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Physiology

EFFECT OF DURATION OF TYPE 2 DIABETES MELLITUS ON PERIPHERAL NERVE CONDUCTION – AN OBSERVATIONAL ANALYTICAL STUDY

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ABSTRACT

Introduction: Diabetic peripheral neuropathy (DPN) is most common complication of diabetes mellitus (DM). In India there are few studies showing association between peripheral nerve conduction and duration of type 2DM in controlled diabetic subjects. Hence, present study was undertaken.

Methods: Group A: 30 age and sex matched healthy controls. 60 type 2DM male patients with controlled blood glucose levels divided into 2 groups. Group B: having DM for 0-5 years and Group C having DM for 5 to 10 years. Nerve conduction study was performed to record electrophysiological parameters.

Results: Sensorimotor conduction was affected in lower limbs; while in upper limbs only sensory conduction was affected over the duration of disease. Percentage reduction in lower limb parameters was more.

Conclusion: Prevention of development of DPN by maintaining precise control of blood glucose levels is importance. Regular screening of peripheral nerve function will definitely help to reduce the morbidity significantly.

KEYWORDS : Type 2 Diabetes Mellitus, Diabetic peripheral neuropathy, Duration of diabetes, Nerve conduction study

INTRODUCTION

Diabetes mellitus is now coming up as an epidemic in India. According to the Lancet study, China, India and USA are among the top three countries with a high number of diabetic populations. Currently, 4.0-11.6 per cent of India's urban population and three per cent of the rural population above the age of 15 has diabetes.[1,2] India has been called "the diabetes capital of the world" and every fifth diabetic in the world is an Indian.[3]

Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation. Diabetic peripheral neuropathy (DPN) is most common and troublesome complication. Prevalence of DPN is ranging from 5% to 60%.[4] DPN has not been defined uniformly all over the world. Hence, detailed studies are lacking. If DPN is detected earlier, progress of neuropathy can be arrested by using appropriate intervention.[5]

Presently, in India there are comparatively few studies showing association between peripheral nerve conduction and duration of type 2 DM in controlled diabetic subjects. Knowledge regarding relation of duration of type 2 DM with severity of neuropathy can give us clue about pathophysiology of neuropathy which may guide us for early intervention and prevention. Nerve conduction studies are very sensitive to assess severity of neuropathy. Hence, present study was undertaken to assess the risk of diabetic neuropathy in relation with duration of type 2 DM.

Material and Methods:

Study Design:

This is an observational analytical study involving 90 subjects (age group of 40-60 years) divided into 3 groups of 30 each. Group A: 30 age and sex matched healthy controls, Group B: 30 male patients having type 2 DM for 0-5 years with controlled blood glucose levels. Group C: 30 male patients having type 2 DM for 5 to 10 years with controlled blood glucose levels.

Inclusion and exclusion criteria: Normotensive patients having controlled glycated haemoglobin (HbA1c) i.e. < 7.0% [6] and taking regular oral hypoglycemic agents as advised by physician, non-smoker, non-alcoholic and non-tobacco chewers were included in the study. Patients having history of insulin treatment, vitamin B_{12} deficiency, intake of drugs causing neuropathy, neurodegenerative diseases, neuromuscular transmission disorders and myopathies, leprosy, acute complication of diabetes, local skin diseases, hypothyroidism, autoimmune diseases like SLE, permanent pacemaker or other such implanted stimulators, chronic diseases like renal failure, liver disease, airway disease, carcinoma, infections and critical illness, familial neuropathy or toxin exposure were excluded from the study.

Method:

After approval from institutional ethics committee; informed written consent, relevant clinical history and details of neurological examination were obtained. Body mass index was calculated as-

BMI = Weight in Kg / (Height in meters) ^{2}

Glycated hemoglobin (HbA1c) was estimated by ion-exchange resin method by the diagnostic glycohemoglobin kit of Asritha Diatech as per the guidelines provided. Evaluation of peripheral nerve function was done clinically as well as electrophysiologically using the standard RMS ALERON 401 machine (Recorders and Medicare systems, India) at fixed room temperature of 30^0C using standard procedure with surface electrodes.[8,9,10,11] Parameters recorded were amplitude of compound muscle action potential (CMAP) and motor nerve conduction velocity (MNCV) of bilateral ulnar motor and peroneal nerves; amplitude of sensory nerve action potential (SNAP) and sensory nerve conduction velocity (SNCV) of bilateral ulnar sensory and sural nerves.

