Original Article

Peripheral Arterial Disease in Community-based Patients with Diabetes in Singapore: Results from a Primary Healthcare Study

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Abstract

Introduction: Peripheral arterial disease (PAD) is an important complication of diabetes mellitus (DM), significantly associated with increased morbidity and mortality secondary to amputations, strokes and coronary artery disease. Information on DM patients with PAD is limited in our ethnically diverse population in Singapore. We aimed to determine the prevalence, risk factors and co-morbidities of PAD in patients managed for DM in the primary care setting. Materials and Methods: A cross-sectional study was conducted among 521 diabetics in 9 of the 18 government-aided clinics in the community. Data including demographics, presence of co-morbidities and vascular risk factors were collected using an interviewer-administered questionnaire, and Ankle-Brachial Index (ABI) was calculated from systolic ankle and brachial pressure measurements. Results: The prevalence of PAD, defined as resting ABI of <0.9 on either leg and/or a history of gangrene or non-traumatic amputation was 15.2% [95% confidence interval (CI), 12.3-18.5]. This prevalence of PAD was higher in patients with pre-existing microvascular and other macrovascular complications. In multivariate analysis, prevalence of PAD was positively associated with increasing age (OR, 1.08; 95% CI, 1.05-1.12), Malay versus Chinese ethnicity (OR, 2.27; 95% CI, 1.09-4.70), low HDL-cholesterol (OR, 1.87; 95% CI, 1.04-3.37), and insulin treatment (OR, 2.98; 95%CI, 1.39-6.36). Conclusion: PAD is an important cause of concern among patients with diabetes, with a high prevalence which further increases with increasing age and duration of DM, and exhibits ethnic variation. Risk factors identified in this study may improve early identification of PAD, allowing for prompt interventions, with a potential to reduce long-term morbidity and mortality.

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Key words: Ethnic variation, Macrovascular complications, Risk factors

Introduction

Peripheral arterial disease (PAD) is a significant complication of diabetes mellitus and accounts for the majority of amputations among these patients with diabetes.[1] In addition, PAD is a manifestation of systemic atherosclerosis and is associated with increased risk of death and ischaemic events.[2] Despite its associations with increased morbidity and mortality, PAD is significantly under-diagnosed and under-treated in the general population. Patients with diabetes have unique problems with PAD as the disease appears to affect distal blood vessels where angioplasty is not an option. Furthermore, pain is often not prominent due to superimposed neuropathy, and this puts them at risk of seeking medical attention only in advanced stages.[3] This in turn leads to increased costly consequences such as hospitalisation for ulcers, revascularisation, amputation, need for rehabilitation and a considerable loss of employability among patients with diabetes.

The prevalence of PAD among patients with diabetes in the Western population ranges from 16% to 22%.[4,5] Comparatively, less is known about PAD among Asian populations although some studies have found lower prevalence rates ranging from 6% to 10%.[6-8] Although this disparity in PAD prevalence between Asian and Western populations could be true, it could also be attributed to

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under-diagnosis of this condition among Asian patients with diabetes.

According to a nationwide cross-sectional study in Singapore in 2004, the prevalence of diabetes among adults aged 18 to 69 years was 8.2%.[9] However there is little data on the prevalence of PAD among diabetic patients. In this study, we measured the prevalence and associated factors of PAD in our community-based patients with diabetes among the Chinese, Malays and Indians in Singapore.

Materials and Methods

Study Population

In our country, patients managed in the primary care setting are seen either by their general practitioners or at 1 of the 18 government-funded polyclinics located nationwide. The subjects in our study were patients with diabetes mellitus consulting a doctor at 9 such polyclinics over a period of 5 consecutive working days in January 2004. The 9 polyclinics that took part in the study are situated in the Northern and Western parts of Singapore and provide government-aided primary healthcare service to approximately half of the population. Patients with diabetes were identified by direct questioning at the time of registration and verified by reviewing medical records for confirmatory blood tests or history of oral hypoglycaemic and/or insulin treatment. Patients who were incapable of providing relevant information due to mental incompetence or speech impairment were excluded from our sampling frame. A sampling rate of 1 in 5 patients with DM was implemented in 6 polyclinics. In the remaining 3 polyclinics where the patient load was approximately twice that of the other clinics, a sampling rate of 1 in 10 was used. In total we sampled 697 patients, and 521 patients agreed to participate in our study. This study was approved by the Department of Epidemiology and Public Health, Student Project Committee.

