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RESEARCH ARTICLE

EFFECT OF DURATION OF TYPE 2 DIABETES MELLITUS ON PERIPHERAL NERVE CONDUCTION IN UPPER LIMBS

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ABSTRACT

Diabetes mellitus (DM) is one of the most common chronic diseases globally. Diabetic peripheral neuropathy (DPN) is the troublesome complication. But exact pathogenesis is not yet known. Studies showing association between duration of DM with severity of neuropathy are less in number. Hence, present study was aimed to compare conduction velocities and amplitudes of sensory-motor nerves of upper limbs in healthy controls and patients with type 2 DM of varying duration and to correlate these parameters with duration of disease. 60 type 2 DM male patients having controlled glycated hemoglobin (Hb A1c), were selected. 30 were having diabetes for 0-5 years (group B) and 30 were having diabetes for 5-10 years (group C). They were compared with 30 healthy controls (group A). Conduction velocity and amplitudes of ulnar motor and ulnar sensory nerves were recorded bilaterally. On analysis, amplitudes and conduction velocities of ulnar sensory nerves were significantly lower in diabetic patients with longer duration of DM. To conclude, DPN worsens with increasing duration of disease. Stringent action has to be taken at an early stage of disease to prevent nerve damage. Early diagnosis of DPN remains the cornerstone of patient follow up.

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INTRODUCTION

Among all the chronic diseases globally, diabetes mellitus (DM) is one of the most common, affecting 8.3% of the world's population. Diabetes mellitus is a cluster of metabolic diseases characterized by increase in blood glucose level resulting from defects in insulin action, insulin secretion, or both. (American Diabetes Association, 2013) Currently in many countries it is a leading cause of disability, death and high health care cost. According to International Diabetes Federation 2014, approximately 387 million people in the world are suffering from diabetes mellitus. Largest numbers of cases are present in China followed by India. (International Diabetes Federation, 2013) Of these; more than 90% patients have type 2 DM. It is usually diagnosed in the middle years of life. (World Health Organization, 2012) Among all the diabetic complications, diabetic peripheral neuropathy (DPN) is the one, which is most common and troublesome complication leading to great morbidity. (Ugoya *et al*., 2008) Approximately, 8% of diabetics have neuropathy at the time of diagnosis. (Pirart, 1978) Prevalence of DPN is ranging from less than 5% to approximately 60%. (Thomas and Eliasson, 1984) Because of lack of uniform definition of DPN, detailed studies are not available. As compared with non-diabetic subjects, the risk of amputation increases 12 times in diabetic patients. (Nathan, 1993) However, if detected earlier, progression of neuropathy can be arrested by appropriate intervention. (Dyck and O' Brien, 1989) Presently, in India there are comparatively few studies showing association between severity of upper limb neuropathy 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. Hence, present study was undertaken to assess the risk of diabetic neuropathy in relation with duration of type 2 DM.

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MATERIALS AND METHODS

Study Design

An observational analytical study was conducted in type 2 DM male patients selected from diabetic OPD of the B. J. Govt Medical College and Sassoon general hospital, Pune. Duration of study was from August 2010 to July 2012. The approval from Institutional Ethics Committee for human studies was obtained prior to study.

Patients in the age group of 40-60 years having controlled blood glucose levels were selected. Informed written consent was taken from all subjects willing to participate in the study. A questionnaire was designed to obtain basic information of subjects. Detailed neurological examination was then carried out.

Sample size

Total sample size was 90 divided into three groups of 30 each, after subjects who withdrew from the study. 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 more than 5 years up to 10 years with controlled blood glucose levels.

Inclusion and exclusion criteria

Normotensive patients having controlled glycated haemoglobin (Hb A1c) i.e. < 7.0% (Powers, 2008) 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 B12 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.

A relevant clinical history and neurological examination was performed. Body mass index was calculated as- (Park, 2011)

$BMI = Weight\ in\ Kg\ /\ (Height\ in\ meters)^2$

Estimation of glycated hemoglobin (Hb A1c): (Nathan, *et al*., 1984)

Glycated hemoglobin (Hb A1c) of all patients was estimated by ion-exchange resin method by the diagnostic glycohemoglobin kit of Asritha Diatech as per the guidelines provided.