Statistical analysis:

The detailed data was entered into the Microsoft excel sheet and subsequently analyzed statistically by using SPSS version 16 software. Values were reported as Mean ± S.D. Comparisons of nerve conduction parameters among groups were done by applying the ANOVA test. Intergroup multiple comparisons were done by using post hoc Dunnet's t test. Significance level was set at $p<0.05$ and considered as significant. To determine the correlation between duration of diabetes and nerve conduction parameters, mean of right and left side was taken for each parameter and then Pearson's correlation coefficient was applied. To understand severity of affection in upper limbs and lower limbs percentage reduction was calculated for group B and Group C in relation to control group and then compared.

Results and Discussion:

Difference in means of age, height, weight, body mass index was not statistically significant among three groups. Though the difference in means of HbA1c was statistically significant ($p<0.05$); all the values were within normal limits.(Table 1)

Table 1: Descriptive statistics:

Parameter	Group A Control (Mean ± SD) (n = 30)	Group B Duration of DM < 5 yr (Mean ± SD) (n = 30)	Group C Duration of DM > 5 yr (Mean ± SD) (n = 30)	p value
Age (years)	50.4 ± 5.4	51.4 ± 6.5	52.9 ± 5.1	> 0.05
Height (cm)	166.6 ± 5.7	166.6 ± 5.6	166.0 ± 4.8	> 0.05
Weight (Kg)	65.4 ± 8.5	66.3 ± 7.2	66.3 ± 7.2	> 0.05

Body mass index (Kg/m^2)	23.9 ± 2.9	23.9 ± 2.6	24.1 ± 2.6	> 0.05
HbA1c (%)	6.1 ± 0.5	6.4 ± 0.4	6.6 ± 0.2	< 0.05*

Table 2: Comparison of amplitude (amp) (mV) of CMAP and velocity (m/s) among three groups: (ANOVA test)

Nerve	Group A Control (Mean ± SD) (n = 30)	Group B Duration of DM < 5 yr (Mean ± SD) (n = 30)	Group C Duration of DM > 5 yr (Mean ± SD) (n = 30)	p value
Right Ulnar amp	34.89 ± 8.90	32.17 ± 10.59	30.22 ± 8.90	> 0.05
Left Ulnar amp	34.19 ± 7.87	32.20 ± 10.54	29.77 ± 9.05	> 0.05
Right Peroneal amp	19.75 ± 2.59	17.69 ± 4.72	15.43 ± 5.26	< 0.05*
Left Peroneal amp	19.39 ± 2.50	17.33 ± 4.74	15.65 ± 5.21	< 0.05*
Right Ulnar MNCV	51.89 ± 2.26	51.79 ± 2.22	51.58 ± 1.90	> 0.05
Left Ulnar MNCV	52.59 ± 2.98	52.04 ± 2.25	51.69 ± 2.79	> 0.05
Right Peroneal MNCV	48.29 ± 4.44	47.68 ± 5.00	43.41 ± 8.26	< 0.05*
Left Peroneal MNCV	48.72 ± 4.48	47.76 ± 5.17	43.30 ± 8.23	< 0.05*

Table 3: Comparison of amplitude (amp) (mV) of CMAP and MNCV (m/s) between groups (Post hoc Dunnet's t test):

