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Study of Peripheral Arterial Disease in Type 2 Diabetes Mellitus Using Ankle-Brachial Pressure Index and Its Correlation with Glycemic Control and Duration of Diabetes

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Abstract

Introduction: Peripheral arterial disease (PAD) is a macro vascular complication of diabetes mellitus. PAD is linked strongly and apparently independently with cardio-vascular morbidity and mortality.

Objectives: To detect the burden of PAD in type 2 Diabetes patients using ABI and to find out its correlation with glycemic control as well as duration of Diabetes Mellitus.

Methodology: This study was conducted on 300, type 2 DM patients from age group of 30-70 years, with diabetes for a minimum period of 5 years. All patients were screened for PAD by Vascular Doppler instrument using ankle brachial index (ABI). Patients with ABI<0.9 are subjected to color doppler to confirm presence of PAD. Blood investigations like Fasting, Post-Prandial blood glucose and Glycated hemoglobin (HbA1c) were also done. Data was analysed by statistical package SPSS Version 20 using appropriate tests.

Results: Prevalence of PAD in diabetes of 5 years duration is 22.6%. Prevalence increases with age and duration of diabetes. There is no difference in males and females. Possibility of PAD increases with BMI. More than half of patients of PAD are asymptomatic (55%). Claudication is the most common symptom of PAD (44%). Increased systolic pressure is associated with PAD. Micro and macro vascular complications are more commonly seen with PAD in diabetic patients.

Albuminuria is more commonly seen with PAD in diabetic patients. Sensitivity and specificity of ABI to diagnose PAD is 89%and 94% respectively. Chronic hyperglycemia (HbA1C) is associated with higher prevalence of PAD. ABI correlates significantly with duration of diabetes, systolic hypertension, LDL cholesterol, age and BMI, post prandial blood sugar level and HbA1C.

Conclusion: Prevalence of peripheral arterial disease in diabetes mellitus is associated with duration of diabetes, age, body mass index, systolic hypertension, Low density lipoprotein and chronic hyperglycemia (HbA1C). It can be easily and reliably diagnosed using ankle brachial index (less than 0.9) which will help for early detection and management.

Keywords: Type 2 Diabetes Mellitus, Peripheral Arterial Disease, Ankle-Brachial Pressure Index, Glycemic Control, Duration of Diabetes.

Introduction

Diabetes mellitus can be defined as a state of chronic hyperglycemia sufficient to cause long-term damage to specific tissues, notably the retina, kidney, nerves, and arteries [(1)]. Today, worldwide, we have 9.3% of adults aged 20–79 years a staggering 463 million people – are living with diabetes & 1.1 million children and adolescents under the age of 20, live with type 1 diabetes[(2)]. Diabetes related complications affect many organs systems and are responsible for the majority of morbidity and mortality associated with the disease. Peripheral arterial disease (PAD) is a macrovascular complication. Cardiovascular disease is the major cause of morbidity and mortality for individuals with diabetes, and the largest contributor to the direct and indirect costs of diabetes [(3)].

PAD is linked strongly and apparently independently with CVD morbidity and mortality; perhaps more strongly than prior myocardial infarction (MI). But PAD is less emphasized and less systematically evaluated than other atherosclerotic conditions or risk factors such as Hyperlipidemia and HTN [(4)]. PAD is a progressive disorder characterized by stenosis and/or occlusion of large and medium-sized arteries, other than those that supply the heart (coronary artery disease, CAD) or the brain (cerebrovascular disease). There was a 36% prevalence of PAD among DM patients in India [(5)].

The treatment of patients with PAD can therefore be expensive, owing to need for a variety of diagnostic tests, therapeutic procedures, and hospitalizations[(6)]. Detection of asymptomatic PAD can reduce morbidity and financial loss due to PAD. It has additional value because it identifies patients at increased risk of atherosclerosis at other sites and most importantly coronary artery disease (CAD). Ankle Brachial pressure Index (ABI) is simple to perform, non-invasive, quantitative measurement of the patency of lower extremity arterial system. It is very convenient to use in routine OPD visits of diabetic patients. However, its reliability is not studied to great extent in Indian population [(7)].

