

## Peripheral Artery Disease in Type 2 Diabetic Patients from the United Arab Emirates

Juma M Al-Kaabi<sup>1</sup>, Fatma Al Maskari<sup>2\*</sup>, Taoufik Zoubeidi<sup>3</sup>, Abdishakur Abdulle<sup>1</sup>, Syed M Shah<sup>2</sup>, Paul Cragg<sup>4</sup>, Bachar Afandi<sup>4</sup> and Abdul-Kader Souid<sup>5</sup>

<sup>1</sup>Departments of Internal Medicine, UAE University, Al-Ain, Abu-Dhabi, UAE

<sup>2</sup>Institute of Public Health, College of Medicine and Health Sciences, UAE University, Al-Ain, Abu-Dhabi, UAE

<sup>3</sup>Department of Statistics, College of Business and Economics, UAE University, Al-Ain, Abu-Dhabi, UAE

<sup>4</sup>Diabetes Center, Tawam-Jones Hopkins Hospital, Al-Ain, Abu-Dhabi, UAE

<sup>5</sup>Pediatrics, College of Medicine and Health Sciences, UAE University, Al-Ain, Abu-Dhabi, UAE

\*Corresponding author: Fatma Al-Maskari, Institute of Public Health, Director of Zayed Bin Sultan Center for Health Sciences. College of Medicine and Health Sciences, UAE University, PO Box 17666, Al-Ain, UAE, Tel: 0097137137452; Fax: 0097137672995; E-mail: [fatma.am@uaeu.ac.ae](mailto:fatma.am@uaeu.ac.ae)

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### Abstract

**Objectives:** Peripheral Artery Disease (PAD) is common in patients with diabetes. Frequently, this complication is only recognized when the symptoms and signs are advanced. This study assessed its prevalence and associated risk factors in patients with type 2 diabetes mellitus who reside in the United Arab Emirates. The main purpose of the study was to identify potential disease modifiers that could be included in diabetic education programs.

**Methods:** This prospective, cross-sectional study assessed PAD in 394 patients with type 2 diabetes mellitus. Each patient was investigated by history, physical examination and measurements of the ankle-brachial index (ABI) by bidirectional doppler.

**Results:** Patients' mean ( $\pm$ SD) age was 54 ( $\pm$ 12) years and duration of diabetes 10 ( $\pm$ 8) years. There were 264 females (67%). HbA1c was  $\geq 7\%$  in 247 (65%) patients, claudication present in 166 (42%) patients, reduced capillary refill time in 69 (17%) patients, retinopathy in 50 (13%) patients, and absent pulse in 20 (5%) patients. ABI was  $\leq 1.0$  in 149 (39%) patients (probable PAD) and  $< 0.9$  in 33 (9%) patients (significant PAD). Current smoking [odds ratio (OR)=3.9; confidence intervals (CI)=1.5-10.3; p-value=0.007], percent HbA1c (OR=3.4; CI=1.2-10.2; p-value=0.028) and hypertension on examination (OR=1.6; CI=1.0-2.6; p-value=0.041) were significant predictors of ABI  $\leq 1.0$ . Current smoking (OR=3.7; CI=1.2-10.8; p-value=0.019) was significant predictor of ABI  $< 0.9$ .

**Conclusions:** These results confirm the deleterious effects of smoking on diabetes-association PAD. Thus, diabetic patients should be engaged in effective smoking prevention programs. Other modifiable interventions are controlling hyperglycemia and hypertension. Patients with abnormal ABI (especially  $< 0.9$ ) should have stringent risk assessments and be started on an individualized risk-reduction program.

**Keywords:** Peripheral arterial disease; Type 2 diabetes mellitus; Prevalence; Risk factors; United Arab Emirates

### Introduction

Type 2 diabetes mellitus, hypertension and dyslipidemia are highly prevalent in the United Arab Emirates (UAE) [1,2]. The hot climate, rapid urbanization, modernized lifestyle, suboptimal diets, smoking habits and physical inactivity are all expected to influence and contribute to the progression of diabetic complications in the region [3-9]. Most of these problems have not been adequately studied. Relevant knowledge of diabetic disease modifiers and patient education programs are also incomplete. Thus, local studies addressing the natural history of diabetes and prevention interventions are needed.

Atherosclerosis and Peripheral Artery Disease (PAD) are common in diabetic patients [10,11]. These serious problems are progressive and usually remain asymptomatic until the diabetes is in an advanced stage, which may be partially due to the associated diabetic neuropathy

[12]. The true prevalence of these disorders is unknown since different diagnostic criteria have been used in the published studies [11,12].