Nerve conduction study: (Misra and Kalita, 2006; Preston and Shapiro, 2005a,b)

Evaluation of peripheral nerve function was done clinically as well as electro physiologically 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. Parameters recorded were amplitude of compound muscle action potential (CMAP), amplitude of sensory nerve action potential (SNAP), motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV) of bilateral ulnar 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 analysis of variance (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.

RESULTS

Difference in means of age, height, weight, body mass index was not statistically significant among three groups. Though the difference in means of Hb A1c was statistically significant ($p<0.05$); all the values were within normal limits. (Table 1) In case of right ulnar nerve, mean values of CMAP amplitude were 34.89 ± 8.90 mV, 32.17 ± 10.59 mV, 30.22 ± 8.90 mV and mean values of MNCV were 51.89 ± 2.26 m/s, 51.79 ± 2.22 m/s, 51.58 ± 1.90 m/s for group A, group B and group C respectively. For left ulnar nerve, mean values of CMAP amplitude were 34.19 ± 7.87mV, 32.20 ± 10.54 mV, 29.77 ± 9.05 mV and mean values of MNCV were 52.59 ± 2.98 m/s, 52.04 ± 2.25 m/s, 51.69 ± 2.79 m/s for group A, group B and group C respectively. The difference in means of CMAP amplitude and MNCV is not statistically significant in group B as well as in group C as compared to group A. (Table 2, Table 3)

Table 1. Descriptive statistics for demographic and baseline characteristics of study population (ANOVA test)

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 (in years)	50.4 ± 5.4	51.4 ± 6.5	52.9 ± 5.1	> 0.05
Height (in cm)	166.6 ± 5.7	166.6 ± 5.6	166.0 ± 4.8	> 0.05
Weight (in Kg)	65.4 ± 8.5	66.3 ± 7.2	66.3 ± 7.2	> 0.05
Body mass index (in Kg/m^2)	23.9 ± 2.9	23.9 ± 2.6	24.1 ± 2.6	> 0.05
Hb A1c (in %)	6.1 ± 0.5	6.4 ± 0.4	6.6 ± 0.2	< 0.05*

* $p<0.05$ statistically significant ** $p<0.001$ statistically highly significant

Table 2. Comparison of motor nerve conduction amplitude (mV) and conduction velocity (m/s) among three groups (ANOVA test)

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
Ulnar motor nerve conduction amplitude (mV)	Right	34.89 ± 8.90	32.17 ± 10.59	30.22 ± 8.90	> 0.05
	Left	34.19 ± 7.87	32.20 ± 10.54	29.77 ± 9.05	> 0.05
Ulnar motor nerve conduction velocity (m/s)	Right	51.89 ± 2.26	51.79 ± 2.22	51.58 ± 1.90	> 0.05
	Left	52.59 ± 2.98	52.04 ± 2.25	51.69 ± 2.79	> 0.05

* $p<0.05$ statistically significant ** $p<0.001$ statistically highly significant

Table 3. Comparison of motor nerve conduction amplitude (mV) and conduction velocity (m/s) between groups (Post hoc Dunnet's t test)

Parameter		I	II	Mean difference (I-II)	Standard error	p value
Ulnar motor nerve conduction amplitude (mV)	Right	Group B	Group A	-2.72	2.45	> 0.05
		Group C	Group A	-4.67	2.45	> 0.05
	Left	Group B	Group A	-1.99	2.38	> 0.05
		Group C	Group A	-4.42	2.38	> 0.05
Ulnar motor nerve conduction velocity (m/s)	Right	Group B	Group A	-0.10	0.55	> 0.05
		Group C	Group A	-0.32	0.55	> 0.05
	Left	Group B	Group A	-0.55	0.70	> 0.05
		Group C	Group A	-0.89	0.70	> 0.05

* p<0.05 statistically significant ** p<0.001 statistically highly significant

Table 4. Comparison of sensory nerve conduction amplitude (µV) and conduction velocity (m/s) among three groups (ANOVA test)

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
Ulnar sensory nerve conduction amplitude (µV)	Right	46.26 ± 5.07	41.37 ± 9.01	40.51 ± 10.35	< 0.05*
	Left	46.41 ± 5.08	41.07 ± 9.58	40.23 ± 10.41	< 0.05*
Ulnar sensory nerve conduction velocity (m/s)	Right	52.52 ± 2.23	51.31 ± 2.11	50.86 ± 2.98	< 0.05*
	Left	52.94 ± 1.99	51.87 ± 2.83	50.83 ± 2.93	< 0.05*