Age, duration of diabetes, peripheral neuropathy, severity and duration of DM are important predictors of PAD. However very few studies have been conducted in Indian diabetic patients to find out the effect of duration and glycemic control on incidence and severity of PAD. Hence, we have conducted this study to detect the burden of PAD in type 2 Diabetes patients using ABI and to find out its correlation with glycemic control as well as duration of Diabetes Mellitus.

Materials and Methods

The present cross-sectional study was conducted on total 300, type 2 diabetes mellitus patients with minimum 5 years duration of diabetes are selected from tertiary care hospital, over a period of 18 months. Case of Diabetes Mellitus was defined as any Patient within age group of 30-70 years, independent of sex, with history of Type 2 diabetes for a minimum period of 5 years duration.

Patients with in age group of 30-70 years, independent of sex, with history of Type 2 diabetes for a minimum period of 5 years duration were included. Patients with conditions which may interfere with measurement of ankle brachial index like limb trauma, surgery or amputation, ulcers, deep vein thrombosis, filariasis or lower limb swelling were excluded. Patients with history of smoking, gestational diabetes mellitus, chronic kidney diseases or patients on vasodilators or vasoconstrictors were excluded.

All the Type 2 diabetic patients are screened by Vascular Doppler instrument, for peripheral arterial disease using ankle brachial index. Patients with ankle brachial index <0.9 are subjected to color doppler of both lower limbs to confirm presence of peripheral arterial disease. Investigations performed include Fasting and/or Post-Prandial blood glucose and/or Glycated hemoglobin (HbA1c).

Data was analysed by statistical package SPSS Version 20. All the continuous variables are presented as mean ± standard deviation (SD). The qualitative data is presented as proportion or ratios. The correlation is evaluated using correlation coefficient. Rest of the results are presented using descriptive statistics.

Ethical Issues

Permission to conduct this study was obtained from the Institutional ethics committee as this study does not deviate from standard treatment, practice or involve only collection and analysis of data.

Results

Out of total 300 patients were included in the study in which, 68 had PAD. Therefore, prevalence of PAD in the study population was 22.6%.

Comparison of Demographic Characteristics of between patients with and without PAD:

Mean age of study population was 53.3 years. Mean age in PAD group was 61.6 years while in non-PAD group was 50.8 years. In age group wise distribution, PAD was not seen in age below 50 years. In 50 to 60 years group, it was seen in 16% and above 60 it was 65%.

Table 1: Comparison of Demographic Characteristics of between patients with and without PAD

Demographic Characteristics	PAD (n=68)	No PAD (n=232)	Total
Mean Age (Years)	61.68	50.85	53.3
Gender Males (%)	38	146	184
Females (%)	30	86	116
Duration (Years)	20.36	9.28	11.8
Weight (Kg)	67.47	61.23	62.65
Height (cm)	163.16	162.98	163.02
BMI (Kg/m^2)	25.28	22.99	23.51

Table 2: Clinico-demographic Factors associated with PAD

Clinico-demographic Factors		PAD	No PAD	Total	Chi Square and p value
Age Group (years)	30-39	0(0%)	10(100%)	10(100%)	105.1, 0.001
	40-49	0(0%)	86(100%)	86(100%)	
	50-59	22(16.4%)	112(83.6%)	134(100%)	
	60-70	46(65.7%)	24(34.3%)	70(100%)	
Gender	Male	38(20.7%)	146(79.3%)	184(100%)	1.102, 0.294
	Female	30(25.9%)	86(74.1%)	116(100%)	
Duration of Diabetes (Years)	Up to 10	0(0%)	168(100%)	168(100%)	204.11, 0.001
	11-15	9(14.5%)	53(85.5%)	62(100%)	
	16-20	27(79.4%)	7(20.6%)	34(100%)	
	> 20	32(88.9%)	4(11.1%)	36(100%)	
Body Mass Index	Below 24	16(8.4%)	175(91.6%)	191(100%)	61.23, 0.001
	Above 24	52(47.7%)	57(52.3%)	109(100%)	
Claudication Grade	Grade 0	38(14.1%)	232(85.9%)	270(100%)	113.7, 0.001
	Grade 1	9(100%)	0(0%)	9(100%)	
	Grade 2	8(100%)	0(0%)	8(100%)	
	Grade 3	13(100%)	0(0%)	13(100%)	
Systolic Blood Pressure	< 140	7 (4.4%)	152(85.6%)	159(100%)	85.033, 0.001
	140-159	32 (31.4%)	70(68.6%)	102(100%)	
	160-180	29 (74.4%)	10(25.6%)	39(100%)	
Total		68(22.7%)	232(77.3%)	300(100%)	