Nerve	I	II	Meandifference(I-II)	Standard error	p value
Right Ulnar amp	Group B	Group A	-2.72	2.45	> 0.05
	Group C	Group A	-4.67	2.45	> 0.05
Left Ulnar amp	Group B	Group A	-1.99	2.38	> 0.05
	Group C	Group A	-4.42	2.38	> 0.05
Right Peroneal amp	Group B	Group A	-2.06	1.12	> 0.05
	Group C	Group A	-4.32	1.12	< 0.001**
Left Peroneal amp	Group B	Group A	-2.06	1.11	> 0.05
	Group C	Group A	-3.74	1.11	< 0.001**
Right Ulnar MNCV	Group B	Group A	-0.10	0.55	> 0.05
	Group C	Group A	-0.32	0.55	> 0.05
Left Ulnar MNCV	Group B	Group A	-0.55	0.70	> 0.05
	Group C	Group A	-0.89	0.70	> 0.05
Right Peroneal MNCV	Group B	Group A	-0.61	1.58	> 0.05
	Group C	Group A	-4.88	1.58	< 0.05*
Left Peroneal MNCV	Group B	Group A	-0.96	1.60	> 0.05
	Group C	Group A	-5.42	1.60	< 0.05*

Table 2 shows that in ulnar nerves, difference in means of amplitude of CMAP as well as difference in means of MNCV among three groups were not statistically significant. But, in case of peroneal nerves these differences were significantly lesser in group B and group C than group A. (p<0.05) Intergroup analysis shows that in peroneal nerves mean difference in amplitude of CMAP as well as in MNCV was statistically highly significant (p<0.001) in group C as compared to group A. (Table 3)

Thus it is observed that both, amplitude and conduction velocity, of peroneal nerves are affected in long duration diabetics; while ulnar motor nerves are normal. Similar results were obtained by Dutta A et al and Kimura J et al. Decrease in amplitude indicates axonal degeneration while decrease in conduction velocity indicates demyelination. Thus, present study shows that with progress of diabetes duration simultaneous axonal and demyelinating degeneration occurs in nerves.

Table 4: Comparison of amplitudes of SNAP (µV) and SNCV (m/s) among three groups: (ANOVA test)

Nerve	Group A Control (Mean ± SD) (n = 30)	Group B Duration of DM < 5 yr (Mean ± SD) (n = 30)	Group C Duration of DM > 5 yr (Mean ± SD) (n = 30)	p value
Right Ulnar amp	46.26 ± 5.07	41.37 ± 9.01	40.51 ± 10.35	< 0.05*
Left Ulnar amp	46.41 ± 5.08	41.07 ± 9.58	40.23 ± 10.41	< 0.05*
Right Sural amp	21.44 ± 3.93	16.55 ± 7.30	14.75 ± 8.47	< 0.001**
Left Sural amp	21.09 ± 3.77	15.95 ± 7.10	13.66 ± 8.28	< 0.001**
Right Ulnar SNCV	52.52 ± 2.23	51.31 ± 2.11	50.86 ± 2.98	< 0.05*
Left Ulnar SNCV	52.94 ± 1.99	51.87 ± 2.83	50.83 ± 2.93	< 0.05*
Right Sural SNCV	45.87 ± 3.62	38.58 ± 10.67	35.44 ± 14.24	< 0.001**
Left Sural SNCV	46.17 ± 3.51	38.71 ± 10.76	35.68 ± 14.44	< 0.001**

Table 5: Comparison of sensory nerve conduction amplitudes (µV) between groups (Post hoc Dunnet's t test):

Nerve	I	II	Meandifference(I-II)	Standard error	p value
Right Ulnar amp	Group B	Group A	-4.90	2.18	< 0.05*
	Group C	Group A	-5.75	2.18	< 0.05*
Left Ulnar amp	Group B	Group A	-5.34	2.24	< 0.05*
	Group C	Group A	-6.17	2.24	< 0.05*
Right Sural amp	Group B	Group A	-4.89	1.77	< 0.05*
	Group C	Group A	-6.70	1.77	< 0.001**
Left Sural amp	Group B	Group A	-5.14	1.72	< 0.05*
	Group C	Group A	-7.43	1.72	< 0.001**
Right Ulnar SNCV	Group B	Group A	-4.90	2.18	< 0.05*
	Group C	Group A	-5.75	2.18	< 0.05*
Left Ulnar SNCV	Group B	Group A	-5.34	2.24	< 0.05*
	Group C	Group A	-6.17	2.24	< 0.05*
Right Sural SNCV	Group B	Group A	-4.89	1.77	< 0.05*
	Group C	Group A	-6.70	1.77	< 0.001**
Left Sural SNCV	Group B	Group A	-5.14	1.72	< 0.05*
	Group C	Group A	-7.43	1.72	< 0.001**

