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Evaluation of Different HbA_{1c} Levels to Assess the Risk of Peripheral Neuropathy Among Type 2 Diabetic Patients Along With Other Conventional Risk Factors

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Abstract

This cross sectional study was carried out in the outpatient department of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders, Bangladesh (BIRDEM) General Hospital, Dhaka, to explore the factors influencing or related to the development of the diabetic peripheral neuropathy (DPN) with specific concern to the HbA_{1c} levels. A total of 400 patients with type 2 diabetic were selected to collect information on socio-demographic, blood pressure, anthropometry and lipid profile. Glycaemic status was assessed by HbA_{1c} and plasma glucose levels. Prevalence of DPN was 16.8%, with male 10.8% and female 20.9%. Increased HbA_{1c} categories above 7.0% were significantly associated with increased prevalence of DPN (9.2 Vs. 10.5 Vs 26.5%; $\chi^2 = 19.446$, p = .000). Logistic regression models showed that the risk of DPN was strongly increased at the HbA_{1c} categories ≥8% (OR = 3.57; 95% CI: 1.75-7.26). Advanced age (OR = 1.97; 95% CI: 1.12-3.47), longer duration of diabetes (OR = 1.81; 95% CI: 1.02-3.19), lacking of physical exercise (OR = 2.60; 95% CI: 1.47-4.58), female gender (OR = 2.17; 95% CI: 1.21-3.89), fasting blood glucose (OR = 1.153; 95% CI: 1.058-1.255) and blood glucose 2 hours after breakfast (OR = 1.096; 95% CI: 1.029-1.168) were significant risk factors of DPN. However, there is need of a large scale community based prospective study to validate the results.

Key words: DPN, HbA_{1c}, Risk factors, Type 2 diabetes.

Introduction

Neuropathy is one of the most common vascular complications of diabetes that can cause significant morbidity and mortality.[1] It is estimated from a comprehensive collection of epidemiologic studies that the prevalence of neuropathy in diabetes patients is approximately 30% in hospital patients and 20% in community patients.[2] A commonly cited study in 1977 reported that roughly 7% of patients had neuropathy upon diagnosis of diabetes, and the incidence approached 50% for patients with diabetes for more than 25 years.[3] However, it is difficult to accurately approximate the true prevalence of diabetic neuropathy, because the criteria for diagnosis vary, epidemiologic studies are limited to patients receiving medical care, and diabetes remains undiagnosed in a large population of diabetes patients.[4]

Diabetic neuropathies are heterogeneous with diverse clinical manifestations. They include focal, diffuse, sensory, motor and autonomic neuropathy. Most common among the neuropathies are chronic sensorimotor diabetic peripheral neuropathy (DPN). DPN accounts for approximately 75% of the diabetic neuropathies.[5] It is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes mellitus (DM), after exclusion of other causes.[6] It affects large and small afferent

nerve fibers to varying degrees, resulting in mixed symptoms and sensoryloss.[1,7] Manifestations classically progress from the most distal extremities (the fingers and toes) in a symmetrical pattern that is generally described as a glove-and-stocking distribution. Typically, patients experience burning pain, electrical or stabbing sensations, paresthesia, hyperesthesia, and deep aching pain but sometimes they may experience simple numbness so it is important to realize that lack of symptoms does not rule out presence of neuropathy. Neuropathic pain is typically worse at night, and the symptoms are most commonly experienced in the feet and lower limbs, although in some cases the hands may also be affected.[7,8] Upto 50% of DPN may be asymptomatic and patients are at risk of insensate injury to their feet.[5] Up to 85% of amputations among diabetic patients are preceded by foot ulcers.[9] Examination of the lower limb usually reveals sensory loss of vibration, pressure, pain, and temperature perception (mediated by small and large fibers) and absent ankle reflexes. Signs of peripheral autonomic (sympathetic) dysfunction are also frequently seen and include a warm or cold foot, sometimes with distended dorsal foot veins (in the absence of obstructive peripheral vascular disease), dry skin, and the presence of calluses under pressure-bearing areas.[8] The prevalence of DPN varies in the literature from 5-100%, which may reflect the different diagnostic criteria and diverse study populations.[10]