Questionnaire and Definitions

The questionnaire was administered through direct questioning by trained interviewers, and translated into Chinese and Malay. The questionnaire included information on demographics, diabetes status, complications of diabetes, and the presence of established risk factors for PAD. The Edinburgh Claudication Questionnaire was included for the diagnosis of claudication. A person with significant smoking history was defined as having smoked daily for at least 6 months. Ex-smokers were subjects who had ceased smoking for more than a year. Significant physical activity was defined as exercising at least 3 times a week for 20 minutes per session in the past month. In addition, medical records of study participants were reviewed for information. History of stroke and ischaemic heart disease was either self-reported or documented in the medical records. History of retinopathy, neuropathy and nephropathy were obtained from documentation in the medical records by the managing physicians. The most recent results of glycosylated haemoglobin (HBA1C) and fasting lipid levels (including total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels) were recorded from the patient medical records. Low HDL was defined as HDL cholesterol <1.0mmol/L in males or <1.3mmol/L in females.

Ankle-Brachial Index (ABI) and PAD

Trained personnel using a mercury sphygmomanometer and hand-held Doppler measured the resting systolic blood pressures of the upper and lower limbs. ABI for each leg was calculated as a ratio of the higher systolic BP between the posterior tibialis of that leg and dorsalis pedis, to the higher of the brachial pressures in the two arms. Between the values from both legs, the lower value was taken as the ABI of the patient.

To access inter-operator variability, the 10 ABI operators obtained common ABI readings in pairs and the intra-class correlation between ABI readings from 2 different operators was 0.908 (P <0.001), thus ensuring that there was excellent inter-operator reproducibility in the measurement of systolic blood pressures. In our study, the ABI operators were also blinded to the information from the patient's questionnaire or medical records.

We defined PAD as having an ABI of less than 0.9 on either leg and/or a history of gangrene or non-traumatic amputation. Non-traumatic amputation was defined as that resulting from gangrene or ulcers.

Statistical Analysis

Continuous variables with a normal distribution were analysed with *t*-tests while continuous variables with a skewed distribution were analysed with the Mann-Whitney U test. Categorical variables were analysed with chi-squared tests. All P values quoted are two-sided and less than 0.05 was considered statistically significant. We used multiple logistic regression models to estimate the odds ratio (OR) and 95% confidence interval (CI) of PAD for each risk factor. In multivariate analysis, we adjusted for vascular risk factors including age (years, continuous), ethnicity (Chinese, Malays and Indians), gender, smoking history (ever, never), duration of diabetes (<10 years, ≥10 years), hypertension (yes, no), low-HDL-cholesterol (yes, no) and current insulin treatment (yes, no). Statistical computing was conducted using SPSS (Version 16.0).

Results

In total we systematically sampled 697 patients from the 3607 patients with diabetes who visited the 9 polyclinics during the study period, giving an overall sampling rate of 19.3%. A total of 521 patients agreed to participate, giving

a response rate of 74.7%. Refusals had the same mean age and ethnic distribution as our respondents. There was a higher proportion of females among the refusals compared to the participants in the study.

Our study population consisted of 67.0% Chinese, 15.2% Malays, 16.1% Indians and 1.7% of other ethnic groups. The prevalence of PAD among the patients with diabetes in our study was 15.2%, with significant difference among Chinese, Malays and Indians. Among Chinese patients, 12.6% had PAD, compared to 17.9% among Indians and 22.8% among Malays ($P = 0.054$) (Table 1). The Edinburgh Claudication Questionnaire (ECQ) was administered in all patients. Among the patients defined to have PAD, only 21.5% (n = 17) of patients had positive history for intermittent claudication by the ECQ. However, the ECQ was negative in all patients without PAD.