The presence of PAD increases the risk of major cardiovascular events, such as stroke and myocardial infarction [13-15]. The PAD severity has been linked to patient's age, duration of diabetes, hyperglycemia and other factors, such as obesity, smoking, hypertension and dyslipidemia [11,12]. Clinically, a critical limb ischemia produces intermittent claudication, pain in the peripheries, foot ulcers and gangrene. The patient's physical signs include pulseless, proximal vascular bruits, hair loss, trophic nails, skin alternations, muscle atrophy, cold feet and pallor on limb elevation [16,17].

The doppler pressure index [ankle-brachial index, (ABI)] has been used reliably in outpatient settings to screen for PAD [18]. There are no absolute diagnostic cutoffs for interpreting ABI [19]. ABI values of  $\leq 1.0$  suggest probable artery disease and  $< 0.9$  suggest significant artery disease [19,20]. Other studies only used ABI  $< 0.9$  as a marker of PAD [11]. Non-invasive investigations also include magnetic

resonance angiography, computerized tomography scan and measurements of foot temperature and hemoglobin-oxygen saturation [11,21]. The invasive diagnostic procedure is arteriography [20].

Diabetes-associated PAD has not been adequately investigated in the UAE. This study determined its prevalence and associated risk factors in patients with type 2 diabetes.

## Materials and Methods

The study design (interviews, questionnaire, data collection and measurements) and patient population were previously described [22]. Briefly, this prospective, cross-sectional study enrolled 394 adults (264 females, 67%) with type 2 diabetes from the Diabetes Center at Tawam-Johns Hopkins Hospital (Al Ain, Abu Dhabi) [22]. The study was approved by Al Ain Medical District Human Research Ethics Committee and informed consent was obtained from each patient. Inclusion criteria were adults with type 2 diabetes for at least 12 months. Exclusion criteria included known causes of vasculopathy, such as vasculitis and collagen vascular disease.

Assessment of peripheral arterial function was performed for each foot. The measurements included skin temperature, color, hair distribution, subcutaneous fat, capillary refill time and pulses in the dorsalis pedis and posterior tibial arteries. Blood pressure (systolic and phase-V diastolic) in the upper extremity was measured after 10 min resting, using validated electronic sphygmomanometers (Omron Hem 907, Omron Healthcare, Kyoto, Japan). Systolic blood pressure in the lower extremity was measured in the supine position by Huntleigh Multi Dopplex II Bi-Directional Doppler (**Huntleigh Diabetic Foot Assessment Kit, Luton, UK**). Systolic blood pressure was also measured at the right and left brachial, posterior tibial and dorsalis pedis arteries. For each side, the highest blood pressure reading in the posterior tibial and dorsalis pedis arteries was recorded. ABI was calculated for each side by dividing ipsilateral pedal arterial pressure over brachial arterial pressure. The lowest ABI was considered for each patient [19].

Eye examination was conducted by an ophthalmologist [22]. Dyslipidemia was defined as triglycerides >1.7 mmol/L, Low-density Lipoprotein (LDL) >2.6 mmol/L, or High-density Lipoprotein (HDL) <1.0 mmol/L for males and <1.3 mmol/L for females [23]. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg [24].

The Statistical Package for Social Sciences (SPSS) software version 19.0 for Windows was used and logistic regression analysis identified independent predictors of neuropathy. A P-value <0.05 was significant. Simple logistic regression was used to investigate associations between risk factors and binary responses. Stepwise logistic and linear regression methods were used to identify better sets of predictors of binary and quantitative response variables, respectively.

## Results

Characteristics of the patients are shown in Table 1; additional features are as previously described [22]. Significant numbers of patients had medical histories of dyslipidemia (73%), hypertension (59%), and lower extremity pain with walking (42%). On examination, hypertension (38%), abnormal gait (17%), retinopathy (13%), and impaired perfusion (reduced capillary refill time and absent peripheral pulses 17%) were also frequent. On investigation, increased body fat

percentage (90%), dyslipidemia (63%), and poor diabetic control (65%; defined as HbA1c ≥7%) were common. Twenty patients (5%) had absent dorsalis pedis or posterior tibial arterial pulse. The prevalence of ABI ≤1.0 (probably arterial disease) was 39% and <0.9 (significant arterial disease) was 9% (Table 1). Sixty-seven percent of the patients were on oral hypoglycemic agent and 29% were on insulin. There was no significant difference in the prevalence of PAD between the two groups (p=0.913).