Age distribution of PAD showed significant difference between the groups (p=0.001). 184 males and 116 females were included; out of which 20.6% males and 25.8% females had PAD on doppler test. The difference in prevalence between males and females was not statistically significant (p=0.294).

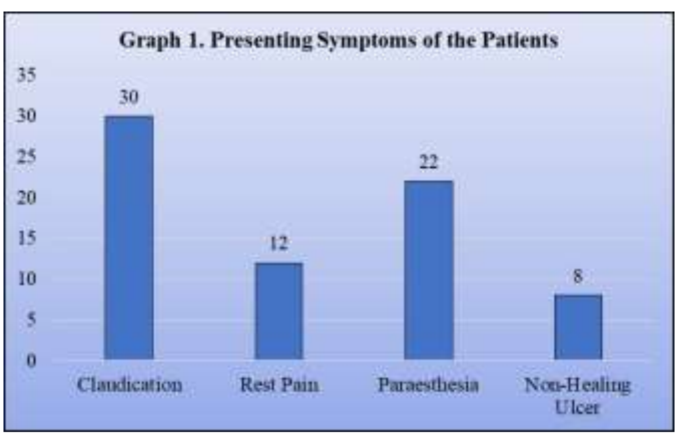
Duration of diabetes was grouped as per the table below. We observed that, as duration increased, the prevalence of PAD also increased. In less than 10 years of diabetes, PAD was 0% while above 20 years duration it was 88% (32 of 36). Body mass index (below 24 and above 24) was compared for the prevalence. PAD was more common in above 24-year group (47.7%) as compared to below 24 group (8.3%). The effect of BMI on PAD was statistically significant (p=0.001).

Claudication was graded from 0 to 3 in which asymptomatic patients were considered grade 0. Presence of claudication indicated PAD. However, 14% of patients without claudication (grade 0) were diagnosed with PAD. Therefore, in total PAD cases, 38 had no symptoms (55.8%).

Systolic pressure was grouped as <140, 140-159 and 160 and above. Prevalence was more in the third group (74%). Blood pressure group vs PAD showed significant p value on chi square test.

Presenting Symptoms of the Patients

Graph 1:



Claudication was most common symptom present in 44.12%. Other symptoms were rest pain, paresthesia and non-healing ulcer.

Table 3: Claudication & ABI Category

Claudication Grades	ABI (0.6-0.79)	ABI (0.8-0.90)	ABI (0.91-onwards)	Total	Chi Square and p value
Grade 0	0(0%)	23(8.5%)	247(91.5%)	270(100%)	311.09, 0.001
Grade 1	3(33.3%)	6(66.7%)	0(0%)	9(100%)	
Grade 2	8(100%)	0(0%)	0(0%)	8(100%)	
Grade 3	13(100%)	0(0%)	0(0%)	13(100%)	
Total	24(8%)	29(9.7%)	247(82.3%)	300(100%)	

Claudication grades were compared with the grades of ankle brachial index (ABI). All the patients with ABI above 0.91 had no symptoms (grade 0). While 13 out of 24 patients with ABI between 0.6 to 0.79 had grade 3 claudication (54.1%). The claudication grades vs ABI category showed significant difference in chi square test (p=0.001).

Table 4: Comparison of Mean SBP, DBP, Ankle Pressure and ABI in patients with and without PAD

Mean SBP, DBP, Ankle Pressure, ABI	PAD	No PAD	Total	P value
Mean SBP (mm of Hg)	156.71	134.09	139.22	0.001
Mean DBP (mm of Hg)	76.65	77.92	77.86	0.853
Mean Ankle Pressure (mm of Hg)	130.5	140.6	138.3	0.001
ABI	0.84	1.052	1.0	0.001

Mean Systolic pressure was higher in PAD patients but diastolic pressure was almost equal. As expected, mean ankle pressure and ABI was lower in PAD patients that non-PAD patients. The difference in systolic pressure, ankle pressure and ABI was significant between the two groups (p=0.001).

