Original Article

Prevalence and Associations of Subclinical Peripheral Artery Disease among Patients with Type 2 Diabetes without Clinical Macrovascular Disease

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Abstract

Background: Peripheral arterial disease (PAD) is an important marker of cardiovascular (CV) risk and the risk of PAD is markedly increased in patients with type 2 diabetes mellitus (T2DM). Consequently, early diagnosis and treatment of PAD in patients with T2DM are critically important to reduce the risk of CV events. The aim of this study was to determine the prevalence of asymptomatic PAD in patients with T2DM and to investigate the demographic and clinical associations of PAD among them. **Methods:** This cross-sectional study included 2423 diabetic patients >20 years old, who were regularly followed up at the regional diabetes clinic, Galle, Sri Lanka. Data were obtained using structured questionnaires for information on demographic characteristics and risk factors. Assessment of ankle-brachial pressure index (ABPI) was performed in all. PAD was diagnosed when ABPI was < 0.9 on either leg. **Results:** The overall prevalence of PAD was 15.3% with no significant age or gender difference. Patients with PAD had significantly higher systolic blood pressure (SBP) (127 vs 125 mmHg, P = 0.002) and diastolic blood pressure (DPB) (80 vs 78 mmHg, P = <0.001) and significantly lower estimated glomerular filtration rate (eGFR) (80 vs 84 ml/min, P = 0.007) than those without PAD. No significant relationships were found between the duration of diabetes mellitus, hypertension, dyslipidemia, and PAD. **Conclusions:** Prevalence of PAD was relatively high in the diabetic population of this study when compared with findings from other countries. There is a significant association of subclinical PAD with reduced eGFR among patients with T2DM.

Keywords: *Diabetes complications, diabetes mellitus, peripheral arterial disease, Sri Lanka*

Introduction

Type 2 diabetes mellitus (T2DM) is associated with almost two fold increased risk of morbidity and mortality due to atherosclerotic vascular diseases (ASVD).[1] Coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral arterial disease (PAD) are the three major clinical types of ASVD. Clinical manifestations of CAD include angina and myocardial infarction, and CVD presents as transient ischemic attack, stroke, and vascular dementia while PAD manifest as intermittent claudication, acute limb ischemia, or non-healing ulcers of lower limbs. Studies have revealed that early detection and appropriate intervention of ASVD can improve morbidity and mortality from devastating clinical outcomes in patients with T2DM.[2-4]

All these three types of vascular diseases may remain asymptomatic or manifests as life-threatening clinical catastrophes. Out of the three major types of ASVD, detection of CAD and CVD in the asymptomatic and subclinical stage often requires invasive investigations such as coronary or cerebral angiograms, whereas asymptomatic PAD can be detected using non-invasive testing by measurement of ankle-brachial blood pressure index (ABPI). Diagnosis of PAD using ABPI in an individual has been identified as an indirect evidence of having subclinical CAD, CVD, or both.[5] It has also been shown that the presence of PAD adversely affect the short- and long-term outcomes in patients who develop acute myocardial infarction irrespective of age, gender, or presence or absence of diabetes.[6] Therefore, measurement of ABPI is recommended by professional organizations such as the American

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Diabetes Association (ADA) as an annual screening test for the early diagnosis of PAD.[7]

T2DM and CAD have become major epidemics in the developing countries including Sri Lanka.[8-10] Detection of PAD using a simple bedside procedure may prove useful for early diagnosis and assessment of the overall burden of ASVD among patients with T2DM in poor resource settings.

Literature on PAD among patients with T2DM in other countries reveals prevalence rates varying from 5–32%.[11-13] However, there is paucity of data on the prevalence of PAD among patients with diabetes in Sri Lanka. Published research on the prevalence of PAD in Sri Lanka is based on studies including both non-diabetic and diabetic subjects and <200 participants.[14]

We aimed to study the prevalence of asymptomatic PAD in patients with T2DM without clinically established CAD or CVD and to describe the demographic, clinical associations of PAD among them.

Methods

In this cross-sectional study, data from patients with T2DM screened at a diabetes center over a period of 4 years from January 2012 to December 2016 were analyzed. All eligible patients were over the age of 18 years and had diabetes diagnosed at least for 1 year. All pregnant females and patients with type 1 diabetes and those with clinical diagnosis of T2DM for <1 year were excluded.