Compared to patients without PAD, patients with PAD were older (66.8 vs 59.1 years of age; $P < 0.001$) and had longer duration of diabetes (13.9 vs 9.8 years; $P < 0.001$). From a prevalence of nearly 5% in those below 40 years of age, the rates increased across the age groups, with nearly 1 in 3 patients above 70 years of age having PAD (Fig. 1). Less than 10% of patients with duration of diabetes less than 6 years had PAD, but prevalence increased with increasing duration, reaching nearly 25% in those who had diabetes for more than 20 years (Fig. 2).

Compared to diabetic patients without PAD, patients with PAD had lower serum HDL-cholesterol levels (1.24 vs 1.38 mmol/L; $P = 0.011$), higher prevalence of self-reported or documented hypertension (72.2% vs 61.1%, $P = 0.039$) and were more likely to be on insulin treatment (24.4% vs 10.2%, $P < 0.001$) (Table 1).

Diabetic patients with PAD were more likely to have ischaemic heart disease, stroke, peripheral neuropathy, nephropathy and retinopathy compared to patients without PAD (Table 1). After adjusting for duration of diabetes, age, gender, ethnicity, presence of hypertension and smoking history, diabetic patients with macrovascular complications such as stroke or ischaemic heart disease, or microvascular complications such as nephropathy, peripheral neuropathy or diabetic retinopathy, were about 2 to 3 times more likely to have PAD compared to patients without these vascular complications (Table 2).

Finally, we examined for factors associated with PAD in a multivariate model and found increasing age, Malay ethnicity (OR, 2.27; 95% CI, 1.09-4.70), having low serum HDL-cholesterol (OR, 1.87; 95% CI, 1.04-3.37) and insulin treatment (OR, 2.98; 95% CI, 1.39-6.36) to be factors significantly associated with an increased prevalence of PAD in this cross-sectional study (Table 3).

Discussion

In this study of patients with diabetes managed in a primary care setting, a relatively high proportion of 15.2% had PAD, which is similar to the rates seen in the Caucasian populations. We found that the prevalence of PAD increased proportionally with age and duration of diabetes. Factors associated with the disease were Malay ethnicity, low HDL-cholesterol and the use of insulin. In addition, there were close associations between other vascular complications and PAD.

The ethnic distribution of our study population is similar to that of a nationwide cross-sectional study on diabetes-related

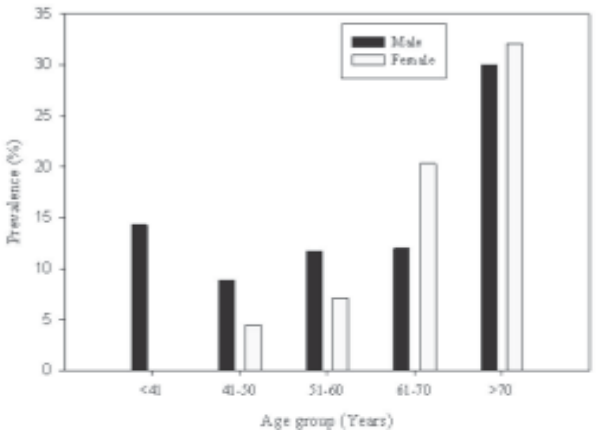

Fig 1. Age specific prevalence of PAD.

The prevalence of PAD for male and females increases across the age groups (P for trend <0.05 for males and P <0.0001 for females). Below the age of 41 years, there are no females with PAD, but there is 1 male who has had diabetes mellitus for 19 years.

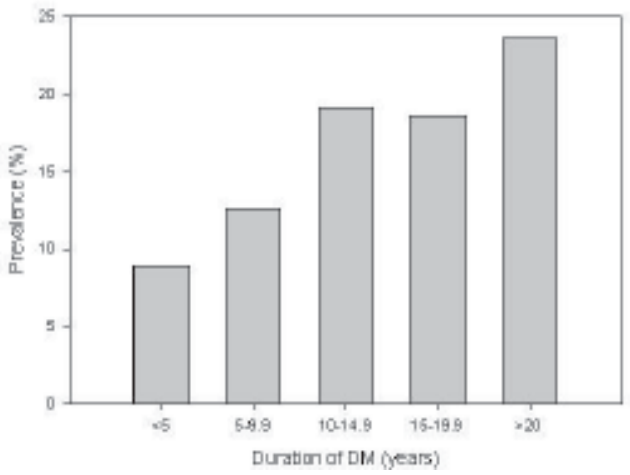

Fig 2. Relationship of PAD prevalence and duration of diabetes.