* p<0.05 statistically significant ** p<0.001 statistically highly significant

Table 5. Comparison of sensory nerve conduction amplitude (µV) and conduction velocity (m/s) between groups (Post hoc Dunnet's t test)

Parameter		I	II	Mean difference (I-II)	Standard error	p value
Ulnar sensory nerve conduction amplitudes (µV)	Right	Group B	Group A	-4.90	2.18	< 0.05*
		Group C	Group A	-5.75	2.18	< 0.05*
	Left	Group B	Group A	-5.34	2.24	< 0.05*
		Group C	Group A	-6.17	2.24	< 0.05*
Ulnar sensory nerve conduction velocity (m/s)	Right	Group B	Group A	-1.21	0.59	> 0.05
		Group C	Group A	-1.53	0.59	< 0.05*
	Left	Group B	Group A	-1.07	0.68	> 0.05
		Group C	Group A	-2.08	0.69	< 0.05*

* p<0.05 statistically significant ** p<0.001 statistically highly significant

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
Ulnar Motor Amplitude	-0.08	> 0.05
Ulnar Motor Velocity	-0.057	> 0.05
Ulnar Sensory Amplitude	-0.089	> 0.05
Ulnar Sensory Velocity	-0.147	> 0.05

* p<0.05 statistically significant ** p<0.001 statistically highly significant

In case of right ulnar nerve, mean values of SNAP amplitude were 46.26 ± 5.07 µV, 41.37 ± 9.01 µV, 40.51 ± 10.35 µV and mean values of SNCV were 52.52 ± 2.23 m/s, 51.31 ± 2.11 m/s, 50.86 ± 2.98 m/s for group A, group B and group C respectively. For left ulnar nerve, mean values of SNAP amplitude were 46.41 ± 5.08 µV, 41.07 ± 9.58 µV, 40.23 ± 10.41 µV and mean values of SNCV were 52.94 ± 1.99 m/s, 51.87 ± 2.83 m/s, 50.83 ± 2.93 m/s group A, group B and group C respectively. Group B and group C have significantly lesser means of amplitudes of SNAP ($p<0.05$) as compared to group A. The mean difference in SNCV is statistically significant among 3 groups ($p<0.05$). Mean difference is not statistically significant in group B as compared to group A, but it is statistically significant in group C ($p<0.05$) as compared to group A. (Table 4, Table 5)

Table 6 shows that on applying Pearson's correlation coefficient, there was no correlation of duration of DM and any of the peripheral nerve conduction parameter under consideration.

DISCUSSION

The present study was aimed to assess peripheral nerve function in type 2 diabetic patients in relation to duration of diabetes and to compare peripheral nerve function between normal healthy controls and short duration and long duration diabetic patients. We recorded amplitude of CMAP, amplitude of SNAP, MNCV and SNCV of bilateral ulnar nerves in normal healthy control group, short duration and long duration type 2 diabetic patients.

Nerve conduction studies are one of the most sensitive indices to assess severity of neuropathy. (Tkac and Bril, 1998) Motor nerve conduction studies assess motor axons by selectively recording muscle responses to nerve stimulation. Sensory nerve conduction studies assess sensory axons by recording electrical activity directly from peripheral nerves. (Brazier, 2012) These tests are used to localize lesions and to describe the type and severity of the pathophysiology, including alterations in function which are not recognized clinically. Subclinical

neuropathy is best detected by the sensory nerve conduction study. (Oh, 2003) Amplitude depends on number and size of functioning axons or muscle fibres. Decrease in amplitude suggests axonal degeneration, whereas decrease in conduction velocity suggests demyelination. (Misra and Kalita, 2006; Preston and Shapiro, 2005a; Partanen *et al*., 1995)

In our study, we found that the difference in means of amplitude of CMAP and MNCV is not statistically significant in short duration as well as in long duration diabetics as compared to controls. But both diabetic groups have significantly lesser means of amplitude of SNAP ($p<0.05$) and SNCV ($p<0.05$) as compared to control group. This suggests that sensory nerve conduction is affected at an early stage of disease than motor nerve conduction. Previous studies also observed that no patient had motor involvement without sensory involvement. (Tesfaye, 2011; Kasznicki, 2014; Andreassen *et al*., 2006; Sumner *et al*., 2003)

We observed significant reduction in SNCV as well as in amplitude of SNAP in diabetic patients. This suggests that, axonal degeneration as well as demyelination, both contribute to the development of DPN. Our results are matching with the results of Bagai K *et al*. (Bagai *et al*., 2008) In short duration diabetic patients; we found significant reduction in amplitude of SNAP, but not in SNCV. Hence, axonal degeneration is the predominant pathology. Partanen *et al* in their study also got more reduction in amplitudes than conduction velocities of nerves indicating predominant axonal degeneration. (Partanen *et al*., 1995) But Fraser *et al*. (Fraser *et al*., 1977) 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.