Table 4 shows that mean value of amplitude of SNAP and mean value of SNCV were less in group B and group C than group A in both, ulnar motor (p<0.05) and sural (p<0.001) nerves.

Table 5 shows that mean difference in amplitude of ulnar SNAP was statistically significant (p<0.05) in both group B and group C when compared individually with group A. Similarly the mean difference for sural nerves was also statistically significant in both group B (p<0.05) and group C (p<0.001) as compared to group A.

Table 5 also shows that mean difference in ulnar SNCV was not statistically significant in group B as compared to group A, but it was statistically significant in group C (p<0.05) as compared to group A. In case of sural nerves, mean difference was statistically significant in both group B (p<0.05) as well as group C (p<0.001) when compared individually with group A.

Table 4 and 5 shows that sensory nerve condction parameters were significantly lowered in both upper amnd lower limbs as compared to control gropus. Tesfaye S et al [14] in their study found stastically significant decrease in sural nerve amplitude over the period of one year. Graf RJ et al [15] also found that, in spite of diabetes treatment sensory nerve conduction velocity worsened over a period of time. However, Pastore C et al[16] did not get significant reduction in amplitude of SNAP as well as SNCV of sural nerve in patients of type 2DM which might be attributed to smaller sample size in their study.

In case of ulnar sensory nerve conduction, we found statistically significant reduction in amplitude of SNAP, but no significant reduction in conduction velocity in short duration diabetics. This suggests that though there is simultaneous axonal as well as demyelinating degeneration, axonal degeneration is the predominent pathology in peripheral nerve dysfunction. Partanen J et al[17] in their study also got more reduction in amplitudes than conduction velocities of nerves indicating predominent axonal degeneration. But Fraser DM et al[18] in their study found segmental demyelination as the predominant feature. They attributed this to more Schwann cell damage. This contradiction may have occurred because of smaller sample size of

their study.

Table 6 - Correlation of peripheral nerve conduction parameters with duration of DM by Pearson's correlation coefficient

Variable n=60		Pearson's Correlation Coefficient 'r'	p value
Motor Amplitude	Ulnar nerve	-0.08	> 0.05
	Peroneal nerve	-0.17	> 0.05
Motor Velocity	Ulnar nerve	-0.057	> 0.05
	Peroneal nerve	-0.067	> 0.05
Sensory Amplitude	Ulnar nerve	-0.089	> 0.05
	Sural nerve	-0.179	> 0.05
Sensory Velocity	Ulnar nerve	-0.147	> 0.05
	Sural nerve	-0.146	> 0.05

Table 6 shows that there was no statistically significant correlation of duration of DM and any of the peripheral nerve conduction parameter under consideration. This clearly shows that in addition to duration of DM, certain other factors must be involved in pathogenesis of diabetic neuropathy. Pastore C et al16 in their study also did not get statistically significant correlation between duration of type 2DM and electrophysiological parameters. However Dutta A et al12 in their study, on multiple logistic regression analysis found that duration of diabetes has maximum contribution to diabetic peripheral neuropathy. This difference in results could be attributed to the fact that they didn't considered glycemic status while correlating nerve conduction parameters with duration.