	Male n=130 (%)	Female n=264 (%)	Total n=394 (%)
<b>History</b>			
Dyslipidemia	102 (78)	187 (71)	289 (73)
High blood pressure	72 (55)	162 (61)	234 (59)
Claudication	48 (37)	118 (45)	166 (42)
Ischemic heart disease	19 (18)	15 (6)	34 (9)
Currently smoking	21 (16)	3 (1)	24 (6)
Stroke	4 (3)	5 (2)	9 (2)
<b>Examination</b>			
High blood pressure	41 (33)	102 (40)	143 (38)
Abnormal gait			
Unsteady/ difficult	18 (18)	23 (11)	41 (11)
Walking with aid	8 (8)	10 (5)	18 (5)
On wheelchair	0	3 (1)	3 (1)
↓Capillary refill time			
Right	34 (27)	35 (13)	69 (17)
Left	31 (34)	35 (16)	66 (16)
Retinopathy			
Background	8 (9)	15 (7)	23 (6)
Pre-proliferative	8 (9)	4 (2)	12 (3)
Maculopathy	2 (2)	1 (<1)	3 (<1)
Proliferative	5 (6)	5 (2)	10 (3)
Advance disease	1 (1)	1 (<1)	2 (<1)
Absent pulse	6 (5)	14 (6)	20 (5)
<b>Investigation</b>			
Increased body fat percentaged	90 (76)	241 (97)	331 (90)
Dyslipidemic	177 (72)	70 (28)	247 (63)
HbA1c <7%	39 (33)	91 (35)	130 (35)
HbA1c ≥7%	81 (67)	166 (65)	247 (65)
Ankle-brachial index			
Right ankle	1.2 ± 0.2	1.1 ± 0.2	1.1 ± 0.2

Left ankle	1.2 ± 0.2	1.2 ± 0.6	1.2 ± 0.5
Ankle-brachial index categories <sup>e</sup>			
Probably no artery disease (1.0<index ≤1.4)	83 (66)	148 (57)	231 (60)
Probable artery disease (index ≤1.0)	42 (34)	107 (41)	149 (39)
Significant artery disease (index <0.9)	11 (9)	22 (9)	33 (9)
Probable artery calcification (index >1.4)	0	5 (2)	5 (1)

Values are number (percent) of patients or mean±SD. The percentages were calculated based on number of patients with available information.

<sup>a</sup>High blood pressure was defined as systolic ≥140 or diastolic ≥90 mm Hg.

<sup>b</sup>Absent posterior tibial or dorsalis pedis arterial pulse on either side.

<sup>c</sup>Dyslipidemia was defined as triglycerides >150 mg/dl (1.7 mmol/l), low density lipoprotein (LDL) >100 mg/dl (2.6 mmol/L) or HDL <40 mg/dl (1.0 mmol/l) in men and <50 mg/dl (1.3 mmol/l) in women.

<sup>d</sup>Abnormal fat composition was as >23% in males and >27% in females.

<sup>e</sup>Lowest determination in each patient; p-value between the genders = 0.071 (Mann-Whitney U test). The categories are based on Al-Qaisi et al., 2009.

**Table 1:** Variables relevant to peripheral arterial disease in the studied patients

Based on ABI ≤1.0, the prevalence of PAD in males was 34% and females 41% (p=0.071). Based on ABI ≤0.9, the prevalence of PAD in males and females was 9% (Table 1). Table 2 shows simple logistic regression analyses of abnormal ABI vs. a few selected parameters. Current smoking (p=0.002) and history of claudication (p=0.005) were significant predictors of ABI ≤1.0. Current smoking was the only significant predictor of ABI <0.9 (p=0.001).

Table 3 (multivariable logistic regression analyses) shows subset of significant predictors of the odds of abnormal ABI vs. predictors. Predictors for ABI ≤1.0 were current smoking (p=0.007), percent HbA1c (p=0.028), and increased blood pressure (p=0.041). Current smoking was associated with 3.9 time increase in the odds for ABI ≤1.0. A 1% increase in HbA1c was associated with 3.4 times increase in the odds for ABI ≤1.0. Hypertension on examination was associated with 1.6 times increase in the odds for ABI ≤1.0 (Table 3). Predictor for ABI <0.9 was only current smoking (p=0.019), Table 3.

The distribution of ABI was bimodal. Mixture analysis was performed using PC-Normix program <http://www.alumni.caltech.edu/~wolfe/normix.htm>. This statistical program searches for clusters with normal distributions within a mixed population (p<0.05) [25]. The results demonstrated two ABI clusters (Figure 1).