Those with a history of hospital admission due to CAD or CVD or having intermittent claudication or previous diagnosis of PAD or undergone amputations were also excluded. Data on age (obtained from the national identity card) and the duration of diabetes to the nearest year (verified from the clinic records) were obtained. Patients' weight and height were measured and their body mass index (BMI) was calculated. Blood pressure was recorded after at least 5 min rest using an electronic instrument (Omron Corporation, Tokyo, Japan), as the mean of two readings taken 5 min apart.

Overnight fasting venous blood samples were collected to measure lipid profile. Glycosylated hemoglobin (HbA1c) level was estimated using high-performance liquid chromatography (HPLC) method. Glomerular filtration rate (GFR) was estimated using modified diet in the renal disease (MDRD) formula. All chemical analyses including HbA1c, serum creatinine, and low-density lipoprotein (LDL) cholesterol were performed in the laboratory attached to the diabetes center and same method of biochemical analysis was used throughout the study period. By using the flow probe of the Doppler as the stethoscope, audible signals were obtained over the posterior tibial artery. Blood pressure cuff of the sphygmomanometer was placed around the ankle just above the malleoli. Systolic blood pressure (SBP) was taken as the measurement of blood pressure at the return of flow signals during the deflation of the cuff. Average of two measurements was taken as the final value. SBP was measured over the arm by the Doppler probe. All the measurements were taken by the same investigator while patient was resting in the supine position.

ABPI was calculated by dividing the ankle blood pressure by brachial artery pressure. The ratio of ankle to arm SBP was calculated for each leg and the lowest value was recorded as ABPI. ABPI was classified as low ≤0.9, normal 0.9–1.3, and high >1.3.[15]

Ethical approval – Ethical clearance for the present study was obtained from the Institutional Ethics Committee of the Faculty of Medicine, University of Ruhuna. Written informed consent was obtained from all study subjects in the local language.

Statistical analysis

All statistical analyses were performed using the SPSS statistical package. Unpaired *t*-test was used to compare continuous variables and the Chi-square test was performed to compare categorical variables between the groups with and without PAD. Logistic regression analyses were performed to detect the determinants and associations of PVD among patients with diabetes. $P < 0.05$ was considered statistically significant.

Results

The baseline characteristics of the study population are summarized in Table 1. There were 2423 T2DM patients, and nearly 65% of them were males. The mean age (standard deviation: SD) was 49.9(10.2) years and females were significant older than males ($P = 0.03$). The mean BMI (SD) was 24.5 (4.3) and 37% and 57% had global and visceral obesity, respectively. Females had significantly higher duration of diabetes, blood pressure, total cholesterol, and LDL cholesterol. The mean values of various anthropometric, clinical, and biochemical variables measured are summarized in Table 1 according to the presence of PAD.

The overall prevalence of PAD was 15.3% with no significant age or gender difference. Patients with PAD had significantly higher SBP (127 vs 125 mmHg, $P = 0.002$) and diastolic blood pressure (DPB) (80 vs 78 mmHg, $P = <0.001$) and significantly lower estimated glomerular filtration rate (eGFR) (80 vs 84 ml/min, $P = 0.007$) than those without PAD [Table 1]. However, factors such as duration of diabetes, BMI, HbA1c, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride (TG) levels were not different between patients with PAD and without PAD.

When logistic regression analysis was performed keeping age, gender, BMI, HbA1C, eGFR, blood pressure, and lipid levels as independent variables, only the eGFR

Table 1: Comparison of clinical characteristics between patients with and without PAD