Table-7: Percentage reduction in nerve conduction parameters of upper limb and lower limb for group B and group C:

Parameter	Nerve	% Reduction	
		Group B	Group B
Amplitude of CMAP	Ulnar nerve	6.81	13.17
	Peroneal nerve	10.52	20.59
MNCV	Ulnar nerve	0.79	1.16
	Peroneal nerve	1.62	10.62
Amplitude of SNAP	Ulnar nerve	11.04	12.90
	Sural nerve	23.59	33.21
SNCV	Ulnar nerve	2.16	3.44
	Sural nerve	16.01	22.72

Table 7 shows that for group B and group C, percentage reduction in all nerve conduction parameters is more in lower limb nerves than upper limb nerves. % reduction is more in sural nerves than peroneal nerves. Fraser DM et al[18] found no abnormalities of ulnar and median nerves, but found abnormal conduction velocity in peroneal nerves. Partanen J et al[17] in their longitudinal study also found that after 5 years there is reduction in amplitude of SNAP and conduction velocity in lower limb. After 10 years of study there were involvements of upper limbs as well. This is because, in distal symmetric type of peripheral nerve dysfunction longest nerve fibers are first to get affected. Thus signs and symptoms initially start in the lower limbs in a 'stocking' type of distribution and then gradually extending to proximal parts of body.[19]

Motor weakness starts later than sensory loss.[20] The present study is also supporting this fact, since we observed involvement of ulnar sensory parameters, but not of the ulnar motor parameters.

Present study has shown that with increase in duration of DM, there is definite fall in the nerve conduction parameters. But since the duration of disease is a non-modifiable factor, we also have to consider modifiable factors contributing to diabetic neuropathy. All the subjects in our study had normal HbA1c levels which shows that they were having controlled glycemic status. However, HbA1c level accounts for blood glucose levels for past 3 months only. Previous prolonged hyperglycemia might have caused irreversible nerve damage.Hence, a long duration prospective study has to be conducted to throw more light on this aspect.

The axons of peripheral nerves and Schwann cells do not require insulin for glucose transport across cell membrane.[21] So glycemic status is directly reflected in cytoplasmic glucose concentration in peripheral nerves and schwann cells. Chronic hyperglycemia which could be asymptomatic or symptomatic, continuous or intermittent in total duration of diabetes, is responsible for target organ damage.

Hyperglycemia causes increase in advanced glycation end products (AGEs), which induce cytokine production. Nonenzymatic glycosylation of nerve cell proteins damages nerves and prevents transmission of signals in response to stimuli. Sorbitol accumulationin nerve cells[22], Na^+/K^+ ATPase pump dysfunction may be responsible to some extent. [23]

Diabetic neuropathy is a highly dynamic disorder. Over a period of time, regenerating ability of nerve is hampered [24] and the balance between nerve degeneration and regeneration shifts more toward degeneration leading to neuronal loss. The degree of neuropathy very well relates to this gradual loss of regeneration.[24] Thus, multiple mechanisms are interacting in DM to cause changes in peripheral nerve function.

Conclusion:

Prevention of development of diabetic neuropathy by maintaining continuous, precise control of blood glucose levels is of utmost importance. It is therefore crucial to submit a diabetic patient to regular examinations which are specifically designed to detect early abnormalities in the peripheral nerves like nerve conduction studies. Once peripheral neuropathy sets in, its regression is difficult. Hence, prompt action should be taken to prevent its progression. Regular screening of peripheral nerve function will definitely help to reduce the morbidity significantly, thereby decreasing the global burden of long term complications of diabetes mellitus.

References:

