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Original Research Article

Potential risk factors for peripheral neuropathy in patients with type 2 diabetes mellitus: a case control study from central Rajasthan

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ABSTRACT

Background: Peripheral neuropathy is one of the most common and debilitating but preventable complications of diabetes mellitus, with significant morbidity as it often leads to foot ulceration and amputation. Therefore, this study was aimed to identify the potential risk factors for diabetic peripheral neuropathy (DPN) which can affect its progression.
Methods: This case-control study was conducted on 240 patients with type 2 diabetes mellitus which included 120 patients with clinical evidence of DPN as cases and 120 patients without clinical evidence of DPN as controls. DPN was assessed clinically by neuropathic symptoms and neurological examination using 10 g 5.07 Semmes–Weinstein monofilament and vibration digital biothesiometer. Data regarding presence of potential risk factors were collected from all participants and analyzed using logistic regression analysis to measure an association with DPN.
Results: A significant and independent association of advancing age, longer duration of diabetes, hyperglycemia, poor glycemic control, autonomic neuropathy and retinopathy with DPN ($p<0.05$) was observed. Hypertension, dyslipidemia, smoking, gender, body mass index, method of diabetes control and angiotensin converting enzyme inhibitor usage were not found be associated with DPN.
Conclusions: Since hyperglycemia and poor glycemic control were only modifiable risk factors for DPN, intensive glycemic control and primary prevention are the cornerstones for reducing the incidence or slowing the progression of neuropathy and improving quality of life in diabetic patients.

Keywords: Diabetes mellitus, Type 2 diabetes mellitus, diabetic peripheral neuropathy, glycemic control, hyperglycemia, risk factors.

INTRODUCTION

Diabetes mellitus (DM) is one of the most widespread chronic diseases in the world and its prevalence is increasing world-wide at an alarming rate. In the year 2021, there were 537 million adults living with diabetes globally, and this number is predicted to rise to 783 million by the year 2045. India stands second to China in relation to the burden of diabetes, with a prevalence of 9.6% and 74.2 million people living with diabetes.[1]

DM is a group of metabolic disorders which is characterized by a long-standing hyperglycemia. Metabolic dysregulation as a result of prolonged hyperglycemic state causes secondary pathophysiologic alterations in multiple organ systems resulting in two types of complications – microvascular and macrovascular. The macrovascular complications include coronary artery disease (CAD), peripheral arterial disease (PAD) and cerebrovascular disease (CVD). The microvascular complications include retinopathy, nephropathy and neuropathy.[2]

Diabetic neuropathy (DN) is one of the most common microvascular complications of diabetes that can involve peripheral, central and/or autonomic nervous systems. Distinct syndromes of DN have been recognized which include peripheral polyneuropathy, autonomic neuropathy, radiculopathy, mononeuropathy and diabetes amyotrophy. Peripheral neuropathy (PN), also known as diabetic peripheral neuropathy (DPN), is the most common variety. The typical DPN is a chronic, distal, symmetrical, length-dependent sensorimotor polyneuropathy.[3] Incidence of polyneuropathy have been reported in 10-50% of patients with diabetes.[4] DPN results in significant disability and morbidity by causing nerve damage in the extremities leading to a number of impairments and functional limitations, including foot ulcers and subsequent lower extremity amputation, increased risk of falling, inability to work due to physical limitations, and frequent hospitalizations. Life time risk of foot amputation is 15% in patients with diabetic polyneuropathy.[5]

Different hypotheses have been proposed to explain the various modes of progression of DPN. Risk factors besides hyperglycemia are probably involved in the evolution of neuropathy and the contribution of risk factors others than blood glucose level have yet to be clearly identified and quantified. Several studies have shown association of DPN with age, duration of disease, metabolic control, cigarette smoking, hypertension, dyslipidemia and retinopathy. The most common risk factors associated with DPN includes advanced age, long duration of diabetes, poor glycemic control, and cigarette smoking.[6-8]

Screening and identification of the various risk factors and thereby retarding progression of DPN should occur at the earliest. This can minimize the damaging effects of this serious but manageable microvascular complication and in turn improve the quality of life among diabetic patients before the onset of significant morbidity. Therefore, this study was aimed to identify potential risk factors associated with DPN development among patients with type 2 diabetes (T2DM) attending the large tertiary care centre in central Rajasthan.