The diagnosis of DPN can only be made after a careful clinical examination, and all patients with diabetes should be screened annually for DPN by examining pinprick, temperature, and vibration perception (using a 128-Hz tuning fork), 10-g monofilament pressure sensation at the distal halluces, and ankle reflexes. Combinations of more than one test have >87% sensitivity in detecting DPN. Loss of 10-g monofilament perception and reduced vibration perception predict foot ulcers. The feet should be examined for ulcers, calluses, and deformities, and footwear should be inspected. Nondiabetic causes of neuropathy including serum B_{12}deficiency, hypothyroidism, uremia and chronic inflammatory demyelinating polyneuropathy should be excluded. A combination of typical symptomatology and distal sensory loss with absent reflexes, or the signs in the absence of symptoms, is highly suggestive of DPN. Different scoring systems have been developed for monitoring progression or response to intervention in clinical trials.[8] Nerve conduction tests (NCS) may show reduced functioning of the peripheral nerves, but seldom correlate with severity of DPN and are not appropriate as routine tests for the condition[11]. The practitioner may wish to refer the more complex patient, or those in whom diagnosis needs confirmation, to a neurologist for specialized examination and testing.[8]

Most investigators now agree that diabetic vascular complications result from the interaction of multiple metabolic, genetic and other factors. The primary risk factor for diabetic neuropathy is hyperglycemia.[2] The annual incidence of diabetic neuropathy in the Diabetes Control and Complications Trial (DCCT) was approximately 2% in conventionally treated patients, but that rate dropped to 0.56% in intensively treated type 1 diabetes mellitus patients.[12] The UK Prospective Diabetes Study (UKPDS)[13] failed to support a similar correlation between the incidence of neuropathy and glycemic control in type 2 diabetes patients, but the progression of diabetic neuropathy is dependent on glycemic control in both type 1 and 2 diabetes patients, and the pathologies are considered similar.[2,3,5] The DCCT and also UKPDS provide evidence that the risk for micro and macro vascular complications begins to increase at an HbA_{1c} level of 6.5%.[12,13] Different randomized controlled trials and observational studies have shown that HbA_{1c} is a good predictor of microvascular complications including neuropathy.[12-16] Sabanayagam et al showed that increasing HbA_{1c} categories had a higher prevalence of peripheral neuropathy.[17] The duration of diabetes also increases the risk of neuropathy, but the association between duration and prevalence may depend in part upon patient age, which itself is a risk factor.[2,18] Cigarette smoking, alcohol consumption, hypertension, retinopathy, obesity, microalbuminuria, height, hyperlipidaemia and hypercholesterolaemia are all considered as potential risk factors for diabetic neuropathy[2,18,19].

Although it is known that the high blood sugar level and increase level of HbA_{1c} results DPN

there are still various open questions related to the HbA_{1c}-based diagnosis. However, perhaps the most important open question is, how well does HbA_{1c} predict complications. An identical statement was made in 2009 by the IEC on the role of the HbA_{1c}.[20] "The ultimate goal is to identify individuals at risk for diabetes complications so that they can be treated." Evidence-based recommendations for care of DPN is mainly based on trials in Anglo-Caucasian populations, but there is very little indication and randomized trial evidence of how well these guidelines are implemented in South Asia specially in Bangladesh. So far, there are a very few clinical studies regarding prevalence and risk factors of DPN[21] but no published data regarding the risk assessment of DPN by different levels of HbA_{1c}in Bangladesh. Therefore, it was attempted to do a clinical study in this regard. The study was aimed to gain new insights into how various risk factors especially different cut-off points of HbA_{1c} affect and reflect the risk of DPN among patients with type 2 diabetes which will provide necessary data to ensure improved preventive measures and care for diabetic patients.

Materials and Methods

This was a cross-sectional study conducted on 400 type 2 diabetic patients under follow-up attending the outpatient department (OPD) of BIRDEM General Hospital from January 2014 to December 2014. Type 2 diabetic patients diagnosed in accordance with the World Health Organization (WHO) criteria for both gender and age group were enrolled in the study. Subjects were of 30-60 years of age, with a duration of diabetes from 2 to 10 years. Patients with vitamin B_{12} deficiency, hypothyroidism, uremia, chronic hepatic diseases, chronic arthritis, alcoholism, cerebro-vascular disease, parkinsonism, uremia and acute or chronic musculoskeletal disorders, pregnant diabetic cases or gestational diabetes, type 1 diabetics and patients of haemoglobinopathies were excluded from the study.