The bars in this figure denote the prevalence of PAD across the different age groups,

P value for overall trend <0.05.

P <0.05 when prevalence compared to those with <5 years duration of DM

P <0.005 when prevalence compared to those with <5 years duration of DM

Table 1. Characteristics of Patients With and Without Prevalent Peripheral Arterial Disease (PAD) [mean (standard deviation) or percent]

Characteristic	PAD (n = 79)	No PAD (n = 442)	*P* value *
Age (years)	66.77 (11.51)	59.07 (11.09)	<0.001
Gender (% of males)	38 (48.1%)	216 (48.9%)	ns (0.054)
Ethnicity (%)			
Chinese	44 (12.6%)	305 (87.4%)	
Malays	18 (22.8%)	61 (77.2%)	
Indians	15 (17.9%)	69 (82.1%)	
Duration of Diabetes (years)	13.92 (9.7)	9.81 (8.32)	<0.001
Hypertension history (%)	57 (72.2%)	270 (61.1%)	0.039
Smoker (%)	25 (31.6 %)	120 (27.4%)	ns
Total Cholesterol (mmol/L)	5.04 (1.20)	5.34 (1.01)	0.049
LDL Cholesterol (mmol/L)	3.04 (0.85)	3.14 (1.08)	ns
Triglycerides (mmol/L)	1.77 (0.96)	1.84 (1.27)	ns
HDL Cholesterol (mmol/L)	1.24 (0.32)	1.38 (0.45)	0.011
HBA1C (%)	8.19 (1.48)	7.89 (1.43)	ns
Presence of Obesity (%)	53.3	42.9	ns
[defined as BMI >25 kg/m2]			
Insulin treatment (% on insulin)	19 (24.4%)	45 (10.2%)	0.001
Vascular Complications			
Ischaemic Heart Disease (%)	23 (29.1%)	61 (13.8%)	<0.001
Stroke (%)	14 (17.7%)	39 (8.8%)	0.025
Peripheral Neuropathy (%)	37 (46.8%)	121 (27.6%)	0.001
Nephropathy (%)	29 (37.2%)	72 (16.4%)	<0.001
Retinopathy (%)	24 (30.8%)	61 (13.9%)	<0.001

**P* value for the difference in characteristics by PAD status based on chi-square or *t*-test, as appropriate.

mortality in 1991, which recorded the ethnic distribution of diabetics identified from death certificates as 70.5% Chinese, 17.0% Malays, 11.2% Indians and 1.3% other ethnic groups.[10] Another earlier study that included diabetic patients attending only one specific polyclinic (Toa Payoh) had an ethnic distribution of 81.9% Chinese, 7.1% Malays and 11.0% Indians.[11] However, since this was a single-centre study, it would be less valid than our current study or the nationwide study in estimating the ethnic distribution of diabetics in Singapore.

The ethnic differences seen in the prevalence of PAD in our study is of great interest. The prevalence of PAD in our Chinese patients is similar to that of other reports on Chinese patients with DM.[7] The prevalence of PAD in Indians in our study is almost 3 times higher than that reported in a population based study in India that included patients with diabetes.[12] However, this is most likely due to the older ages of our patients compared to the patients in the Indian study.

In the Singapore Malay Eye Study, the prevalence of PAD among diabetic Malay was found to be only 7.6% which is much lower than what was found in this study.[13] This study is a community-based survey of 3280 Singaporean Malays aged between 40 and 80 years old (78.7% response rate), and included the measurement of random glucose for the diagnosis of diabetes in previously undiagnosed cases. In addition, the refusals or non-respondents among those with diabetes could possibly be those with medical complications such as PAD, which precluded them from going to the study centres for the survey. Hence, the prevalence of PAD from such a study is expected to be significantly lower than the prevalence reported among patients actively seeking treatment at the polyclinics in our study.