Table 5: Crosstab of ABI Vs Doppler

Clinical Diagnosis	Doppler		Total
	PAD	No PAD	
Yes (ABI < 0.9)	61(81.3%)	14(18.7%)	75(100%)
No (ABI> 0.9)	7(3.1%)	218(96.9%)	225(100%)
Total	68(22.7%)	232(77.3%)	300(100%)

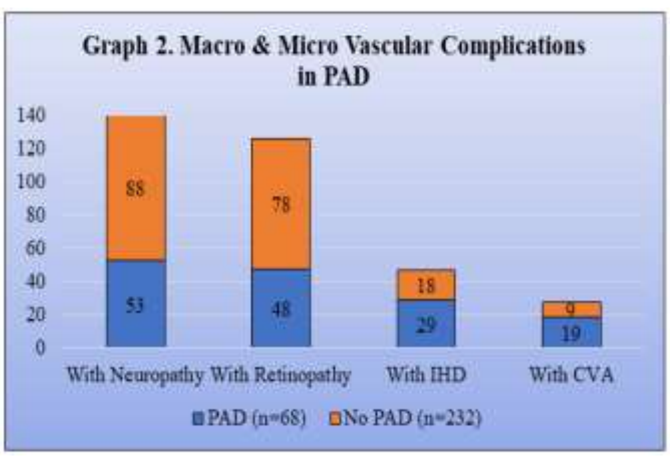
Clinical diagnosis using ABI was compared with the gold standard test of doppler. ABI less than 0.9 was considered positive. Using the cross tab in the above table we could calculate the performance of the ABI test. Sensitivity was 89.7 and specificity 94% using above cut off value of ABI with Positive Predictive Value 81.3% and Negative Predictive Value 96.9%.

Table 6: Glycemic Control in Study Population

Glycemic Control Parameters		PAD	No PAD	Total	P value
F Blood Sugar (mg/dL)		114.12	114.42	114.35	0.920
PP Blood Sugar (mg/dL)		187.15	182.63	183.65	0.239
HbA1C (%)		9.76	7.13	7.72	0.001
HbA1C (%)	< 7 (Good)	6(5.2%)	110(94.8%)	116(100%)	0.001
	7-10 (Fair)	37(24.1%)	117(75.9%)	154(100%)	
	> 10 (Poor)	25(83.3%)	5(16.7%)	30(100%)	

Fasting and post prandial blood sugars were almost similar in two groups. HbA1C value was greater in PAD group. When compared using ANOVA, HbA1C was significantly more in PAD group. Only 5% PAD patients had HbA1C less than 7. The same percentage was 24 and 83 in 7-10 and > 10 group respectively. Therefore, good glycemic control favored less PAD. The difference was significant suggesting effect of long-term glycemic control on PAD.

Graph 2: Macro & Micro Vascular Complications in PAD:



We have studied prevalence of microvascular (neuropathy, retinopathy) and macrovascular (Ischemic Heart Disease, Cerebro Vascular Accidents) complications. All complications were more prevalent in PAD group. Neuropathy was most common amongst all. The difference in prevalence between the two groups was significant for all the complications (p=0.001).

Table 7: Hematological and Biochemical Parameters & PAD:

Haematological and Biochemical Parameters		PAD	No PAD	Total	p value
Hb (g/dl)		12.99	12.96	12.97	0.812
WBC (/cmm)		7373.9	7571.7	7486.3	0.453
PLT (*1000/cmm)		304.25	298.93	301.41	0.659
Total Cholesterol		227.37	226.34	226.91	0.840
Triglyceride		188.07	184.72	185.72	0.544
LDL		136.13	129.20	132.29	0.035
HDL		47.07	47.21	47.18	0.890
Serum Creatinine		1.50	1.48	1.48	0.758
Urine albumin to creatinine ratio (ACR) (mg/g)	<30 (Normal)	6(3.4%)	169(96.6%)	175(100%)	90.56, 0.001
	30-300 (Microalbuminuria)	48(52.7%)	43(47.3%)	91(100%)	
	>300 (Macroalbuminuria)	14(41.2%)	20(58.8%)	34(100%)	
Total		68(22.7%)	232(77.3%)	300(100%)	

Hematological parameters did not show any significant p value on comparison between PAD vs non- PAD. LDL mean was significantly greater in PAD group as compared to non-PAD group. Other biochemical parameters did not show any significant p value on comparison between the two groups.