METHODS

Study design and study population

This case-control study was conducted from October 2016 to March 2018 in Department of Medicine, JLN hospital, Ajmer among 240 adult (age ranging between 35-80 years) patients with T2DM. A total of 120 consecutive patients with clinical evidence of DPN were selected as cases and 120 consecutive patients without clinical evidence of DPN were served as controls. All subject included in this study were known T2DM patients with variable duration and were on oral hypoglycaemic agents (OHA) and/or insulin. Patients with Type 1 diabetes mellitus patients, gestational diabetes and identifiable causes of neuropathy example-uraemia, carcinoma, vitamin deficiency (including vitamin B12), chronic liver disease, malabsorption, human immunodeficiency virus infection, lymphoma, multiple myeloma, hypothyroidism, leprosy, Guillain-Barre syndrome, critical illness (sepsis), drug and toxin-induced (chronic alcoholism, isoniazid, amiodarone, arsenic, solvents etc.) were excluded from the study. Patients who underwent amputation of the whole foot, below knee and above knee amputations were also excluded from the study.

The study was approved by the Institutional Ethics Committee and conducted in accordance with the Code of Ethics of the World Medical Association (principles of Declaration of Helsinki) and the regulations of the local Institutional Ethics Committee. A written informed consent was obtained from all participants before they were enrolled in the study.

Study procedure

Each subject underwent a detailed clinical history and complete clinical examination. Baseline blood samples were collected for measurement of fasting blood sugar (FBS), 2-hours post prandial blood sugar (PPBS), glycosylated haemoglobin (HbA1c), total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol. Other investigations included the urinary albumin excretion rate measured from a single 24-hour urine collection, fundoscopy and 12-lead electrocardiogram (ECG).

Clinical data were obtained on age, sex, body mass index (BMI), smoking habit, duration of diabetes, mode of treatment (insulin, OHA or both), degree of glycemic control (assessed by HbA1c), angiotensin converting enzyme inhibitor (ACEI) usage, and the presence of hypertension, dyslipidemia (assessed by serum lipid level), autonomic neuropathy, diabetic retinopathy, diabetic nephropathy, CAD, CVD, and PAD.

DPN was diagnosed clinically using neuropathic symptoms like presence of neuropathic pains and paraesthesia, and neurological examination including touch sense using 10 g 5.07 Semmes–Weinstein (SW) monofilament, vibration sense using digital biothesiometer and deep tendon reflexes (ankle and knee reflex) using hammer.

Operational definitions

DPN was defined if two or more of the following three abnormalities were present:[9]

The presence of one or more neuropathic symptoms. The decreased or absent two or more reflexes of the ankle or knee tendons. A vibration perception threshold (VPT) that was abnormal for the patients age (>15 volts) or increases threshold for light touch/pressure (insensitive foot).

Diabetic foot was confirmed by visual examination of ulcers or amputations and a documented diagnosis of diabetic foot.

The quality of diabetes control (glycemic status) was classified according to the HbA1c. HbA1c <7.0% was considered as good quality control; HbA1c 7.0-8.0% was considered as fair control, and HbA1c >8.0% as poor control.[10] BMI ≥25 kg/m2 was considered as increased (overweight or obese).[10] Smoker was defined as a person who smokes at least 1 cigarette, pipe, cigar or bidi per day. Hypertension was defined by either a documented diagnosis of hypertension, the patient taking antihypertension medications, or the latest (within three months) blood pressure (BP) readings (either systolic ≥140 or diastolic ≥90).[10] Dyslipidemia was defined based on either a documented diagnosis of dyslipidemia or the patient taking any lipid-lowering medications.[10] Nephropathy was defined as the presence of persistent albuminuria at levels 30–299 and levels ≥ 300 mg/24 h urine collection sample.[11] Diabetic retinopathy diagnosis was based on dilated fundus examination carried out by experienced ophthalmologists. CAD was defined as a previous diagnosis of CAD by angiography or ECG, and/or on current treatment for CAD. CVD was defined as a history of physician-diagnosed CVD (example- previous stroke) and/or on current treatment for CVD. PAD was defined as a previous history of PAD and/or on current treatment for PAD.