To our knowledge, this is the first study to report the increased risk of PAD in Malay diabetics as compared to the Chinese and Indians after adjusting for possible confounders. In the general population, earlier studies in Singapore have found that the incidence of acute myocardial infarction (AMI) was highest in ethnic Indians while Malays had the highest case-fatalities from AMI.[14] Ethnicity can contribute to disease risk due to complex differences in cultural, socio-economic, dietary, lifestyle or genetic factors. How

Table 2. Associations between the Presence of Vascular Complications and Prevalence of PAD

	PAD present	Crude OR (95% CI)	Adjusted OR (95% CI)*
Nephropathy			
Absent (n = 410)	49 (12%)	1.00	1.00
Present (n = 100)	29 (29%)	3.01 (1.78-5.09)++	2.84 (1.60-5.05)++
Peripheral neuropathy			
Absent (n = 362)	42 (11.6%)	1.00	1.00
Present (n = 159)	37 (23.3%)	2.31 (1.42-3.77)++	2.45 (1.42-4.23)++
Retinopathy			
Absent (427)	54 (12.6%)	1.00	1.00
Present (n = 84)	24 (28.6%)	2.76 (1.59-4.80)++	2.83 (1.54-5.19)++
Self reported IHD			
Absent (n = 437)	56 (12.8%)	1.00	1.00
Present (n = 84)	23 (27.4%)	2.57 (1.47-4.47)++	2.09 (1.14-3.85)+
Self reported stroke			
Absent (n = 468)	65 (13.9%)	1.00	1.00
Present (n = 53)	14 (26.4%)	2.23 (1.15-4.33)+	1.92 (0.93-3.94)

* adjusted for duration of DM (continuous), age (continuous), gender, ethnicity, smoking (ever, never) and hypertension status

+ indicates $P < 0.05$

++ indicates $P < 0.005$

ethnicity contributes to differences in risk of coronary and extra-coronary atherosclerosis in the general population and specifically among diabetic patients needs to be elucidated by future studies.

Similar to previous studies, we noted a positive association between duration of diabetes and the development of PAD[15,16] even after adjustment for age. This is likely attributable to the presence of increased atherosclerotic burden due to the cumulative effect of longer duration of exposure to metabolic derangements resulting from diabetes and its complications.[17]

Hypercholesterolemia is a major risk factor for atherosclerotic disease.[18,19] It has been suggested that hypercholesterolemia has greater impact on the risk of coronary artery disease and less in PAD.[20] In our study, we found no significant difference in LDL-cholesterol levels between patients with and without PAD. The lack of difference could be contributed by the fact that a majority of patients in our study were on lipid modifying therapy. However similar to previous studies showing a relationship between HDL-cholesterol levels and PAD, we found that patients with PAD had lower HDL-cholesterol and this association remained after adjusting for other risk factors of PAD.[21] This suggests interventions to raise HDL-cholesterol levels, such as increasing physical activity, and may be even more important for the prevention of PAD.

We found that patients who were on insulin treatment had a three-fold increased risk of PAD after adjusting for age, duration of diabetes, glycosylated haemoglobin levels (data not displayed), and other factors of PAD (Table 3). The role of hyperinsulinaemia as a cardiovascular risk factor remains controversial. While some studies have suggested that hyperinsulinaemia due to insulin resistance could be an independent coronary risk factor,[22] others have observed that such an association between hyperinsulinaemia and coronary events disappeared after adjusting for dyslipidemia, obesity and hypertension.[23] In large prospective studies like the UKPDS,[24] intensive glycaemic control with insulin therapy was not associated with increased risk of peripheral artery disease. Our findings could possibly be contributed to by our definition of PAD used. We included patients who had gangrene and non-traumatic amputations and these patients are more likely to have received inpatient care, initiated and maintained on insulin therapy.

PAD is known to be associated with generalised atherosclerosis and is a strong predictor of cardiovascular ischaemic events.[25,26] Our data reinforces the strong associations of PAD with cerebrovascular and coronary heart disease. This highlights the importance of screening for cerebrovascular disease and coronary heart disease in the presence of PAD, and likewise screening for PAD in the presence of any of the other two manifestations of atherosclerotic disease. The consequences of unrecognised disease for anyone of these 3 conditions can be serious and potentially fatal.

