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Original Research Article

Study of Peripheral Arterial Disease in Type 2 Diabetes Mellitus and its Correlation to Poor Glycemic Control

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Abstract

Aim: The aim of the present study was to assess the correlation between peripheral arterial disease (PAD) and poor glycemic control in type 2 diabetes mellitus patients.

Methods: The Cross sectional analytical study was conducted at General Medicine Department, Central Hospital, South Eastern Railway, Garden Reach, Kolkata for the period of 2 years. Type 2 Diabetic 100 patients including both male and female attending the OPD and indoor wards of General Medicine Department/Endocrinology OPD/Cardiology OPD, Central Hospital, South Eastern Railways, Garden Reach, Kolkata, were included in the study.

Results: Majority of the patients with peripheral arterial disease had age between 61-70 years (47%) followed by 51-60 years (37.0%). There were 5% patients who had age between 41-50 years whereas another 11% patients were older than 70 years. Majority of the patients with peripheral arterial disease were males (60%) compared to 40% females. Majority of the patients with peripheral arterial disease had a duration of disease between 1-5 years (48%) followed by 40% patients who had diabetes since 6-10 years(9%) where as 3% patients had diabetes for more than 15 years.

Conclusion: So it can be concluded that strict glycemic control as monitored by HbA1c levels along with control of hypertension, dyslipidemia and dietary modifications are necessary in patients with Diabetes Mellitus to prevent development of macrovascular complications like Peripheral Arterial Disease.

Keywords: Peripheral arterial disease, Diabetes mellitus, glycemic control

Introduction

Peripheral arterial disease (PAD) is a chronic complication of diabetes mellitus (DM) and a risk factor for foot ulceration and amputation- more than two-thirds of patients with diabetic foot ulceration had associated PAD. [1] This arthero – occlusive disease of the extremities does increase the risk of coronary artery disease as well. [2,3] Although PAD occurs in non- diabetic patients, it is up to four times more common in patients with DM. [4] Symptoms such as intermittent

claudication and calf pain at rest suggest PAD but in DM, these symptoms may be obscured by the concomitant presence of peripheral neuropathy. [5]

The prevalence of PAD differs depending on the modality used. [6] Studies have used the presence of symptoms, the absence of peripheral pulses in the extremities and more recently, ankle brachial index (ABI) to assess determined by ABI varies from 9 to 20% [3,7,8] in Western countries and from 3.2–24.1% [9–12] in Asia. People with diabetes are 2-3 times more likely to die from any cause. [13] Additionally, despite improvements in public health promotion and life expectancy increases, diabetes still has the second-largest negative overall influence on lowering global health adjusted life expectancy globally. [14]

Diabetes is a chronic condition that worsens with time. These major complications raise expenses for the family, the community, and the healthcare system. Uncontrolled diabetes raises the risk of vascular disease. Diabetes is a disease that is strongly associated with both microvascular and macrovascular complications; including retinopathy, nephropathy, and neuropathy (microvascular) and ischemic heart disease, peripheral vascular disease, and cerebrovascular disease (macrovascular), resulting in organ and tissue damage. [13]

Lower extremity atherosclerotic occlusive disease is known as peripheral artery disease (PAD). The risk of lower extremity amputation is enhanced by PAD, which is also a marker for atherothrombosis in the cardiovascular, cerebral, and renovascular systems. Therefore, patients with PAD has a six to seven times higher risk of coronary artery disease, heart attack, stroke or a transient ischemic attack (mini-stroke) than the general population. [15] Furthermore, PAD significantly impairs patients with diabetes over the long run. [16]

Glycemic control has been shown to be more significantly related with microvascular disease than macrovascular disease in persons with type 1 and type2 diabetes, respectively, in the Diabetes Control and Complications Trial and U.K. Prospective Diabetes Study trials. It's possible that atherosclerosis in larger arteries is less responsive to chronically increased glucose levels than pathologic alterations in smaller vessels. The presence of microvascular components in some cardiovascular (large vessel) outcomes has also been proposed. [17] Although, the link between chronic hyperglycemia and the development of atherosclerosis and subsequent macrovascular events, such as PAD, in people with diabetes is debatable. Diabetes patients' HbA1c (A1c), a marker of long-term glycemic control, is monitored and used to direct clinical care. A1C measurements of chronic hyperglycemia are a recognized risk factor for diabetes-related microvascular disease. [18]

The aim of the present study was to assess the correlation between peripheral arterial disease (PAD) and poor glycemic control in type 2 diabetes mellitus patients.