Statistical analysis

The normality of distribution for continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean and standard deviation (SD), and categorical variables as frequency (n) and percentage (%). The significance of difference was analyzed using Student's t-test for continuous variables and using Pearson's chi-squared ($\chi 2$) test or Fisher's exact test for categorical values as appropriate. The logistic regression analysis was used to calculate odds ratios (OR) and corresponding 95% confidence interval (CI) as a measure of the association between potential risk factors and DPN. Variables found to be significant ($p<0.05$) in univariate analysis were finally included in multivariate analysis in order to identify their independent association with DPN after adjusting all other potential confounders. A two-tailed p value < 0.05 was considered as statistically significant. The statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software version 16.0 for Windows (Version 16.0 for Windows; Statistical package for social sciences (SPSS) Inc., Chicago, Illinois, USA).

RESULTS

Baseline clinical characteristics of participants

The baseline clinical characteristics of the study population are depicted in Table 1. The mean age, duration of diabetes, FBS, PPBS and HbA1c were significantly higher among patients with DPN compared to controls. The mean age of case group versus control group was 62.9±12.0 years vs 58.7±10.73 years ($p<0.01$).

Table 1: Baseline clinical characteristics of participants.

Variable	Cases (n=120)	Controls (n=120)	P value
Age (years)	62.9±12.0	58.7±10.73	0.005
Sex			
Male	96 (80)	84 (70)	0.101
Female	24 (20)	36 (30)	
BMI (kg/m^2)	23.57±3.38	22.74±5.61	0.166
Smoker	36 (30)	25 (20.8)	0.138
Durations of diabetes (year)	11.5±7.06	5.5±4.14	<0.001
Mode of treatment			
OHA alone	84 (70)	90 (75)	0.470
Insulin alone	8 (6.7)	10 (8.3))	0.807
Both	28 (23.3)	20 (16.7)	0.258
ACEI usage	76 (63.3)	65 (54.2)	0.189
Systolic BP (mmHg)	148.46±30.78	143.8±17.10	0.148
Diastolic BP (mmHg)	92.14±8.51	90.33±9.24	0.116
FBS (mg/dl)	179.9±74.64	157.6±34.09	0.003
PPBS (mg/dl)	233.4±102.05	205.0±51.19	0.007
HbA1c (%)	9.53±1.09	8.18±0.75	<0.001
Total cholesterol (mg/dl)	188.46±50.35	197.3±61.07	0.222
Triglyceride (mg/dl)	180.16±87.34	191.5±45.75	0.209
LDL (mg/dl)	112.32±41.88	118.54±60.24	0.354
HDL (mg/dl)	40.94±3.35	40.43±1.67	0.136

Abbreviations: BMI, Body mass index; OHA, Oral hypoglycemia agents; ACEI, Angiotensin converting enzyme inhibitor; BP, Blood pressure; FBS, Fasting blood sugar; PPBS, Postprandial blood sugar; HbA1c, Glycosylated hemoglobin; LDL, Low-density lipoprotein; HDL, High-density lipoprotein. Data are expressed as mean ±SD (Standard deviation) or numbers (percentages).

The majority of subjects in the case group were of older age in 6th and 7th decade of life The mean duration of the diabetes of subjects with DPN vs controls was 11.5±7.06 years vs 5.5±4.14 years ($p<0.001$). The mean FBS, PPBS and HbA1c levels of cases vs controls were 179.9±74.64 mg/dl vs 157.6±34.09 mg/dl ($p<0.01$), 233.4±102.05 mg/dl vs 205.0±51.19 mg/dl ($p<0.01$) and 8.53±1.09% vs

7.18±0.75% (p<0.001), respectively. The subjects with DPN had poor glycemic control compared to control group as evident from HbA1c level.