1. Park K. Park's textbook of preventive and social medicine. 21st ed. Jabalpur: M/s Banarsidas Bhanot; 2011. Epidemiology of chronic non-communicable diseases and conditions; pp. 363–4.
2. 6. India, world diabetes capital. Hindustan Times [newspaper on the Internet]. 2007 Sep 03 [cited 2013 May 25]; para 1-5. Available from: http://www.hindustantimes.com/India-worlddiabetes-capital/Article1-245889.aspx.
3. Joshi SR, Parikh RM. India - diabetes capital of the world: now heading towards hypertension. J Assoc Physicians India. 2007;55:323–324.
4. Thomas, P.K., Eliasson, S.G. 1984. Diabetic neuropathy. In: Dyck PJ, Thomas PK, Lambart EH, Bunge R (eds). Peripheral neuropathy. 2nd ed. Philadelphia: W. B. Saunders Co., pp. 1773-1810.
5. Dyck, P.J., O' Brien, P.C. 1989. Meaningful degrees of prevention or improvement of nerve conduction in controlled clinical trials of diabetic neuropathy. Diabetes Care, 12(9): 649-652.
6. Powers, A.C. 2008. Diabetes mellitus. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL (eds) Harrison,s principles of internal medicine. 17th ed. USA: Mc Graw Hill, pp. 2275-2304.
7. Nathan DM, Singer DE, Hurxthal K, Goodson JD. The Clinical Information Value Of The Glycosylated Haemoglobin Assay. N Eng J Med 1984;310:341-346.
8. Misra UK, Kalita J. Nerve conduction study. In: Clinical Neuophysiology. 2nd ed. New Delhi, India: Elsevier; 2006. p. 21-128.
9. Preston DC, Shapiro BE. Basic nerve conduction studies. In: Electromyography and neuromuscular disorders. 2nd ed. Philadelphia, USA: Elsevier; 2005. p. 25-45.
10. Preston DC, Shapiro BE. Routine upper extremity and facial nerve conduction techniques. In: Electromyography and neuromuscular disorders. 2nd ed. Philadelphia, USA: Elsevier; 2005. p. 117-44.
11. Preston DC, Shapiro BE. Routine lower extremity nerve conduction techniques In: Electromyography and neuromuscular disorders. 2nd ed. Philadelphia, USA: Elsevier; 2005. p. 145-60.
12. Dutta A, Naorem S, Singh P, Wangjam K. Prevalence of peripheral neuropathy in newly diagnosed type 2 diabetics. Int J Diab Dev Ctries 2005; 25: 30-33.
13. Kimura J, Yamada T, Stevland NP. Distal slowing of motor nerve conduction velocity in diabetic polyneuropathy. J Neurol Sci 1979; 42(2): 291-302.
14. Tesfaye S, Tandan R, Bastyr EJ 3rd, Kles KA, Skljarevski V, Price KL; Ruboxistaurin Study Group. Factors that impact symptomatic diabetic peripheral neuropathy in placebo-administered patients from two 1-year clinical trials. Diabetes Care 2007; 30(10): 2626-32.
15. Graf RJ, Halter JB, Pfeifer MA, Halar E, Brozovich F, Porte D Jr. Glycemic control and nerve conduction abnormalities in non-insulin- dependent diabetic subjects. Ann intern Med 1981; 94(3): 307-11.
16. Pastore C, Izura V, Geijo-Barrientos E, Dominguez JR. A comparison of electrophysiological tests for the early diagnosis of diabetic neuropathy. Muscle Nerve. 1999; 22(12): 1667-73.
17. Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa M. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 1995; 333(2): 89-94.
18. Fraser DM, Campbell IW, Ewing DJ, Clarke BF. Mononeuropathy in diabetes mellitus. Diabetes 1979; 28(2): 96-101
19. Said G. Diabetic neuropathy-a review. Nat Clin Pract Neurol 2007; 3(6): 331-40.
20. Booya F, Bandarian F, Larijani B, Pajouhi M, Nooraei M, Lotfi J. Potential risk factors for diabetic neuropathy: a case control study. BMC Neurol 2005; 5: 24.
21. Greene DA, Winegrad AI. In vitro studies of the substrates for energy production and the effects of insulin on glucose utilization in the neural compartments of peripheral nerve. Diabetes 1979; 28(10): 878-87.
22. Grenfell A, Watkins PJ. Clinical diabetic nephropathy: natural history and complications. Clin Endocrionol Metab 1986; 15(4): 783–805.
23. Krishnan AV, Kiernan MC. Altered nerve excitability properties in established diabetic neuropathy. Brain 2005; 128(Pt 5): 1178-87.
24. Polydefkis M, Griffin JW, McArthur J. New insights into diabetic polyneuropathy. JAMA 2003; 290(10): 1371-6.