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Risk Factors for Asymptomatic Peripheral Artery Disease in Type II Diabetes Mellitus Patients, a Cross-Sectional Study at Tertiary care Hospital

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Authors' contributions

This work was carried out in collaboration among all authors. Author S. Shaikh conceived and designed the study. Authors S. Shaikh, MMA and S. Saifullah acquired, analysed and interpreted the data, drafted and revised the work. Author S. Shaikh read and approved the final manuscript.

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ABSTRACT

Aims: The study was conducted to check the association of risk factors with asymptomatic peripheral artery disease (PAD) in patients with type 2 diabetes mellitus in local population.
Study Design: Cross sectional study.
Place and Duration of Study: Department of Medicine in public sector university from 14th June 2013 to 13th December 2014.
Methodology: Male & female patients with ≥ 35 years of age, having type II diabetes mellitus for ≥ 5 years duration were included in the study. Enrolled patients were evaluated for peripheral artery disease by doing color Doppler study and their Ankle-brachial index was calculated. Ankle-brachial index < 0.9 was criteria for Peripheral arterial disease. Data was analyzed using statistical software SPSS version 21.
Results: Of 385 consecutive patients, 212 (55%) were male and 173 (45%) were female. 134 (34.8%) patients had peripheral artery disease. Mean age of PAD patients was 46.52 ± 8.67 years. The Proportion of males was 64.2% for PAD and 50.2% for Non-PAD patients. Association was

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found between peripheral artery disease and gender (male); OR 1.77 (1.15- 2.73), Age; OR 0.96 (0.93 - 0.99), smoking; OR 6.96 (3.45- 14.03) Hba1C; OR 2.74 (1.83 - 4.13), with significant P-value of 0.01, 0.04, < 0.001 and < 0.001 respectively.

Conclusion: Asymptomatic peripheral artery disease is common in type 2 Diabetic patients particularly those who are aged male, have uncontrolled diabetes, has longer duration and are smokers as well.

Keywords: Asymptomatic peripheral artery disease; type 2 diabetes mellitus; Ankle Brachial Index.

1. INTRODUCTION

Diabetes mellitus is being considered as global epidemic according to International Diabetes Federation (IDF) with current estimates of 463 million people which is likely to reach 700 million by 2045 among those 80% patients live in low and middle income countries [1]. Currently in Pakistan 19.4 million people are suffering from diabetes which is estimated to rise to 37.1 million by 2045 ranking Pakistan the 3rd country unless preventive measures are taken to control the disease [1,2]. Nowadays disability parameters such as Years of life lost (YLL), years of life lived with disability (YLD) and disability adjusted life years (DALY) has been considered as important measures of burden of disease. Currently diabetes rank 19th among the most common conditions causing years of life lost (YLL) surpassing the previous 27th rank [3]. There is tremendous increase in number of amputations due to diabetes by 130.9%, vision loss due to diabetes by 368.6%, rise of chronic kidney disease by 61.5% and diabetic nephropathy by 54.2% [3]. The number of people with diabetes is growing in Pakistan as a result of urbanization, physical inactivity and obesity [4]. Diabetes has a significant impact on health because of its microvascular and macrovascular complications [5]. Macro-vascular complications are due to atherosclerosis of the blood vessels. It clinically manifests as cerebrovascular accident (CVA), coronary artery disease (CAD) and/ or peripheral arterial disease (PAD) [6].

Peripheral Arterial Disease (PAD) defined as the group of disorders that affects any artery other than those which supply the heart [7]. It has been found to be very common in different cultural settings [8]. Screening for PAD is important for two main reasons. First, the majority of patients with PAD are asymptomatic, even in symptomatic patients atypical symptoms are common [9]. Moreover asymptomatic disease can significantly increase the rate of progression to intermittent claudication, which could adversely affect the quality of life [10]. Second, PAD indicates generalized atherosclerosis and thus carries a very high risk for cardiovascular (CV) morbidity and mortality [11].