Table 2: Other vascular complications of diabetes in the study population.

Complication	Cases (n=120)	Controls (n=120)	P value
Autonomic neuropathy	44 (36.6)	16 (13.3)	<0.001
Retinopathy	75 (62.5)	55 (45.8)	0.014
Nephropathy	57 (47.5)	48 (40)	0.298
CAD	48 (40)	44 (36.6)	0.690
PAD	12 (10)	10 (8.3)	0.823
CVD	20 (16.7)	16 (13.3)	0.588

Abbreviations: CAD, Coronary artery disease; PAD, Peripheral arterial disease; CVD, Cerebrovascular disease. Data are expressed as numbers (percentages).

No significant differences were found between two groups with regard to gender, BMI, smoking habit, diastolic and/or systolic blood pressure (BP), serum lipid profile, method of diabetes control (OHA, insulin or both) and ACEI usage (Table 1).

Other vascular complications of T2DM

Table 2 shows the other vascular complications in study population. A significantly higher number of patients with DPN compared to controls had autonomic neuropathy (44 versus 16; p<0.001) and retinopathy (75 versus 55; p<0.05). No statistically significant difference was evident between case group and control group with respect to nephropathy, CAD, PAD, and CVD (p>0.05).

Potential risk factors associated with diabetic peripheral neuropathy

Table 3 shows the univariate analysis of various risk factors associated with DPN. The factors that were significantly associated with DPN (p<0.05) were age (OR: 2.10 [95% CI: 1.30-3.38]), age ≥50 years (OR: 3.05 [95% CI: 1.11-8.36]), mean duration of diabetes (OR: 2.20 [95% CI: 1.48-3.26]), duration of diabetes ≥5 years (OR: 4.52 [95% CI: 1.84-11.09]), FBS (OR: 2.31 [95% CI: 1.36-3.92]), PPBS (OR: 2.12 [95% CI: 1.42-3.15]), FBS ≥126 mg/dl (OR: 4.31 [95% CI: 1.74-10.68]), PPBS ≥200 mg/dl (OR: 3.00 [95% CI: 1.22-7.35]), HbA1c (OR: 2.48 [95% CI: 1.57-3.92]), poor glycemic control (OR: 6.90 [95% CI: 2.36-20.20]), autonomic neuropathy (OR: 3.04 [95% CI: 1.23-7.50]) and retinopathy (OR: 1.56 [95% CI: 1.06-2.29]).

Table 3: Univariate logistic regression analysis of potential risk factors associated with DPN.

Variable	Coefficient	SE	P value	OR*	95% CI
Age (years)	0.717	0.219	0.003	2.10	1.30-3.38
Age ≥ 50 years	1.227	0.435	0.002	3.05	1.11-8.36
Sex					
Male	0.074	0.022	0.073	1.07	0.77-1.80
Female	0.000	0.001		1	1
BMI (kg/m^2)	-0.026	0.035	0.163	0.97	0.91-1.04
BMI ≥ 25 kg/m^2	-0.058	0.045	0.207	0.94	0.86-1.03
Smoking status					
Smoker	0.002	0.006	0.103	1.06	0.70-1.38
Non smoker	0.000	0.000		1	1
Durations of diabetes (year)	0.788	0.201	<0.001	2.20	1.48-3.26
Duration of diabetes ≥5 years	1.509	0.481	<0.001	4.52	1.84-11.09
Mode of treatment					
OHA alone	0.000	0.000	0.411	1.02	0.95-1.06
Insulin alone	-0.021	0.026	0.759	0.98	0.93-1.03
Both	0.000	0.001		1	1
ACEI usage	-0.229	0.270	0.186	0.79	0.47-1.35
Systolic BP (mmHg)	-0.254	0.354	0.143	0.78	0.39-1.55
Diastolic BP (mmHg)	-0.183	0.154	0.112	0.81	0.60-1.10
Hypertension					
Systolic	0.003	0.021	0.285	1.00	0.96-1.04
Diastolic	0.037	0.324	0.136	1.06	0.56–2.01
FBS (mg/dl)	0.764	0.244	0.001	2.31	1.36-3.92
PPBS (mg/dl)	0.742	0.226	0.004	2.12	1.42-3.15
Hyperglycemia					
FBS ≥126 mg/dl	1.357	0.457	0.004	4.31	1.74-10.68

Continued.