Materials and Methods

The Cross-sectional analytical study was conducted at General Medicine Department, Central Hospital, South Eastern Railway, Garden Reach, Kolkata for the period of 2 years. Type 2 Diabetic 100 patients including both male and female attending the OPD and indoor wards of General Medicine Department/Endocrinology OPD/Cardiology OPD, Central Hospital, South Eastern Railways, Garden Reach, Kolkata, were included in the study.

Inclusion criteria

Case of Type 2 Diabetes Mellitus with clinically suspected peripheral arterial disease

Exclusion criteria

1. Patients with Type 1 DM
2. Age below 18 years of population
3. Non-willing to provide written informed consent

All the study participants underwent detailed history, clinical examination and laboratory investigations and vascular imaging including ABI and Arterial Color Doppler Study using proforma designed for this study. Proper informed consent from the patient was taken prior to including them in study. Patient were informed about the need for minimal investigation at his/her own cost and then only he/she was included in the study, with proper consent form. Colour Doppler was done and ABI was measured as a part of routine investigation and no extra cost was incurred. Institutional Ethics Committee approval was obtained before starting the study.

Methodology

Type 2 Diabetic patients including both male and female attending the OPD and indoor wards of General Medicine Department/Endocrinology OPD/Cardiology OPD, Central Hospital, South Eastern Railways, Garden Reach, Kolkata were chosen.

Biochemical parameters were measured by obtaining venous blood samples from all patients under aseptic precautions after at least 10-12 hours of overnight fasting and 2 hours post prandial. The collected blood samples were centrifuged at 4000 rpm for 15 mins in a centrifuge machine to separate plasma / serum on the same day of sample collection. After this the sugars and lipid profile were analyzed on the biochemical analyser Beckman Coulter .Whole-blood samples from patients were thawed and assayed for A1C using high-performance liquid chromatography instrument.

Coloured Doppler study of 4 lower limb arteries were done (femoral, popliteal, posterior tibial, dorsalis pedis using a 5-10 MHz linear array transducer. Various transducer positions used were lateral, postero-lateral, anterior and transverse. Transducer frequency of 10MHz was used for superficial arteries like superficial femoral artery, whereas 5 MHz frequency was required for deeper arteries e.g., tibio-peroneal arteries. Scanning of lower limb arteries was performed in supine position using a linear array transducer placed directly over the vessel at an angle of incidence of 45 to 60 degrees. Arteries were examined from cephalad to caudal position first for any localization of plaque deposition and their surface & internal characteristics. For intimal medial thickness maximum measurements were taken at the level of the straight segment of the femoral artery. The Maximum intima media thickness (and not the mean) was taken into consideration. Raised lesion and plaques were excluded while calculating the maximum intima media thickness. Peak systolic velocities were measured and degree of post stenotic flow disturbances.

Statistical analysis

Categorical variables will be expressed as Number of patients and percentage of patients and compared, if required, using Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test as appropriate. Continuous variables will be expressed as Mean ± Standard Deviation and compared using unpaired t test/One Way ANOVA if the data follows normal distribution or Median and Inter-quartile Range and compared using Mann-Whitney U test/Kruskal Wallis Test if the data does not follow normal distribution. Association between continuous variables will be captured by Pearson's Correlation Coefficient, if the data follows normal distribution or Spearman's Rank Correlation Coefficient if the data does not follow normal distribution. The statistical software SPSS version 22 will be used for the analysis.

Results

Table 1: Patient Characteristics

Variables	% Age
Age groups (Years)	
41-50	5.0
51-60	37.0
61-70	47.0
71-80	11.0
Sex	
Female	40.0
Male	60.0
Diabetes duration (years)	
1-5	48.0
6-10	40.0
11-15	9.0
16-20	3.0

Majority of the patients with peripheral arterial disease had age between 61-70 years (47%) followed by 51-60 years (37.0%). There were 5% patients who had age between 41-50 years whereas another 11% patients were older than 70 years. Majority of the patients with peripheral arterial disease were males (60%) compared to 40% females. Majority of the patients with peripheral arterial disease had a duration of disease between 1-5 years (48%) followed by 40% patients who had diabetes since 6-10 years(9%) where as 3% patients had diabetes for more than 15 years.

Table 2: History, Presence of complications, Glycemic control based on HbA1c, Symptoms

History	% Age	
HTN	No	47.0
	Yes	53.0
Smoking	No	59.0
	Yes	41.0
Dyslipidemia	No	54.0
	Yes	46.0
Presence of complications		
Microvascular	Retinopathy	44.0
	Nephropathy	29.0
	Neuropathy	25.0
Macro vascular	CAD	35.0
	CVD	24.0
Glycemic control	Good	51.0
	Poor	49.0
Symptoms	Rest pain	29.0
	Intermittent Claudication	20.0
	Numbness	16.0
	Skin changes	12.0

Among the patients with peripheral arterial disease, hypertension was reported in 53% patients, 41% were smokers and 46% patients had dyslipidemia. Among the

patients with peripheral arterial disease, in microvascular disease category, 44% had retinopathy, 29% had nephropathy and 25% had neuropathy. In macro vascular category, 35% patients had CAD whereas 24% patients had CVD. On analyzing the glycemic control among the patients with peripheral arterial disease it was revealed that 49% had poor glycemic control whereas 51% had good glycemic control as per HbA1c level. Most common symptoms of peripheral arterial disease reported in present study were rest pain in 29%, followed by intermittent claudication in 20%, numbness in 16% and skin changes in 12% patients.