This is attributed to the fact that most of these patients have CV risk factors [12]. Therefore, diagnosing PAD would be helpful to identify and modify the risk factors to decrease the burden of CV morbidity and mortality [13]. Peripheral artery disease (PAD) is associated with a prevalence of 4 to 12% in the adult population, and it may present up to 20% in the elderly (i.e.>70 years old) [14]. Symptomatic PAD may be observed as frequently as cardiac angina, with an estimated annual incidence of 26/10,000 in the male and 12/10,000 in the female population [15]. Several studies have shown a relationship of age, duration of diabetes, hypertension, smoking, obesity and urine albumin excretion rate with PAD [16]. Diabetes mellitus is especially considered as an important risk factor for PAD. Peripheral arterial disease (PAD) is more than twice as common among diabetic compared with nondiabetic individuals and is a strong predictor of subsequent cardiovascular morbidity and mortality [17]. PAD is four times more prevalent in diabetics than in non-diabetics and can lead to foot ulcers and amputations [18]. Patients with diabetes have unique problems with PAD as the disease appears to affect distal blood vessels and pain is often not prominent due to concomitant neuropathy, and this places them at risk of seeking medical attention only in advanced stages [19]. The role of the ankle/brachial index (ABI) in the detection of asymptomatic PAD, including that in diabetic individuals, is well established [20]. Most epidemiologic and clinical studies have used a noninvasive measurement, the ankle-brachial index (ABI), to diagnose PAD. Ankle brachial index (ABI) is the ratio of systolic blood pressure recorded at ankle arteries to the brachial artery. In clinical practice, an ABI of < 0.9 has been shown to be 95-96% sensitive and 94 – 100% specific in detecting angiogram positive PAD and it takes 10-15 minutes and can be performed in an outpatient department (OPD) or clinic with the

4 – 8 MHz hand-held Doppler and a sphygmomanometer [21]. In diabetics, PAD is commonly under diagnosed and results in increased morbidity complicated by peripheral neuropathy and susceptibility to infection, which leads to foot ulceration, gangrene and amputation of the affected extremity. PAD accounts for half of all amputations among diabetics. To ascertain the prevalence of PAD in different populations, many studies have been performed.

In a recent survey the prevalence of PAD among people with type 2 diabetes was around 20.1% in patients above 40 years of age [22]. In a study by Hittel and Donnelly [23], 15% of patients with diabetes 10 years after the initial diagnosis and in 45% of patients 20 years after diagnosis.

Early identification of high risk T2DM patients, asymptomatic for PAD may guide preventive strategies, as few options exist for established, symptomatic and advanced PAD; moreover it can also indicate the CAD related risk in the patient [24]. There are many studies that have been done on this topic but there is no definite study available in our country, even though burden of diabetes is very high. The rational of this study is to diagnose peripheral artery disease (PAD) at an early stage, so the early intervention will prevent long term morbidity and economic burden.

The purpose of this study was to determine the presence and also to observe the factors influencing the occurrence of asymptomatic peripheral artery disease (PAD) in patients with type 2 diabetes mellitus.

2. METHODS

2.1 Study Design and Population

This cross sectional descriptive study was conducted at Department of Medicine at public sector University from 14th June 2013 to 13th December 2014. 385 consecutive patients of type II diabetes mellitus of either sex having age ≥ 35 years with ≥ 5 years duration of diabetes were included in the study. Patients with Leg ulcers other than diabetic foot ulcer, Type 1 diabetes, Pregnancy, Anemia, Burger's disease were excluded from the study.

The patients fulfilling the inclusion criteria were further evaluated for peripheral artery disease (PAD) by calculating Ankle-brachial index (ABI) by Pulse wave form (PVW) Doppler. Presence of asymptomatic peripheral artery disease (PAD) was confirmed if ankle brachial index was < 0.9 as recommended by American Diabetes Association [25]. The ABI was measured by The Summit Doppler Vantage machine in radiology department of Liaquat University Hospital. Patients' glycosylated hemoglobin (HbA1c) were recorded to confirm diabetes. Patients having HbA_1C ≤ 7.5% were labeled as controlled diabetics and HbA1c > 7.5% labeled as uncontrolled diabetics despite taking medical therapy [26]. All investigations were conducted from Liaquat University Research laboratory.

2.2 Sample Size

Sample size was calculated on the basis of 25% prevalence of asymptomatic peripheral artery disease (PAD) in diabetic patients, with 95% CI and 5% margin error, is reported by the following statistical formula, our sample size came out to be approximately on 385 patients through Raosoft [27].

Formula:

$$n = Z^2 \times p\,(1 - p) / d^2 \text{ where,}$$

n = sample size

(Z1-alpha/2)2 = $(1.96)^2$ (i.e. square of 1.96) this is normal value corresponding 95%, d^2 is the square of the margin of error, p is the proportion of success, (1-p) is the proportion of failure.