Variable	Patients without PAD	Patients with PAD	*P*	Total
Number (%)	2058 (83%)	365 (15.%)	-	2423
Age (years)*	52 (11)	53 (10)	0.31	52 (10.7)
Age groups				
20-40	562 (27%)	16 (4%)		578
41-60	1116 (54%)	182 (50%)		1298
>60	380 (18%)	167 (46%)		547
Males (number, %)**	1307 (64%)	227 (62%)	0.36	1534 (63%)
Mean duration of diabetes (years)*	9 (3)	9 (3)	0.99	9 (3)
Duration of diabetes - newly diagnosed				
1-10 years				
>10 years				
Age at onset of diabetes (years)*	43 (10)	44 (10)	0.27	43 (10)
Mean BMI (kg/m^2)*	24.4 (3.9)	24.5 (4.1)	0.74	24.4 (4)
BMI categories				
<18				
18-23				
>23				
HbA1C (%)*	7.4 (0.7)	7.5 (0.6)	0.66	7.4 (0.7)
Mean SBP (mmHg)*	125.7 (17)	127.1 (17)	0.002	126.3 (17)
Mean DBP (mmHg)*	78.6 (8)	79.6 (8)	<0.001	78.9 (8)
TC (mg/dL)*	200.6 (34.9)	200.7 (36.6)	0.96	200.7 (35)
LDL (mg/dL)*	125.3 (33.7)	126.9 (33.9)	0.40	125.3 (33)
TG (mg/dL)*	118.1 (40.1)	112.6 (42.1)	0.06	117.1 (41)
HDL (mg/dL)*	50.6 (7.8)	51.1 (7.9)	0.26	50.1 (8.8)
Microalbuminuria				
Present				
Absent				
eGFR (ml/min)*	84 (25)	80 (22)	0.007	83 (24)

*Unpaired *t*-test, **Chi-square test. PAD=Peripheral arterial disease; BMI=Body mass index; HbA1c=Glycosylated hemoglobin; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; TG=Triglyceride; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; eGFR=Estimated glomerular filtration rate

was significantly associated with presence of subclinical PAD [odds ratio (OR) 0.988; 95% confidence interval (CI); 0.981–0.996] [Table 2].

Discussion

This cross-sectional study from a developing country with rising incidence of diabetes and CVD revealed that 15% of patients with T2DM with no clinical evidence of coronary or CVD had asymptomatic PAD. The other main finding is the significantly association of asymptomatic PAD with deteriorating renal function as evidenced by reduced eGFR.

Studies on PAD in patients with T2DM from different settings have reported varying prevalence rates.[16,17] Variations in the reported prevalence rates are mainly due to differences in the demographic and clinical profiles of patients included in the samples studied. Prevalence rates of PAD as high as 70% has been reported in studies of patients with T2DM with severe diabetic foot disease including those referred for amputations or those with established coronary or CVD.[18,19] Studies including newly diagnosed patients with diabetes and those without established vascular complications have reported lower prevalence rates of PAD ranging from 3–10%.[12]

Ethnic variations in the prevalence of PAD among the individuals with and without diabetes have been reported. A recent systemic review of PAD in population based studies has reported that overall prevalence of PAD (among individuals with and without diabetes) is highest among blacks (6.7%) and lowest among Asians (3.5%), $P = 0.005$.[20] The same meta-analysis revealed that among patients with diabetes, the mean PAD prevalence rates for whites, blacks, East Asians, and South Asians were 17%, 25.3%, 13.5%, and 7.6%, respectively. In this meta-analysis, diabetic population of South Asian ethnicity had a lower PAD prevalence compared to whites ($P < 0.001$); there was no significant difference between blacks and whites. The finding of lower rates of PAD in the South Asian individuals compared to Caucasians is in contrast to the higher prevalence of other types of CVD such as CAD in the South Asian ethnicity.[21] A population-based study from multi-ethnic setting in the United Kingdom has also reported a significantly lower PAD prevalence among

Table 2: Results of logistic regression analysis for factors associated with PAD

Variables	OR	95% CI	*P*
Gender	1.042	0.39-1.56	0.904
Age at presentation	0.991	0.45-2.31	0.252
Duration	1.006	0.38-2.12	0.546
BMI	1.021	0.64-1.56	0.186
HbA1c	1.059	0.59-2.01	0.509
TC	0.998	0.34-2.65	0.694
LDL	1.004	0.51-2.11	0.475
TG	0.998	0.27-2.09	0.254
HDL	1.008	0.54-1.98	0.324
Systolic blood pressure	1.007	0.78-1.65	0.184
Diastolic blood pressure	1.015	0.65-1.34	0.135
eGFR	0.993	0.98-0.99	0.047

PAD=Peripheral arterial disease; BMI=Body mass index; HbA1c=Glycosylated hemoglobin; LDL=Low-density lipoprotein; TG=Triglyceride; HDL=High-density lipoprotein; eGFR=Estimated glomerular filtration rate

the South Asians compared to Europeans.[22] In this survey involving 15,692 patients with diabetes (11.9% South Asians), South Asian ethnicity had significantly lower PAD prevalence and foot ulcers than Europeans. A community-based study conducted in 1755 patients with diabetes in South India has revealed an overall prevalence of PAD of 8.3%.[23] This prevalence rate is similar to the previously quoted PAD prevalence (7.6%) among the South Asians in the meta-analysis.