Variable	Coefficient	SE	P value	OR*	95% CI
PPBS ≥200 mg/dl	1.036	0.373	0.007	3.00	1.22-7.35
HbA1c (%)	0.919	0.261	<0.001	2.48	1.57-3.92
Glycemic control					
Poor	1.818	0.557	<0.001	6.90	2.36-20.20
Fair	1.517	0.494	0.043	4.66	1.68-12.89
Good	0.000	0.000		1	1
Total cholesterol (mg/dl)	-0.041	0.111	0.217	0.96	0.77-1.19
Triglyceride (mg/dl)	-0.104	0.107	0.206	0.90	0.73-1.04
LDL (mg/dl)	-0.023	0.189	0.351	0.98	0.89-1.09
HDL (mg/dl)	-0.107	0.101	0.132	0.88	0.63-1.24
Dyslipidemia	-0.203	0.081	0.191	0.83	0.63-1.09
Autonomic neuropathy	1.218	0.393	<0.001	3.04	1.23-7.50
Retinopathy	0.558	0.201	0.014	1.56	1.06-2.29

Abbreviations: DPN, Diabetic peripheral neuropathy; BMI, Body mass index; OHA, Oral hypoglycemia agents; ACEI, Angiotensin converting enzyme inhibitor; BP, Blood pressure; FBS, Fasting blood sugar; PPBS, Postprandial blood sugar; HbA1c, Glycosylated hemoglobin; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; OR, Odds ratio; CI, Confidence interval; SE, Standard error; 1, Reference group.*Crude OR

Table 4: Multivariate logistic regression analysis of potential risk factors associated with DPN.

Variable	Coefficient	SE	P value	OR*	95% CI
Age (years)	0.790	0.204	0.002	2.09	1.30-3.35
Age ≥ 50 years	1.064	0.243	0.009	2.78	0.98-7.85
Durations of diabetes (year)	0.788	0.201	0.001	2.05	1.33-3.15
Duration of diabetes ≥5 years	1.198	0.346	0.001	3.38	1.28-8.91
FBS (mg/dl)	0.281	0.141	0.003	1.53	0.77-3.04
PPBS (mg/dl)	0.524	0.177	0.002	1.92	1.24-2.95
Hyperglycemia					
FBS ≥126 mg/dl	1.172	0.327	0.006	3.06	1.13-8.24
PPBS ≥200 mg/dl	0.671	0.188	0.016	1.99	0.74-5.34
HbA1c (%)	0.980	0.340	0.011	2.44	1.22-4.86
Glycemic control					
Poor	1.650	0.673	<0.001	5.88	1.26-27.38
Fair	0.970	0.282	0.004	2.32	0.82-6.55
Good	0.000	0.000		1	1
Autonomic neuropathy	0.943	0.209	0.005	2.12	0.81-5.55
Retinopathy	0.162	0.124	0.022	1.42	0.97-2.09

Abbreviations: DPN, Diabetic peripheral neuropathy; FBS, Fasting blood sugar; PPBS, Postprandial blood sugar; HbA1c, Glycosylated hemoglobin; OR, Odds ratio; CI, Confidence interval; SE, Standard error; 1, Reference group. *Adjusted OR

Variables which showed significant association with DPN (p<0.05) in univariate analysis were included in the multivariate logistic regression analysis and results are presented in Table 4. The results obtained in univariate analysis did not substantially change after adjustment for all potential confounders in multivariate analysis, and all factors continued to show a significant and independent association with DPN.