BIRDEM is a 550-bed general tertiary level hospital with the most modern disciplines. The patients were registered in BIRDEM after confirmation of diabetes and pre-diabetes. During registration, each patient was given a 'reference number (Ref No)' with a 'diabetic guide book'. This registered medical book printed with specific 'Ref No' contains all baseline information of the patient and necessary advices related to diabetic management, advices and results of screening tests for different diabetic complications and blank pages for subsequent follow-up information. For subsequent follow-up which were given by doctors appointed in BIRDEM outdoor, patients come at a specified date and time written in diabetic guide book. Detection and management of different diabetic complications were done by specialized doctors in outdoor and they keep record in the guidebook.

In this study, a total of 400 type 2 diabetic patients were interviewed with pre-designed and pre-tested questionnaire, included information on sociodemographic (age, sex, family history of diabetes, geographical location, socioeconomic factor, educational history, occupational history), lifestyle characteristics (physical activity, smoking history etc.), blood pressure and anthropometry (height, weight, calculated body mass index) of the participants were collected. The duration of diabetes was also recorded. The selected patients were evaluated for the presence of peripheral neuropathy through reviewing the physicians' notes in the patients' medical report which were recorded in their diabetic guide book. They diagnosed the patients on the basis of symptom profiles and neurologic examinations. Symptoms profile includes burning, numbness, tingling, fatigue, cramping, aching feelings in the lower extremity (feetor in the calf), nocturnal exacerbation of the symptoms or present equally at day and night, the symptoms awake the patient from sleep and walking or standing maneuvers reduce the symptoms. For neurologic examination the procedure was explained and the tests applied on the patient's hand prior to the examination. The patient had to close the eyes during the examination of the Achilles tendon reflex by the broad end of the reflex hammer, vibration perception by biothesiometer, thermal sensation by cold sponge at the dorsum of the

foot, and tactile sensation by pin-prick at the cuticle of the 1st toe. In this study, 96 were DPN patients amongst the 400 type 2 diabetic patients. Of them, 11 patients were sent for nerve conduction study (NCS) to evaluate further complications of the disease. The glycaemic status of the participants were assessed by HbA_{1c}, FBG and two hours ABF. In the current study participants were categorized into 3 groups by 3 HbA_{1c}level. These were good control group (HbA_{1c}<7.0%), average control group (HbA_{1c} 7-7.9%) and poor control group (HbA_{1c} ≥8.0%). The participants were compared in these 3 HbA_{1c} categories. HbA_{1c} was measured by BIO-RAD variant which was modified HPLC method. Fasting lipid profile was also measured. Ethical clearance was obtained from the Institutional Ethical Committee of the BIRDEM Hospital.

Statistical analysis: To compare the different variables among the groups, Chi-square tests were done for categorical data and Student's t-test for quantitative data. Univariate and multivariate logistic regression analysis were performed to estimate the casual effect of each predisposing factor on response variable i.e. development of peripheral neuropathy or remained normal. Odds ratio (OR) with 95% confidence interval (CI) were provided. All statistical tests were considered significant at a level of $p < 0.05$. SPSS software, version 21 was used for the statistical analysis.

Results

Amongst the study subjects, 41.5% (166) were male and 58.5% (234) were female. The mean age of the study participants was 50.05 (±7.528) years. The range of duration of diabetes was 2-10 years and mean duration of 6.41 (±3.06) years. The mean HbA_{1c} was 7.99% (±1.80). The overall prevalence of peripheral neuropathy was 16.8%; male 10.8% and female 20.9%. The age group ≥50 years was significantly associated with peripheral neuropathy (20.6Vs 11.6%; $\chi^2 = 5.677$, $p = 0.017$) than age group <50 years. The female participants demonstrated higher peripheral nephropathy than their male counterparts and the difference was significant (20.9 Vs. 10.8%; $\chi^2 = 7.100$, $p = .008$). The disease was also higher among non-urban patients (25.7 Vs. 13.4%; $\chi^2 = 8.584$, $p = 0.003$), patients with longer duration of diabetes (20.0 Vs. 12.1%; $\chi^2 = 4.315$, $p = 0.038$) and who did not do the regular physical exercise (22.9Vs 10.3%; $\chi^2 = 11.506$, $p = 0.001$). Educational status and hypertension did not show any significant association with peripheral neuropathy (table I).