With this background, finding of a comparatively higher PAD prevalence (15.3%) in our study is of concern and need explanations. Our findings are based on data from a single center and the lower prevalence rates are found in community based studies. Participants in the South Asian study included previously diagnosed as well as newly diagnosed patients with diabetes and the lower PAD in the latter group could have diluted the overall prevalence. Differences in the impact of major risk factors for PAD in the participants such as smoking, suboptimal glycemic (mean HbA1c 7.4%) lipid (mean LDL 124 mg/dL) control, and increased diabetes duration (mean 9 years) could also influence the relatively high PAD prevalence observed in our study.

The other main finding in this study is the significant association of asymptomatic PAD with reduced eGFR. Although significant, this observation is not novel as several previous studies from different settings have reported association of both parameters of diabetes nephropathy, namely albuminuria and eGFR with PAD. National Health and Nutrition Examination Survey in the United States in a large sample (n = 6951) of patients with diabetes has reported that both albuminuria and eGFR are strongly associated with PAD with odds ratio for prevalent PAD associated with albuminuria alone, reduced eGFR alone, and both reduced eGFR and albuminuria compared to those without albuminuria or reduced eGFR were 1.72 (95% CI 1.16–2.55), 1.58 (95% CI 1.09–2.29), and 2.26 (95% CI 1.30–3.94), respectively.[24] Another study from Japan including 2057 patients with T2DM has shown that ABPI was significantly correlated with low eGFR ($P < 0.01$).[25] Association of chronic kidney disease (CKD) with arterial stiffness and subsequent macrovascular disease is a well-established phenomenon.[26] It can be postulated that PAD is a manifestation of arterial stiffness associated with onset of CKD. It is also possible that hypertension resulting from arterial stiffness can further deteriorate renal function. Therefore, the presence of PAD in patients with reduced eGFR may indicate role of "the cause and the effect" association between the two.

Whether it is the cause or the effect, higher prevalence of PAD in patients with lower eGFR has several clinical implications. As a clinical marker, finding of subclinical PAD with reduced ABPI on routine screening in a patient with T2DM should expedite other screening procedures for macrovascular diseases. Guidelines recommend therapeutic initiation of high intensity statins as a primary prevention strategy to reduce CVD events for patients with CKD both with and without diabetes.[27] Presence of PAD has also shown to provide useful prognostic information for patients with end-stage renal disease undergoing renal transplant. A prospective study of 1055 renal transplant recipients have revealed that low ABPI was associated with a threefold greater risk of renal graft failure, a twofold greater risk of death transplant.[28] Therefore, ABPI of less than 0.9 or reduced eGFR in a patient with T2DM call for further screening tests for detection of other macrovascular diseases and intensification of therapeutic strategies to reduce future risks of CVD and progression of CKD to improve overall morbidity and mortality in the affected patients.

This study which yielded clinically important issues such as a higher PAD prevalence than the previously reported figures from the region and its association with reduced eGFR in patients with T2DM in Sri Lanka has few limitations. Being a single center study is the main limitation. However, large sample size and inclusion of patients with T2DM with varying duration with a mean duration of 9 years make the findings of this study more valid. In the absence of any previous studies reporting on the prevalence of PAD in Sri Lanka in the literature, findings of this study serve as an eye opener to the rising macrovascular disease burden among patients with T2DM in a developing country.

In conclusion, our findings revealed that one in seven patients with T2DM without the clinical evidence of macrovascular disease have subclinical PAD, indicating the possible co-existence of other atherosclerotic cardiovascular disease (ASCVD) in these patients as well. This study

further confirmed the association of subclinical PAD with reduced eGFR among patients with T2DM.

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Conflicts of interest

There are no conflicts of interest.

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