	Coefficient	p-value	OR	95%CI for OR
Current smoking (ref. = no)	1.42	0.002	4.12	1.67 – 10.19
Claudication (ref. = no)	0.62	0.005	1.85	1.21 – 2.84

Past smoking (ref. = no)	0.56	0.106	1.75	0.89 – 3.45
Abnormal body fat percentage (ref. = normal)	0.39	0.268	1.48	0.74 – 2.96
Leg/ foot burning pain (ref. = no)	0.37	0.101	1.41	0.95 – 2.14
Male gender (ref. = female)	0.36	0.118	1.43	0.91 – 2.23
LDL >2.5 mmol/L (ref. = ≤2.5)	0.27	0.210	1.31	0.85 – 2.02
Triglycerides:HDL ratio	0.25	0.105	1.29	0.95 – 1.75
Hypertension (ref. = no)	0.19	0.380	1.21	0.79 – 1.85
Urinary albumin:creatinine ratio (mg/mmol)	0.17	0.487	1.19	0.73 – 1.92
↑Triglycerides (ref. = normal)	0.15	0.566	1.16	0.70 – 1.91
Leg pain with walking (ref. = no)	0.11	0.623	1.11	0.73 – 1.69
Percent HbA1c	0.09	0.105	1.09	0.98 – 1.22
HbA1c ≥7% (ref. = <7%)	0.04	0.878	1.04	0.67 – 1.61
Age (yr)	0.01	0.350	1.01	0.99 – 1.03
Duration of diabetes	0.001	0.386	1.00	0.99 – 1.003
Walking for purpose of exercise (ref. = no)	-0.38	0.084	0.69	0.46 – 1.05
HDL <1.0 mmol/L (ref. = ≥1.0)	-0.34	0.111	0.71	0.47 – 1.08
↓Capillary refill time (ref. = normal)	-0.24	0.707	0.79	0.23 – 2.73
Pulse not felt (ref. = normal pulse)	-0.09	0.831	0.91	0.39 – 2.14
Retinopathy (ref. = no)	-0.02	0.959	0.98	0.53 – 1.82

Caseness represented by ankle-brachial index ≤1.0 (n=149)  
OR: Odds ratio; CI: Confidence interval; ref: Reference category

**Table 2:** Simple logistic regression of abnormal ankle-brachial index vs. selected predictors

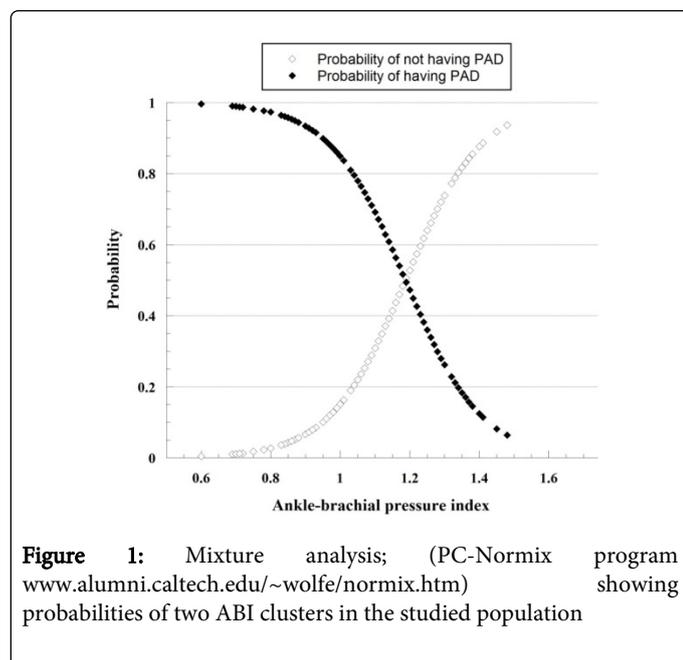
	Coefficient	OR	95% CI for OR	p-value
<b>Ankle-brachial index ≤1.0 (n=149)<sup>a</sup></b>				
Current smoking (ref. = no)	1.35	3.9	1.5 – 10.3	0.007
HbA1c (%)	1.23	3.4	1.2 – 10.2	0.028

↑Blood pressure (on examination) (ref. = no)	0.49	1.6	1.0 – 2.6	0.041
<b>Ankle-brachial index &lt;0.9 (n=33)<sup>b</sup></b>				
Current smoking (ref. = no)	1.30	3.7	1.2 – 10.8	0.019
<sup>a</sup> Likelihood ratio test of model significance: p-value <0.001 (Nagelkerke R <sup>2</sup> = 0.102). <sup>b</sup> Likelihood ratio test of model significance: p-value = 0.033 (Nagelkerke R <sup>2</sup> = 0.030). OR: odds ratio; CI: confidence interval; ref: reference category Variables that were dropped out of the multivariable logistic regression using the stepwise-backward elimination method were age, leg pain with walking, HDL, LDL and Michigan-sign score.				