2.3 Data Analysis Procedure

Data were entered and analyzed using SPSS version 21.0. Frequency & percentages were calculated for categorical variables. The χ^2-test was used to compare categorical variables. To analyze and compare risk factors between PAD and Non PAD patients, we employed independent t-test for continuous variables and the χ^2-test for categorical variables. Multinomial logistic regression analysis were carried out to determine the association among risk factors and PAD. Mean ± standard deviation was calculated for numerical variables.

3. RESULTS

Of 385 consecutive patients, 212 (55%) were male and 173 (45%) were female. Of total 134 (34.8%) patients had peripheral artery disease confirmed by Ankle Brachial Index (<0.9). Mean age of PAD patients was 46.52 ± 8.67 years. The

Proportion of males was 64.2% for PAD and 50.2% for Non-PAD patients. There was no significant difference in age, BMI and duration of diabetes between PAD and Non-PAD patients. Baseline characteristics are presented in 'Table 1'.

Association was found between peripheral artery disease and gender (male); OR 1.77 (1.15- 2.73), Age; OR 0.96 (0.93 - 0.99), smoking; OR 6.96 (3.45- 14.03) Hba1C; OR 2.74 (1.83 - 4.13), with significant P-value of 0.01, 0.04, < 0.001 and < 0.001 respectively (Table 2). In our study population BMI; OR 1.08 (0.96 - 1.20) and Duration of diabetes OR 1.05 (0.94 - 1.08) affected peripheral artery disease but association was not significant (P-value = 0.19 and P-value = 0.85 respectively), demonstrated: 'Table 2'. Weak association was found between Family history of Diabetes; OR 0.27 (0.12 - 0.59) and Peripheral artery disease with P-value of 0.001. Odds ratios for specific risk factors are depicted as forest plot in Fig. 1.

4. DISCUSSION

In this cross-sectional study asymptomatic peripheral artery disease was observed in 134 (34.5%) patients. A strong relationship was observed between the presence of peripheral artery disease and sex, age, control of diabetes, duration of diabetes and smoking.

Table 1. Baseline characteristics of the patients (N=385)

Variables		PAD patients (N=134)	Non-PAD patients (N=251)	P-Value [a]
Gender	Male	86 (64.2%)	126 (50.2%)	0.01‡
	Female	48 (35.8%)	125 (49.8%)	
Age (years)		46.52 ± 8.67	46.55 ± 8.52	0.97
Smokers N (%)		80 (59.7%)	44 (17.5%)	<0.001 [b]
Family History of Diabetes N (%)		90 (67.2%)	230 (91.6%)	<0.001 [b]
BMI (kg/m^2)		27.22 ± 5.08	27.16 ± 5.57	0.92
Duration of Diabetes (years)		14.27 ± 6.43	13.86 ± 5.76	0.53
Hba1C (%)		14.02 ± 6.09	12.45 ± 5.58	0.01

PAD= Peripheral Arterial Disease.
a Independent T-test for numerical variables, α = 0.05.
b Chi-square for Categorical Variables, α = 0.05

Table 2. Association of factors with peripheral arterial disease (N=385)

Variables	PAD Patients (N=134)	Non-PAD Patients (N=251)	OR, PAD Vs No PAD (95% CI)	P-Value [a]
Gender, male (%)	86 (64.2%)	126 (50.2%)	1.77 (1.15- 2.73)	0.01
Age (years)	46.52 ± 8.67	46.55 ± 8.52	0.96 (0.93 - 0.99)	0.046
Smoking, N (%)	80 (59.7%)	44 (17.5%)	6.96 (3.45 - 14.03)	<0.001
BMI (kg/m^2)	27.22 ± 5.08	27.16 ± 5.57	1.08 (0.96 - 1.20)	0.19
Normal (< 25)	45 (33.6%)	80 (31.9%)	___	__
Overweight (>25)	48 (35.8%)	91 (36.3%)	0.47 (0.18 - 1.24)	0.13
Obese (>30)	41 (30.6%)	80 (31.9%)	0.34 (0.07 - 1.43)	0.14
HbA1c (%)	14.02 ± 6.09	13.86 ± 5.76	2.74 (1.82 - 4.13)	<0.001
Duration of Diabetes (years)	14.27 ± 6.43	13.86 ± 5.76	1.05 (0.94 - 1.08)	0.85
Family History of Diabetes N (%)	90 (67.2%)	230 (91.6%)	0.27 (0.12 - 0.59)	0.001

PAD= Peripheral Arterial Disease (Ankle Brachial Index < 0.9). OR= Odds Ratio. CI= Confidence Interval
a Multinomial logistic regression analysis, at 95% confidence interval