Table 3: Palpable Arteries

			% Age
RIGHT	FA	Absent Feeble Palpable	0 9.0 91.0
	DPA	Absent Feeble Palpable	21.0 1.0 78.0
	POPA	Absent Feeble Palpable	16.0 1.0 83.0
	PTA	Absent Feeble Palpable	15.0 10 84.0
LEFT	FA	Absent Feeble Palpable	0 8.0 92.0
	DPA	Absent Feeble Palpable	1.0 25.0 74.0
	POPA	Feeble Palpable	18.0 82.0
	PTA	Feeble Palpable	15.0 85.0

On analyzing the palpable arteries of right side; FA was palpable in 91%, DPA was palpable in 78%, POPA was palpable in 83% and PTA was palpable in 84% patients. Whereas in left side FA was palpable in 92%, DPA was palpable in 74%, POPA was palpable in 82% and PTA was palpable in 85% of the patients.

Table 4: Doppler flow pattern, Obstruction

Colour Doppler	**Femoral %**	**Popliteal %**	**Dorsalis pedis %**	**Posterior tibial %**
Monophasic	8	12	11	16
Biphasic	46	39	62	55
Triphasic	46	49	27	29
Obstruction				
Normal	51	35	17	24
Mild	22	37	53	45
Moderate	18	16	22	20
Severe	9	12	8	11

On analyzing the Doppler flow pattern, it was observed that majority of the patients with peripheral arterial disease had biphasic flow. The triphasic flow in

femoral artery is 46%, biphasic flow 46% and monophasic flow that shows severe obstruction is 8%. Popliteal artery has triphasic flow 49%, biphasic 39% and 12% had monophasic flow. Dorsalis pedis has triphasic flow in 27% cases, biphasic in 62% and monophasic flow in 11%. Posterior tibial has triphasic flow in 29% cases, biphasic in 55% and monophasic in 16% cases. Majority of the patients with peripheral arterial disease had mild obstruction in all the peripheral arteries. The patients had mild obstruction 22%, moderate 18% and severe obstruction of 9% in femoral artery; mild obstruction of 37%, moderate 16% and 12% patients had severe obstruction flow in popliteal artery. Similarly the patients had mild obstruction 45%, moderate 20% and severe obstruction 11% in posterior tibial artery; mild 53%, moderate obstruction 22% and 8% patients had severe obstruction in dorsalis pedis artery.

Table 5: ABPI vs glycemic control

ABPI		HbA1c Group		Total	P value
		Good	Poor		
Right	Mild	1	10	11	<0.001
	Moderate	0	11	11	
	Normal	50	27	77	
	Severe	0	1	1	
Left	Mild	1	1	2	<0.001
	Moderate	1	23	24	
	Normal	49	24	73	
	Severe	0	1	1	

A significant association was obtained between severity as per ABPI and glycemic control among the patients with peripheral arterial disease. Those with poor glycemic control with right side peripheral arterial disease, majority had mild-moderate ABPI (n=21) and 1 patient had severe ABPI and only 27 patients had normal ABPI, however those with good glycemic control majority had normal ABPI (n=50) and only 1 patient had mild ABPI ($p<0.001$). Similar trend was observed for patients with left side peripheral arterial disease. Those with poor glycemic control, majority had mild-moderate ABPI (n=24) and 1 patient had severe ABPI and only 24 patients had normal ABPI, however those with good glycemic control majority had normal ABPI (n=49) and only 1 patient each had mild and moderate ABPI ($p<0.001$).

Discussion

Atherosclerosis is a progressive process affecting multiple vascular beds; its clinical consequences, which include coronary artery disease (CAD), cerebrovascular disease, and peripheral arterial disease (PAD), are potentially life threatening.[19] Atherosclerotic disease in one vascular bed indicates possible disease in others.[20] The risk of atherosclerotic disease is markedly increased among individuals with diabetes. The increased risk is independent of, and additive to, other cardiovascular risk factors. Atherosclerosis causes most of the death and disability in patients with diabetes, particularly in the type 2 diabetic patient population. [21]

In our study majority of the patients with peripheral arterial disease were male (60%) and belongs to age group of 61-70 years (47%) followed by 51-60 years (37.0%). Marso et al. reported that using ABI to identify PAD, the prevalence of PAD in people with DM over 40 years of age has been estimated to be 20%. This prevalence increases to 29% in patients with DM over 50 years of age. [22] In the

present study, no significant association of gender was observed with prevalence of PAD though a higher percentage of males (60%) had PAD.