**Table 3:** Subset of significant predictors of the odds of abnormal ankle-brachial index vs. selected predictors

## Discussion

This study was the first in UAE to use ABI to screen for PAD in patients with type 2 diabetes. The probability distribution of ABI in the studied population is shown in Figure 1. The prevalence of significant PAD (ABI <0.9) was 9% and probable PAD (ABI ≤1.0) was 39% (Table 1). Previous studies in the UAE used pulse deficits (reduced/ absent) and showed a PAD prevalence of 11-12% [3,9].



A cross sectional study in primary health care facility from Saudi Arabia found ~12% of diabetic patients had ABI <0.9, and over 90% of these patients were asymptomatic [26]. In South Asia, the prevalence of ABI <0.9 was 4-9% [27-29]. In a large Asian study (Korea, China, Taiwan, Hong Kong, Indonesia, Thailand and the Philippines), the prevalence of ABI <0.9 was about 18% [30].

This study hypothesized that PAD is common because of frequent risk factors for atherosclerosis in our diabetic patients (smoking, hypertension, poor diabetic control, obesity, physical inactivity, etc.).

Current smoking, increased HbA1c and hypertension (on examination) were independent risk factors for PAD (Table 3). PAD was 3.9 times higher in smokers (Table 3). The majority of published studies show a high incidence of PAD in smokers. In one study, smokers with PAD were twice as likely to undergo lower limb amputation compared to non-smokers with PAD [17]. Smoking is thought to promote atherosclerosis by increasing LDL oxidation and augmenting endothelial dysfunction (by reducing in nitric oxide-dependent vasodilatation)[31,32].

As in this study, the severity of hyperglycemia has frequently been shown to increase PAD [33]. Hyperglycemia is linked to the pathogenesis of atherosclerosis via the following three major mechanisms: advanced glycated end products, oxidative stress and protein kinase C activation [34]. There is no conclusive evidence, however, to suggest that optimal glycemc control lowers the risk of PAD in type 2 diabetic patients.

The finding that hypertension is an independent risk factor for PAD (Table 3) is also consistent with published literature. For example, Framingham studies showed the risk of developing PAD in hypertensive patients was twice that of normotensive patients [10,35].

Seventy-three percent of our patients had medical history of dyslipidemia (Table 1). This high prevalence may explain the insignificant associations between lipid profile and PAD in the studied population (Table 2). In other studies, increased LDL was shown to be an independent predictor of PAD [36]. In the Framingham Heart Study, elevated cholesterol was an important risk factor of claudication [10,35].

Patient symptoms do not correlate well with ABI, emphasizing the need for screening of all patients with suspected PAD [37]. In clinical practice, PAD is under-diagnosed, particularly in diabetic patients due to their being asymptomatic until disease reaches an advanced stage, poor reporting of symptoms and loss of pain perception due to a co-existing neuropathy. In one study, PAD was found to be seven times more common in diabetic patients than none diabetic patients; PAD was also found to be asymptomatic until advanced stages [11]. It is worth noting that absence of peripheral pulses on palpation is not always diagnostic of arterial disease, since the dorsalis pedis pulse could be absent congenitally in 10-15% of the population [38].

Patients with abnormal ABI (especially <0.9) should have stringent risk assessments and started on individualized risk-reduction program. Follow-up and repetitive measurements are necessary. Further assessments may include magnetic resonance angiography and computerized tomography angiography scan.

Figure 1 shows the Mixture analysis model for probability of having PAD for any given value of ABI. This approximation was based on the PC-Normix Program, which identified two clusters of normal distributions within our studied patients (p<0.05) [25]. The model predicted a probability of PAD of about 80% for ABI of 1.0.

The study limitations included lack of confirmatory tests, such as magnetic resonance angiography, computerized tomography scan and invasive arteriography. The study is based on a single large diabetes center and thus the prevalence of PAD cannot be generalized for the whole UAE. Multicenter study is needed. It is a cross sectional study and thus did not establish causality. Follow up studies are needed to assess the progression of PAD with various risk factors and outcome of using different classes of medications.

Sixteen percent of the approached patients declined to participate [22]. This problem might have produced a selection bias, since symptomatic patients were more likely to be included than asymptomatic patients.

## Conclusions

The important finding is this study is that current smoking is most significant predictor of PAD ( $p=0.007$ ). Other modifiable risk factors include hyperglycemia and hypertension. The high prevalence of PAD in our studied diabetic population points out to the need for routine screening and structured managements. These tasks require active measures that include patient education, risk assessment, and timely intervention.

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