Table 3. Associations between Factors and Peripheral Artery Disease (PAD)

	Crude OR (95% CI)	Age-adjusted OR (95% CI)	Fully adjusted OR*(95% CI)
Age, years	1.07 (1.04-1.10) ++	1.08 (1.05-1.17) ++	
Gender			
Female	1.00	1.00	1.00
Male	1.03 (0.64 -1.67)	0.98 (0.60-1.62)	1.06 (0.54-2.07)
Ethnicity			
Chinese	1.00	1.00	1.00
Malay	2.05 (1.11-3.78) +	2.91 (1.50-5.14) ++	2.27 (1.09-4.70)+
Indian	1.51 (0.79-2.86)	2.17 (1.10- 4.29) +	1.89 (0.89-4.03)
Duration of Diabetes			
< 10 years	1.00	1.00	1.00
≥ 10 years	2.24 (1.38-3.63) ++	1.98 (1.20-3.26) +	1.48 (0.83-2.64)
HDL Cholesterol			
Normal	1.00	1.00	1.00
#Low	1.76 (1.05-2.96) +	2.01 (1.17-3.48) +	1.87 (1.04-3.37) +
Self-reported history of Hypertension			
No	1.00	1.00	1.00
Yes	1.65 (0.97-2.80)	1.19 (0.69-2.07)	1.19 (0.64-2.24)
Smoking			
Never	1.00	1.00	1.00
Ever	1.23 (0.73-2.06)	1.18 (0.69-2.01)	1.15 (0.56-2.37)
Insulin Treatment			
No	1.00	1.00	1.00
Yes	2.84 (1.55-5.19) ++	4.24 (2.19-8.20) ++	2.98(1.39-6.36) ++

* Adjusted for age, gender, ethnicity, low HDL Cholesterol, self reported history of hypertension, smoking status, insulin treatment, and duration of diabetes more than 10 years.

\# Low HDL cholesterol defined as HDL-cholesterol <1.0mmol/L for males, <1.3 mmol/L for females

\+ indicates P <0.05

++ indicates P <0.005

The Edinburgh Claudication Questionnaire (ECQ) is a well accepted screening tool for intermittent claudication, an important symptom of clinically significant PAD. ECQ has been tested in different populations with a sensitivity ranging from 14.3% to 91.3%[27-29] for diagnosing claudication. We found that only a minority of our patients had intermittent claudication as diagnosed by the ECQ. Concomitant neuropathy was present in 46.8% of patients with PAD, possibly explaining the reduced prevalence of intermittent claudication in our study.

Our cross-sectional study demonstrates several strengths. We had an adequately large sample size of 697 patients with a relatively high response rate. The use of systematic sampling minimised selection bias. Analysis of population demographics showed our study population to be representative of the diabetic population in the community (data not shown). We also took important measures to minimise biases in the interview process as well as the measurement of ABI.

One limitation of our study lies in the fact that for logistic reasons, it was conducted only in government-aided polyclinics, thus leaving out the private general practice clinics, a significant sector of the primary healthcare population. As such, subjects of a higher socio-economic stratum may have been excluded. In turn, this may reduce the external validity of our study, by limiting our ability to extrapolate our results to all patients with diabetes managed under primary health care in the community. Another limitation is that our definition of PAD may have resulted in an underestimation of the true prevalence. Although about 10% of lower limb ulcers in patients with diabetes are due to vascular causes,[30] we used a conservative definition of PAD,

which excluded a history of lower limb ulcers as a criterion. Additionally, ABI may be falsely elevated in patients with diabetes due to calcified, non-compressible vessels, further contributing to some degree of underestimation. Finally, the presence of retinopathy, neuropathy and nephropathy was based solely on the documentation by the managing physicians in the medical notes. We are aware that patients documented to have these complications could be the ones with more severe symptoms. However, since the reviewers of notes were blinded to the information from the patients' ABI readings and hence PAD status, any misclassification would be non-differential and result in an underestimation of the actual association between these diabetic complications and PAD.

Despite these limitations, data from our study show the prevalence rates as similar to those in the West, and has revealed important messages in understanding PAD in patients with diabetes. Understanding and identifying risk factors and associated co-morbidities will help towards targeted screening and therapeutic strategies to prevent PAD and its complications and contribute towards improving overall patient outcomes.

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