rising to 5.6 when only cardiovascular deaths were considered.[106] Several studies have shown the importance of the ABI as a predictor of cardiovascular or all-cause mortality in asymptomatic patients. A meta-analysis of 16 population cohort studies suggested the presence of 'J' or 'U'-shaped association in which both low and high ABI are associated with increased cardiovascular morbidity and mortality.[76,107] Criqui et al.[108] has evaluated a

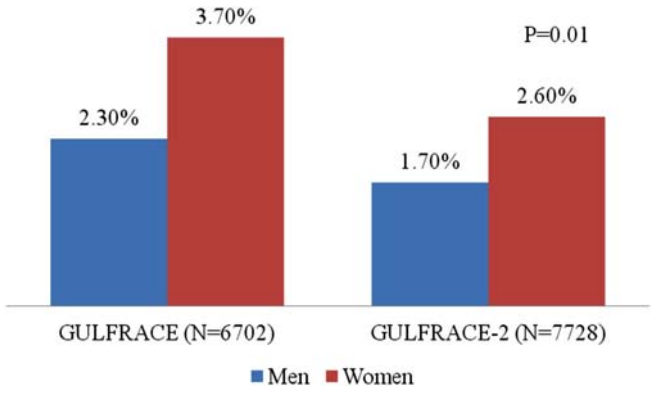

Figure 3. Prevalence of PAD in men and women from the Arab Middle East presenting with ACS.

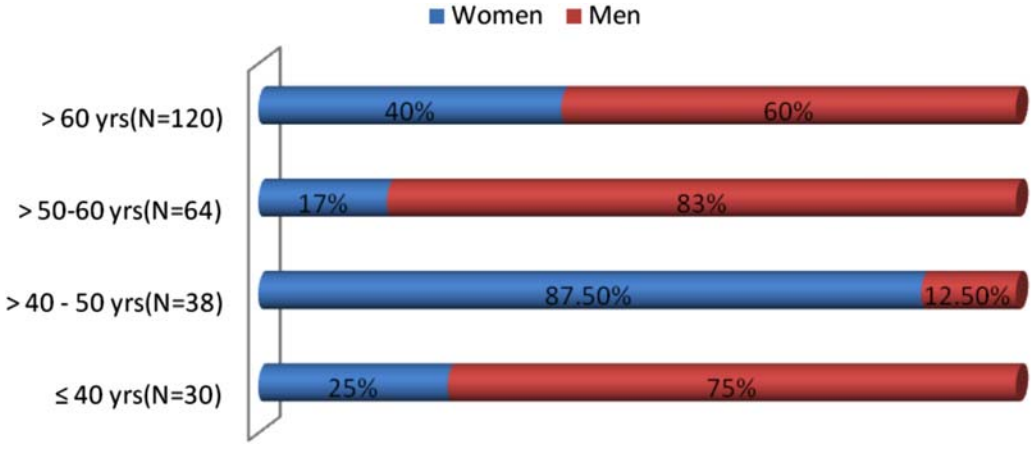

Figure 4. Percent of PAD among hemodialysis patients stratified by gender and age in Qatar (adapted from [28]).

Table 8. Men and Women in AGATHA-ME study in the Gulf region.[25]

	Men	Women	P-value
Age (mean; years)	56	63	0.001
Hypertension (%)	96	98	NS
Diabetes mellitus (%)	44	65	0.001
Dyslipidemia (%)	85	82	NS
Smoking (%)	41	5	0.002
Abnormal ankle-brachial index (%)	24	41	0.001
PAD plus CAD (%)	5	8	0.001
PAD plus CVD (%)	1.4	3.2	0.001
PAD plus CAD plus CVD (%)	1.2	2.5	0.01

10-year follow up of 67 patients with a diagnosis of PAD and a ABI of 0.80 or less, showed significant increase in rate of mortality in both men (61.8%) and women (33.3%) when compared with men and women (11.6%) without disease.[67,68] Our previous experience in the gulf region showed that patients with PAD had worse outcome when presented with ST-elevation myocardial infarction (STEMI), whereas in NSTEACS; PAD was associated with higher rate of heart failure in comparison to non-PAD patients. In diabetics, PAD was associated with 2-fold increase in mortality when compared to non-PAD ($P = 0.028$). Moreover, after adjustment, PAD was associated with higher mortality in STEMI (adjusted OR 2.6; 95% CI 1.23-5.65, $P = 0.01$).[26] Table 9 shows outcome in patients with PAD.[44,68,70,108–111]

Table 9. outcomes (Relative Risk) in PAD patients (adapted from [89]).

Study	ABI value	Mortality	CV death	MI	Fatal CHD	Stroke
Criqui et al.[108]	<0.8 vs > 0.8	3.1	5.9	–	6.6	–
Newman et al.[16]	<0.9 vs >0.9	3.8	3.7	–	3.2	–
Newman et al.[91]	<0.9 vs >0.9	2.4	2.8	2.0	–	1.6
Vogt et al.[109]	<0.9 vs >0.9	3.1	4.0	–	3.7	–
Leng et al.[110]	<0.9 vs >0.9	1.8	2.3	1.4	2.2	1.9
Ogren et al.[111]	<0.9 vs >0.9	2.3	2.6	2.3	–	2.0
Resnick et al.[70]	<0.9 vs >0.9-1.4	2.1	3.8	–	–	–

CONCLUSIONS

Consistent with the global trend, PAD among Middle Eastern patients is associated with poor outcome. However, the prevalence and impact of PAD in our region seems to be underestimated. As the prevalence of DM, metabolic syndrome and renal failure in the Middle East and particularly in the Gulf region is high, ABI cutoff value should be revised. Increased awareness and further research is urgently needed to control this “silent or underestimated killer” in the Middle East.

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