Urine albumin to creatinine ratio was tested using strips. Micro and macro albuminuria was present in 91 and 34 patients respectively. In PAD normal, micro and macro levels of ACR were seen in 8.8%, 70.5% and 20.5% respectively. Prevalence of albuminuria was significantly different between the two groups (p=0.001).

Table 8: Correlation between ABI and clinical and biochemical parameters (parameters affecting ABI)

Parameter	Value	Significance
Age	0.440	0.001
BMI	0.391	0.001
Creatinine	0.051	0.378
HbA1C	0.553	0.001
Duration of Diabetes	0.560	0.001
SBP	0.625	0.001
FBS	0.055	0.343
PPBS	0.116	0.046
Total Cholesterol	0.067	0.245
Triglycerides	0.038	0.513
LDL	0.125	0.03
HDL	0.002	0.975

In order to find out the parameters affecting ABI, we have done correlation test for clinical and laboratory parameters. HbA1C, post prandial (PP) sugar, LDL, duration of diabetes and systolic blood pressure were significantly corelated with ABI as shown in the following table. Fasting sugar, triglycerides, cholesterol and creatinine were not correlated.

Discussion

In the study out of 300 patients, 68 patients had PAD and 232 were free of PAD. Prevalence of PAD was 22.6%. Diabetes is a most important risk factor for PAD as seen in many studies till now. Al-Delaimy WK noticed relative risk of 2.61 in diabetic patients for PAD development[(8)]. Beks PJ et al observed prevalence of PAD as 41.8% in diabetic patients[(9)]. Investigators have found different prevalence which can be explained by different sample size, ethnic groups and unidentified confounding factors.

Mean age of study population, PAD and non-PAD groups were 53.3, 61.6 years and 50.8 years respectively. PAD was seen in older age group as it was found to be related to duration of diabetes. PAD was not seen below 50 years in our study. Prevalence increased as age increased. The correlation was significant (p=0.001).

Mean age in most of the studies is about 50 to 60 years which is matching with our study. Meta- analysis by Fowkes et al showed increasing prevalence of PAD with age[(10)]. Adler AI et al also observed age as a risk factor for PAD in diabetic patients[(11)].

Males and females having PAD were about 20% and 25% in the study population. PAD was not significantly related to gender distribution (p=0.294). Fowekes et al with very large sample size in their study also noted that there is no sex specific difference in PAD[(10)]. However, some investigators like Yonas et al have observed significant preponderance of male patients in prevalence of PAD[(12)] .

Duration of diabetes had significant impact on the prevalence (p=0.001). As duration increased from 0 to 20 years and above, the percentage of patients diagnosed with PAD increased from 0 to 88%. Most of the investigators have similar findings in their study. In a cohort study by Al-Delaimy WK, the relative risk of PAD in diabetics was as follows- 1.39 (95% CI: 0.82 to 2.36) for 1 to 5 years of diabetes, 3.63 (95% CI: 2.23 to 5.88) for 6 to 10 years, 2.55 (95% CI: 1.50 to 4.32) for 11 to 25 years, and 4.53 (95% CI: 2.39 to 8.58) for >25 years of diabetes (P for trend < or =0.0001). Hence, they concluded that the duration of type 2 diabetes is associated strongly with the risk of developing peripheral arterial disease [(8)].

Obese patients with BMI more than 24 were also found to be prone for PAD than those with BMI less than 24 (p=0.001). A study by Hicks et al has revealed that a higher body mass index (BMI), increases the risk of developing PAD [13]. Some research has indicated that obesity may cause an inflammatory response in the body. The resulting inflammation may be the cause of PAD in obesity. Most pf the investigators have noted effect of obesity on PAD but Yonas et al did not find it significant [12]. Small sample size (278) or inclusion of one particular ethnic group could be the reason for this descripancy.