Patients aged 50 years and older were 2.78 times more likely to develop DPN compared with patients younger than 50 years (adjusted OR: 2.78 [95% CI: 0.98-7.85]; p=0.009) after controlling all other confounding factors. Similarly, patients with 5 years and greater duration of diabetes were 3.38 times more likely to develop DPN as compared to those with shorter duration of diabetes (adjusted OR: 3.38 [95% CI: 1.28-8.91]; p=0.001) after controlling for other variables. Likewise, patients who had poor glycemic control were 5.88 times more likely to develop DPN as compared to patients with good diabetes control (adjusted OR: 5.88 [95% CI: 1.26-27.38]; p<0.001). Also, patients who had uncontrolled hyperglycemia with FBS ≥126 mg/dl and PPBS ≥200 mg/dl were 2 to 3-fold more prone to develop DPN as compared to patients with controlled blood sugar (adjusted OR: 3.06 [95% CI: 1.13-8.24]; p=0.006 and 1.99 [95% CI: 0.74-5.34]; p=0.016, respectively). Finally, patients with DPN suffered from autonomic neuropathy 2.12 times (adjusted OR: 2.12 [95% CI: 0.81-5.55]; p=0.005) and retinopathy 1.42 times (adjusted OR: 1.42 [95% CI: 0.97-2.09]; p=0.022) more often than patients without DPN (Table 4).

DISCUSSION

DPN is a common complication of DM with high morbidity and impairment of quality of life. The current study was conducted to determine the potential risk factors of DPN among adult patients with T2DM attending a large tertiary care hospital.

In our study, although the proportion of males affected by DPN was more than females, no statistically significant association was found between DPN and gender (OR: 1.07 [95% CI: 0.77–1.80]; p=0.073). Studies by Bansal et al and Lu et al also reported that there were no sex-specific differences.[12,13] However, in studies by Kiani et al and Booya et al, a statistically significant association was found between neuropathy and gender.[8,14] D'Souza et al and Jember et al observed that male gender was significantly associated with the development of DPN.[7,15]

In the present study, majority of the patients with DPN belonged to the older age group in 6th and 7th decade of life. Moreover, patient's age ≥ 50 years had a significant and independent association with DPN (adjusted OR: 2.78 [95% CI: 0.98-7.85]; p=0.009). Our study findings were similar to those reported from other parts of India and abroad.[7,8,12,14-22] Possible reasons for this association could be justified as peripheral neuropathy is a chronic complication of diabetes and takes time to develop, so it is expected in older diabetic patients. In addition, the nervous system is increasingly vulnerable to continual metabolic stress and degenerative nature of physiological well-being with aging.[15] The effect of aging combined with deleterious effects of hyperglycaemia can result in increased prevalence of DPN as one gets old.

In this study, DPN was more prevalent among those with longer duration of the disease. Duration of diabetes ≥5 years was found to be significantly and independently associated with DPN. Our study result was in agreement with various other studies.[6-8,12,14,18-22] This association can be explained by fact that the longer duration of diabetes being associated with chronic hyperglycemia causes activation of multiple biochemical pathways due to accumulation of glycosylation end products which induces oxidative stress and endothelial damage in diabetic neurons, and leads to nerve damage and neuronal ischemia.[23,24] It can also be explained by possible late diagnosis.

In the present study, DPN was found to significantly and independently associated with hyperglycemia as assessed by FBS and PPBS, and poor glycemic control assessed by raised HbA1c level. Our study results were in line with other studies conducted in this part of world and globally which had shown a significant and independent association of DPN with fasting plasma glucose, total hyperglycemia, and glycemic status assessed by HbA1c level.[6,12,14,18,20,22,25,26]