Presently, greatest public health challenge for developing countries like India is the control T2DM and its complication like PAD, which is causing mortality at a rate double than those for communicable diseases. [23] South Asians are more susceptible to the detrimental effects of oxidative stress induced by hyperglycemia even at lower glucose thresholds than white Europeans. [24] Chronic hyperglycemia as seen in T2DM is related to increased risk for PAD. [25] Level of glucose fluctuation plays a significant role in vascular endothelial dysfunction in T2DM. [26]

The fact that Indian patients with diabetes have poor foot care practice, [27] warrants further studies to assess the use of ABPI as screening tool on a wide scale and intensification of the concept of a strict glycemic control for better prognosis of PAD and other complications of the disease. Hyperglycemia and insulin resistance are key features of T2DM that causes vascular disease by: (i) critical role of endothelium in obesity‐induced insulin resistance; (ii) hyperglycemia‐dependent microRNAs deregulation and impairment of vascular repair capacities; (iii) alterations of coagulation, platelet reactivity, and micro particle release; (iv)epigenetic‐driven transcription of ROS ‐generating and proinflammatory genes. [28]

We observed that majority of the patients (>90%) with peripheral arterial disease had a duration of diabetes less than 10 years. The prevalence of PVD in diabetics increases with the duration of diabetes from 15% to 45% at 10 to 20 years respectively after the diagnosis of diabetes.[22] The association was particularly strong among men with hypertension or who were current smokers. Adler et al. estimated the prevalence of PAD up to 18 years after the diagnosis of diabetes in 4,987 subjects. [29] The data showed a higher prevalence of PAD in those with longer duration of diabetes. Another important risk factor is dyslipidemia. We reported nearly half of the PVD patients with Dyslipidemia. Indeed, lipid-lowering treatment is one of the main therapeutic strategies in patients with PAD.

Diabetes is a disease that is strongly associated with both microvascular and macrovascular complications, including retinopathy, nephropathy, and neuropathy (microvascular) and ischemic heart disease, peripheral vascular disease, and cerebrovascular disease (macrovascular), resulting in organ and tissue damage in approximately one third to one half of people with diabetes. [18]

In the present study, the glycemic control among the patients with peripheral arterial disease it was revealed that 49% had poor glycemic control whereas 51% had good glycemic control as per HbA1c level. We did not find a significant association of PAD with any of the glycemic control markers studied (fasting blood sugar, PP blood sugar and HbA1c levels). In our opinion, current poor glycemic control adjudged as a risk factor for PAD that has occurred retrospectively is not a justified option unless the current glycemic control is proven to be a reflection of a long-term glycemic status of patient. However, contrary to our view point, a study has shown the current glycemic status to have a significant association with PAD. Most common symptoms of peripheral arterial disease reported in present study were rest pain in 29%, followed by intermittent claudication in 20%, numbness in 16% and skin changes in 12% patients. Peripheral artery disease is characterized by occlusion of the lower-extremity arteries, which can cause intermittent claudication and pain, especially upon exercise and activity, and

which can result in functional impairments and disability.

On analyzing the Doppler flow pattern it was observed in our study that biphasic flow pattern was more than triphasic flow pattern in Posterior Tibial and Dorsalis pedis , triphasic pattern was more than biphasic pattern in Popliteal , biphasic pattern was equal to triphasic pattern in Femoral artery. In study by Tripathi et al. observed that in diabetics, without symptoms mostly waves were biphasic and triphasic, while in diabetics with symptoms mostly waves were monophasic and biphasic except in popliteal artery where wave pattern was similar to asymptomatic group. [30] ABPI is a widely acknowledged criteria for classification of peripheral arterial disease and has quite frequently been used for assessment of peripheral arterial disease among diabetic patients. [31,32] ABPI is an objective criteria which is reliable and widely accepted and validated criteria and in many studies symptom profile has validated the usefulness of this criteria. [33,34,35]

Conclusion

So it can be concluded that strict glycemic control as monitored by HbA1c levels along with control of hypertension, dyslipidemia and dietary modifications are necessary in patients with Diabetes Mellitus to prevent development of macrovascular complications like Peripheral Arterial Disease. As Diabetes is a major public health problem, hence prevention of early PVD by early detection and treatment will prevent major valuable human lives and limbs; mortality and morbidity.

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