Table I Association of different sociodemographic characteristics of the study participants with peripheral neuropathy.

Variables	Total subjects (n=400)	Neuropathy no of cases (%)	*p* value
Age group (years)			
<50	172	20 (11.6)	0.017
≥ 50	228	47 (20.6)	
Duration of diabetes (years)			
2-5	165	20 (12.1)	0.038
6-10	235	47 (20.0)	
Gender			
Male	166	18 (10.8)	0.008
Female	234	49 (20.9)	
Residence			
Urban	291	39 (13.4)	0.003
Not urban	109	28 (25.7)	
Educational status			
Schooling	310	46 (14.8)	0.057
No schooling	90	21 (23.3)	
Exercise done by patients			
Yes	195	20 (10.3)	0.001
No	205	47 (22.9)	
Presence of hypertension			
Yes	267	50 (18.7)	0.134
No	133	17 (12.8)	

Results showed a significantly higher mean age in patients with peripheral neuropathy than the patients without peripheral neuropathy (51.93 ± 6.330 Vs. 49.68 ± 7.7, $p = .025$). Duration of diabetes (7.22 ± 2.656 Vs. 6.25 ± 3.122, $p = 0.017$) also showed significant difference between the patients with and without peripheral neuropathy. HbA_{1c}% (8.649 ± 1.914 Vs. 7.864 ±

1.755, p = .001), FBG (10.268 ± 3.034 Vs. 9.002 ± 2.733, p = .001) and blood glucose 2 hours ABF (14.369 ± 3.937 Vs. 12.819 ± 4.005, p = .004) were significantly higher in patients with peripheral neuropathy. BMI, systolic blood pressure, diastolic blood pressure and lipid profile did not show any significant difference (table II).

Table II Clinical variables related to peripheral neuropathy

Total participants(n=400)			
Variables	**With Neuropathy (n= 96) Mean ± SD**	**Without Neuropathy (n= 304) Mean ± SD**	***p* value**
Age (years)	51.93 ± 6.330	49.68 ± 7.70	.025
Duration of diabetes (years)	7.22 ± 2.656	6.25 ± 3.122	.017
HbA_{1c} (%)	8.649 ± 1.914	7.864 ± 1.755	.001
FBG (mmol/L)	10.268 ± 3.034	9.002 ± 2.733	.001
2 hours ABF (mmol/L)	14.369 ± 3.937	12.819 ± 4.005	.004
BMI (kg/m^2)	24.53 ± 3.485	24.979 ± 3.515	.341
SBP (mm of Hg)	129.33 ± 14.665	127.12 ± 12.615	.204
DBP (mm of Hg)	82.16 ± 9.504	80.92 ± 6.256	.178

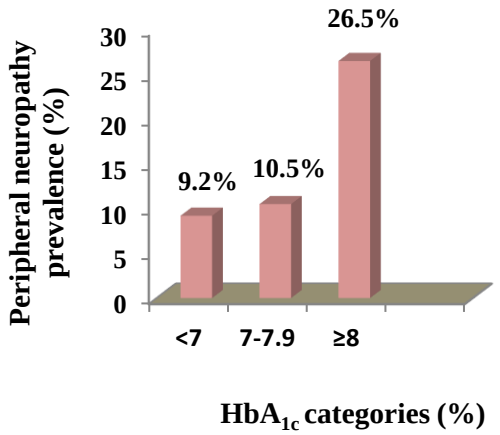
*FBG – Fasting blood glucose, 2 hours ABF - blood glucose 2 hours after breakfast, BMI- Body mass index, SBP- Systolic blood pressure, DBP- Diastolic blood pressure.

On univariate logistic regression analysis, we observed that advanced age (OR = 1.97; 95% CI: 1.12-3.47), longer duration of diabetes (OR = 1.81; 95% CI: 1.02-3.19), lacking of physical exercise (OR = 2.6; 95% CI: 1.47-4.58), FBG (OR = 1.153; 95% CI: 1.058-1.255), blood glucose 2 hours ABF (OR = 1.096; 95% CI: 1.029-1.168), had significant association with peripheral neuropathy. It was also found that female (OR = 2.17; 95% CI: 1.21-3.89) had significant risk than their male counterpart for developing peripheral neuropathy. Hypertension, SBP and DBP did not show any significant association with peripheral neuropathy (table III).