Atherosclerosis risk factors are thought to promote DN. In our study, no statistically significant association was found between BMI and presence of DPN. This finding was congruent with other studies wherein anthropometric variables were not identified as risk factors.[12,25] On the other hand, several studies had shown a significant association of DPN with higher BMI, obesity, height and weight.[6-8,18,22,27] Smoking was not observed to be a significant and independent risk factor associated with DPN (OR: 1.06 [95% CI: 0.70-1.38]; p=0.103) in the present study. Similar finding was observed in a case control study performed by Booya et al in Iran.[14] However, an association between smoking and DPN was observed in other studies conducted elsewhere in India as well as abroad.[6,15,18,22] Although nearly three-fourths of patients with DPN had BP ≥140/90 mmHg in our study, we could not show statistically significant association between DPN and BP levels (systolic and/or diastolic). Booya et al and Mørkrid et al also showed no significant relationship between distal symmetric sensory/motor polyneuropathy and BP levels.[14,17] However, a study conducted by Dutta et al identified contribution of systolic BP to diabetic neuropathy, while a study by Tesfye et al showed a significant association with diastolic BP.[16,18] This could be due to common non-modifiable risk factors such as age in these studies. We did not observe association between DPN and dyslipidemia in this study similar to a case control study by Booya et al.[14] Tesfaye et al found that higher levels of total cholesterol, triglycerides and LDL were significantly associated with the cumulative incidence of neuropathy, while Maser et al had shown an association of neuropathy with reduced HDL level.[6,22]

In our study, DPN was not significantly related to modality of diabetes control (Insulin and/or OHA) and ACEI usage. The previous trial by diabetic complications and the research group showed that early intensive insulin therapy reduced neuropathy symptoms compared to conventional treatment.[28] A previous study by Alvarsson et al had shown that early initiation of insulin therapy prolongs endogenous insulin secretion and provides better metabolic control.[29] Qiang et al suggested that consumption of OHA such as glyburide and ACEI inhibit the progression of neuropathy irrespective of blood glucose level.[30] Further studies using a randomized clinical trial are needed to evaluate the effects of treatment modality and ACEI use on DPN.

Finally, we found a significant association of autonomic neuropathy and retinopathy with DPN. Concordant with our results, a study by Bansal et al had shown that other vascular complications like diabetic retinopathy were more in patients with DPN.[12] Other studies had also shown an association of neuropathy with retinopathy.[22,26] Hence, patients with DPN are more likely to have a second vascular complication leading to the speculation that all three cardinal complications of diabetes represent separate manifestations of a global "microvascular" process and other microvascular complications go hand in hand with DPN.

The current study also has some limitations. First, the causal association of various potential risk factors with DPN could not be assessed due to cross-sectional study design. Second, the duration of diabetes as measured in this study might not reflect the true duration of the disease, but the time since diagnosis and actual diabetes onset might precede diagnosis in type 2 DM. Third, the nerve conduction velocity (NCV) study, the gold standard diagnostic test for confirmation of DPN, was not performed due to non-affordability and the low resources available for the study, which may have led to underestimated diagnosis. Finally, since, this is a health facility-based study which covers only that part of the diabetic population who approached for the assistance of clinicians in hospitals for follow up and management of their condition, the conclusions deduced from this study cannot be generalized to all diabetic patients. Nonetheless, the present study has some strength in terms of use of digital biothesiometer for diagnosis of neuropathy on an adequate sample of patients with reasonably good response rate among them. Digital biothesiometer is a valid, easy to use and widely available clinical tool for quick screening of neuropathy in a busy outpatient clinic or in a small center where facility of NCV is not available.

CONCLUSION

In conclusion, the present study has shown a significant and independent association of advancing age, longer duration of diabetes, hyperglycemia, poor glycemic control, autonomic neuropathy and retinopathy with DPN. Since hyperglycemia and poor glycemic control were only modifiable risk factors for DPN, intensive glycemic control is the cornerstone of managing T2DM and is essential for reducing the incidence or slowing the progression of neuropathy and improving quality of life in these patients. Primary prevention through lifestyle modifications which delay the onset of disease should be made as an essential component of everyday practice. Early detection and appropriate interventions should be done in elderly diabetic patients with longer duration of disease and poor diabetes control.

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