Claudication was most common symptom (44%). However, even in PAD cases, 55% patients were asymptomatic. Those having claudication grade 1 to 3 were found to have ankle brachial index (ABI) less than 0.9. Lower ABI was related to severe grades of claudication (p=0.001). In one study, asymptomatic PAD was found to be 33% [14]. However, in this study only ABI was used to diagnosed PAD and not doppler study.

Mean systolic pressure (brachial) was greater while ankle pressure and ABI was lesser in PAD patients (p=0.001). Diastolic pressures were similar in the two groups (p=0.853). We also noticed that poor the systolic pressure control, more is the prevalence of PAD (0.001). In a study by Fowkes FG et al, they observed hypertension as a risk factor for development of PAD with odds ratio 1.36 to 1.55[10].

Adler AI et al have concluded in their prospective study of diabetes that, 10 mm rise in systolic blood pressure is associated with 25% increased risk of PAD[11]. Micro and macro vascular complications of diabetes were more commonly seen in PAD patients than in patients without PAD (p=0.001). Neuropathy was most common and CVA was least common amongst them. Neuropathy and retinopathy are known risk factors for PAD[11].

Complete blood count, creatinine and lipid profile were not significantly different between the two groups (p>0.05) except LDL level (p=0.035). Some investigators have observed increased risk of PAD in hypercholesterolemia with odds ratio 1.14 to 1.19[10].

In PAD group, about 70% had micro and 20% had macroalbuminuria. The percentage in non-PAD group was 18 and 8 respectively. The obvious difference seen was statistically significant (p=0.001). The cross-sectional association between albuminuria and PAD in diabetic and nondiabetic subjects was assessed in a multi-ethnic study by K Wattanakit. They noted that among diabetic subjects, those with albuminuria (micro and macroalbuminuria combined) were 1.90 times more likely to have PAD; therefore, the presence but not magnitude of albuminuria is a risk factor for PAD in diabetic patients[15].

Performance of ABI was confirmed by doppler test. Sensitivity and specificity of ABI was 89 and 94% with cut off value 0.9. In PARTNERS study, most clinicians believed that the ABI was useful in the diagnosis and management of both symptomatic (96%) and asymptomatic (89%) peripheral arterial disease[16]. Nearly all (88%) clinicians believed that it was feasible to incorporate ABI into daily practice. Overall, most clinicians (57-75%) believed that ABI was equal to, or more useful, than other widely available and reimbursed screening tests in preserving their patients' health. The study concluded that, the ABI is a simple peripheral arterial disease detection tool that can be successfully applied in primary care office practices. Beks PJ et al in their study observed 20.9% of diabetic patients with ABI less than 0.9 while actual prevalence of PAD was 41.8%[9].

Various investigators have found sensitivity of ABI 70 to 90% and specificity from 80-99% as shown in the above table. They all have taken 0.9 as cut off value. However, they have compared it with angiography reports as gold standard.

Fasting sugars had no significant effect on prevalence (p>0.05). HbA1C which is considered the indicator of long-term glycemic control, was significantly higher in PAD group (p=0.001). Poor the long-term glycemic control, more was the prevalence of PAD. Similar findings were also noted by Adler AI et al in their prospective diabetes study and it was independent of other risk factors[11]. In the same study they observed that 1% rise in HbA1C is associated with 28% increase in risk of peripheral vascular disease. In one meta-analysis, chronic hyperglycemia (raised HbA1C) was related to macrovascular complications with relative risk of 1.8[17]. However, Beks PJ et al observed HbA1C as well as fasting and post prandial sugar significantly associated with PAD[9]. Correlation of age, BMI, HbA1C, duration of diabetes and systolic BP post prandial sugar and LDL was significant with ankle brachial index in our study. The similar observations are noted in other studies[8,10,11].

Conclusion

Prevalence of peripheral arterial disease in diabetes mellitus is associated with duration of diabetes, age, body mass index, systolic hypertension, Low density lipoprotein and chronic hyperglycemia (HbA1C). It can be easily and reliably diagnosed using ankle brachial index (less than 0.9) which will help for early detection and management.

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