Table III Univariate logistic regression analysis showing different variables associated with peripheral neuropathy

Variables	**Odds Ratio (95% CI**	***p***
HbA_{1c} (%)		
<7	1.0	
7-7.9	1.16 (.493-2.75)	.727
≥8	3.57 (1.75-7.26)	.000
Age (years)		
<50	1.0	
≥50	1.97 (1.12-3.47)	.019
Gender		
Male	1.0	
Female	2.17 (1.21-3.89)	.009
Duration of diabetes (years)		
≤2-5	1.0	
>6-10	1.81 (1.02-3.19)	.040
Exercise done by patients		
Yes	1.0	
No	2.60 (1.47-4.58)	.001
Presence of hypertension		
No	1.0	
Yes	1.57 (.867-2.85)	.136
FBG	1.153 (1.058-1.255)	.001
2hours ABF	1.096 (1.029-1.168)	.005
SBP	1.013 (.993-1.033)	.204
DBP	1.026 (.988-1.065)	.178

Figure 1: Relationship of peripheral neuropathy with HbA_{1c}



It was to be found that the increasing HbA1c categories showed higher prevalence of peripheral neuropathy compared with the lower category which is statistically significant (9.2 Vs. 10.5 Vs. 26.5%; $\chi 2$ = 19.446, p = .000). The univariate logistic regression analysis was used to quantify the individual effect of HbA1c and other risk factors with peripheral neuropathy as dependent variable (table VI).

HbA1c category ≥8% (OR = 3.57; 95% CI: 1.75-7.26) was found to be a significant risk factor for developing peripheral neuropathy.

Table IV: Relationship between peripheral neuropathy and HbA_{1c} categories

HbA_{1c} categories (%)	With peripheral neuropathy	Without peripheral neuropathy	Total	χ^2	p value
<7	11 (9.2%)	109 (90.8%)	120		
7-7.9	12 (10.5%)	102 (89.5%)	114	19.446	**.000**
≥8	44 (26.5%)	122 (73.5%)	166		
Total	67 (16.8%)	333 (83.3%)	400		

On multivariate analysis after adjusting potential confounding factors (advanced age, longer duration of diabetes, gender, hypertension, lacking of physical exercise) it was to be found that HbA_{1c} category ≥8% (OR = 2.97; 95% CI: 1.407-6.271), advanced age (OR = 1.959; 95% CI: 1.064-3.606), female gender (OR = 2.012; 95% CI: 1.070-3.783) and lacking of physical exercise (OR =1.881; 95% CI: 1.010-3.503) were important risk factors for peripheral neuropathy (table V).

Table V: Multivariate analysis of risk factors for peripheral neuropathy.

Variables	Odds Ratio (95% CI)	*p*-value
$wHbA_{1c}$ (%)		
<7	1.0	
7-7.9	.824 (.336-2.024)	.673
≥8	2.971 (1.407-6.271)	.004
Age (years)		
<50	1.0	
≥50	1.959 (1.064-3.606)	.031
Gender		
Male	1.0	
Female	2.012 (1.070-3.783)	.030
Duration of diabetes (years)		
≤2-5	1.0	
>6-10	1.183 (.632-2.215)	.600
Exercise done by patients		
Yes	1.0	
No	1.881 (1.010-3.503)	.047
Presence of hypertension		
No	1.0	
Yes	1.320 (.700-2.486)	.391