We did not get any significant correlation between duration of type 2 DM and peripheral nerve conduction parameters under consideration. This may be because of smaller sample size of our study or it shows that in addition to duration of diabetes mellitus, certain other factors must be involved in pathogenesis of DPN. Pastore *et al* in their study also did not get statistically significant correlation between duration of type 2 DM and electrophysiological parameters. (Pastore *et al*., 1999)

However, Dutta A *et al* in their study found statistically highly significant correlation between duration of diabetes and DPN ($p<0.001$). (Dutta *et al*., 2005) Similar significant correlation was also found by Valensi P *et al* and Fedele D *et al*. (Valensi *et al*., 1997; Fedele *et al*., 1997) This difference in results could be attributed to the fact that we have included only those patients who had controlled blood glucose levels. Above mentioned studies had not considered glycemic status while correlating nerve conduction parameters with duration of diabetes. In our study, mean difference in SNCV is significantly lesser in long duration diabetics ($p<0.05$), but not in short duration diabetics as compared to controls. This definitely shows the role of duration of diabetes in the development of diabetic neuropathy. Many previous studies also highlighted the role of duration of diabetes in development of DPN. (Ugoya *et al*., 2008; Dutta *et al*., 2005; Lee *et al*., 2010; Moglia *et al*., 1994)

The present study has shown that with increase in duration of diabetes mellitus, 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 that could have contributed to DPN. All the subjects in our study had normal Hb A1c levels which shows that they were having controlled glycemic status. However, Hb A1c level accounts for blood glucose levels for past 3 months only. (Vasudevan *et al*., 2011) This is the limitation of our study, since we were not aware of previous glycemic status of the patients. Previous chronic hyperglycemia would have led to permanent nerve damage in the patients. This needs further confirmation by doing longitudinal study.

Pathophysiological machanisms leading to DPN are not fully elucidated. But certainly they are muitifactorial and interrelated. Many different theories have been proposed to identify them. They are attributable to microvessel and metabolic disorders related to chronic hyperglycemia and diabetes duration. Oxidative stresses in neurons and glial cells may lead to oxidative injury. Mitochondrion of hyperglycemic neurons is specifically affected, where the reactive oxygen species are produced. The proteins that control mitochondrial function undergo deregulation leading to apoptosis and degeneration. (Schmeichel *et al*., 2003; Leinninger *et al*., 2006) Nerve cell proteins undergo nonenzymatic glycosylation and permanent damage, thereby preventing transmission of signals. Glycosylation of myelin form products that are degraded by macrophages hence, leading to demyelination. (Vlassara *et al*., 1983, 1885) Increse sorbitol accumulation via polyol pathway may lead to osmotic damage and direct toxicity. (Dyck *et al*., 1988)

Advanced glycation end products induce monocytes and endothelial cells, which in turn increase cytokine production leading to perineurial and endoneurial vasculitis of blood vessels. (King, 2001; Dyck *et al*., 1999) This subcellular inflammation causes abnormal cytokine production, which in turn causes activation of more inflammatory signaling pathways leading to further lesions of blood vessels. (Hotamisligil, 2006) These changes possibly lead to decrease in blood flow and ischaemic changes in nerves. (Low, 1987) Thus both metabolic as well as ischaemic mechanisms might be responsible for all changes observed in our study.

Conclusion

The present study concludes that diabetic patients with longer duration of disease are at increased risk of diabetic peripheral neuropathy. It can worsen with increasing duration of diabetes. Since exact pathogenesis of diabetic peripheral neuropathy is not clear, a multipronged approach should be used while treating such patients.

Stringent action has to be taken at an early stage of disease to prevent nerve damage. Currently treatment of diabetic neuropathies is directed to prevent their progress, to reduce symptoms and to prevent neuropathic complications. Nevertheless, early diagnosis of diabetic neuropathy remains the cornerstone of patient follow up.

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