Factors	PAD Patients (N=134)	Non-PAD Patients (N=251)	P-Value*
Gender, male (%)	86 (64.2%)	126 (50.2%)	0.01
Age (years)	46.52 ± 8.67	46.55 ± 8.52	0.046
Smoking, N (%)	80 (59.7%)	44 (17.5%)	<0.001
HbA1c (%)	14.02 ± 6.09	13.86 ± 5.76	<0.001
BMI (kg/m^2)	27.22 ± 5.08	27.16 ± 5.57	0.19
Duration of Diabetes (years)	14.27 ± 6.43	13.86 ± 5.76	0.85

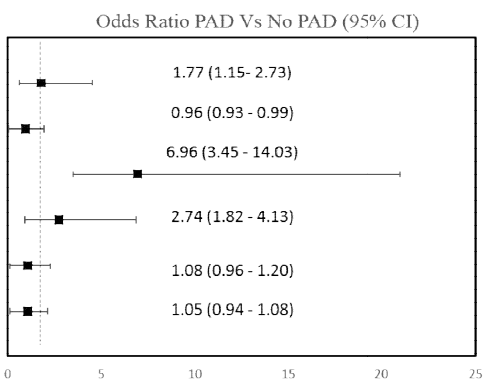

Fig. 1. Forest plot, risk factors odds ratios for peripheral artery disease
ORs and statistical P-value was calculated using Multinomial Logistic Regression Analysis

Our result is comparably higher than previously reported study by Maeda et al. [28] that depicted peripheral artery disease in 17.7% of study population. The higher number of PAD patients in our study was due to the fact that we enrolled patients with asymptomatic PAD in contrast to other studies which included symptomatic PAD. In our study, PAD was confirmed by using ankle brachial index [29]. A strong relationship was observed between the presence of peripheral artery disease and gender (male) in our study population i.e. also evident from published study that depicted non-significant higher prevalence of PAD in male patients [30]. Selvin et al. did not find clear sex-related differences in PAD prevalence in their research with 2,174 participants aged 40 years and older from the 1999–2000 National Health and Nutritional Survey [31]. In a large population-based study of PAD the GetABI research, the prevalence of both symptomatic and asymptomatic PAD was higher among female > 85 years of age [32]. The reasons for more prevalent limb ischemia in female was presumed to be due to higher number of female compared to men with hypercholesterolemia (88.2% vs 73).

Age is also found to be risk factor for peripheral artery disease in our study, specifically age more than 40 years is considered as important risk factor risk factor for PAD in previously reported studies as well [31].

In our study 59.7% of diabetic patients were smokers which is also found to be the important risk factor for PAD with significant P-value of <0.001. In the Framingham Heart Study cigarette smoking was found to have 1.4 fold increase in risk for PAD [15].

In one published study, uncontrolled diabetes (Hba1C > 7.5%) developed intermittent claudication and hospitalization for PAD more than five times compared to individuals with good glycemic control (HbA1c 6%) that is also evident in our study as Hba1C is significantly associated with peripheral artery disease [33]. In one meta-analysis poorly glycemic control in type 2 diabetes mellitus patients increased the relative risk of peripheral artery disease by 1.28 (CI,1.18 to 1.39) [34].

Obesity is one of the major risk factor for PAD, which seems to be contrary as obesity is not associated with peripheral artery disease in our study population [35]. This might be because of 'The Obesity Paradox' as usually overweight & obese patients get guideline recommended therapy, leading to lower or weak association of obesity with PAD in this study [36].

In this study, duration of diabetes has affected PAD with strong association that is evident from the published study in which duration of type 2 diabetes was strongly associated with the risk of developing peripheral arterial disease [37].

5. LIMITATION

This is a cross-sectional study. A prospective cohort study would have been a good option in order to determine whether asymptomatic PAD is associated with higher rates of limb amputation or critical limb ischemia.

6. CONCLUSION

Asymptomatic peripheral artery disease is common in type 2 Diabetic patients particularly those who are aged male, have uncontrolled diabetes, has longer duration and are smokers as well. PAD is a marker of coronary artery disease and those who suffer from it has poor quality of life. Diagnosing PAD is important as early as possible because it can progress to critical limb ischemia ultimately leading to amputation of affected limb.

ETHICAL APPROVAL AND CONSENT

As per international standard or university standard written ethical approval has been collected and preserved by the author(s). Written informed consent was obtained from each patient.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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