Discussion

In this study, the prevalence of DPN was 16.8% with male 10.8% and female 20.9% with mean age of the DPN participants 51.93 ± 6.33years and mean duration of diabetes was 7.22 ± 2.656 years. A study in Bangladesh reported that the prevalence of diabetic peripheral neuropathy in type 2 diabetic patients was 19.7% (mean age in the DPN-group: 55.1 ± 10.5 years, mean duration of diabetes: 7.7 ± 1.9 years).[21] This result indicate that the mean age and mean duration of diabetes are decreasing for development of DPN in Bangladesh. A study from a diabetic center in India, reported that a neuropathy prevalence of 19.1% among type 2 diabetic outpatients and the prevalence rate was similar to the prevalence rate found in the current study (mean age in the DPN-group: 62 ± 8 years, mean duration of diabetes: 12 ± 8 years).[22] As compared to the results from India, the diabetic complications in Bangladeshi subjects emerged earlier, both in respect to age of the patient and duration of diabetes. The prevalence rate of DPN in Bangladeshis lower compared to European studies,[23-25] , which have reported an overall DPN prevalence of 32.1% (mean age: 63 years, mean duration of diabetes: six years);[23] 35.4% (mean age: 61.3 years, mean duration of diabetes: 9.7 years)[24] and 60.0% (mean age: 57.2 ± 10.3, mean duration of diabetes: 8.52 ± 7.13 years)[25] among type 2 diabetic hospital outpatients. Studies from the UK showed a lower DPN prevalence among type 2 diabetic South-Asian patients compared with European patients living in the UK even after adjusting for age.[26,27] However, this difference may be due to diagnostic criteria used in those western studies differ from the current study, which was also suggested by Morkid and associates.[21] The mean age of our subjects was 51.93 ± 6.33 years, which may confirm that the diabetes population in this part of the world is relatively young compared to the West.[21,28,29]

It was observed in this study that the advanced age and longer duration of diabetes were important and significant risk factors for peripheral neuropathy. These results were consistent with findings of other studies.[21,30,31]It was to be found that the peripheral neuropathy was more common in females than males which was also observed by Alam[32] but contrast to other studies.[21,22,24,33] This study also revealed a significant association of peripheral neuropathy with non-urban(rural and semi urban) residence. The higher prevalence of DPN in non-urban participants may be due to referral bias, as this center was offering advance services for diabetic

complications and commonly complicated than non-complicated diabetic patients from rural and suburban area came here. It was observed that HbA_{1c}, blood glucose levels in fasting and two hours after breakfast were important risk factors of peripheral neuropathy. These findings were consistent with other studies[30,34]. It was not observed any significant association of systolic and diastolic blood pressures with peripheral neuropathy. Ramachandra et al[35] also did not report any significant association of hypertension with diabetic neuropathy, but others were in contrast with this current study.[30,36] Lack of physical exercise was also a contributing factor in this study.

Several studies indicated that HbA_{1c} may show a glycaemic threshold with micro and macro vascular complications of diabetes, suggesting it may additionally be useful biomarker to identify individuals at risk for different vascular complications.[17,37,38] In this study, it was observed that increasing HbA_{1c} categories above 7.0% were significantly associated with increased prevalence of DPN. Logistic regression models of univariate analysis showed that the risk of DPN strongly increased at the HbA_{1c} categories ≥8%. Even on multivariate analysis after adjusting potential confounding factors (advanced age, longer duration of diabetes, gender, hypertension, lacking of physical exercise) we found that HbA_{1c} category ≥8% is important risk factors for peripheral neuropathy. Results of this study were consistent with Sabanayagam et al[17] who reported that increasing HbA_{1c} categories had a higher prevalence of any retinopathy, mild retinopathy, moderate retinopathy, CKD, micro or macro-albuminuria and peripheral neuropathy. Another study also found the similar association of HbA_{1c} with retinopathy, nephropathy and neuropathy.[30] Zoungas et al observed that for microvascular events the apparent threshold of HbA_{1c} level was 6.5%.[38] They also revealed that above thresholds, a higher level of HbA_{1c} was significantly associated with higher risks of microvascular events in a log-linear manner. Below these thresholds, there was no significant relationship between mean HbA_{1c} level and risks. In the current study there were relatively few DPN events observed at HbA_{1c} levels less than 7.0% may be due to small sample size so it could not properly be evaluated the HbA_{1c} levels below 7.0% in DPN.

Conclusion

Findings of this study suggest that increasing HbA_{1c} categories above 7.0% were significantly associated with increased prevalence of DPN and the risk increases markedly at HbA_{1c} levels ≥8%.The prevalence and risk of DPN also increased with advanced age, longer duration of diabetes, poor glycaemic control, lack of physical exercise, female gender etc. Careful assessment of the risk factors of DPN among diabetic patients, and control of HbA_{1c} and appropriate preventive measures are thus recommended.

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