Research Article

Effect of glycemic status on peripheral nerve conduction in lower limbs in type 2 diabetes mellitus patients

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ABSTRACT

Background: Diabetes mellitus (DM) is one of the most common chronic diseases globally. Diabetic neuropathy is the most common & troublesome complication. But exact pathogenesis is not yet known. Comparatively there are few studies showing relation between glycemic status & diabetic neuropathy. Hence present study was conducted, which was aimed to assess the same in lower limbs in type 2 DM.

Methods: 60 type 2 diabetes mellitus male patients were selected from diabetic OPD. 30 were having glycated hemoglobin (HbA1c) 6%-9% (group B), 30 were having HbA1c > 9% (group C). They were compared with age and sex matched 30 normal healthy controls (group A). Conduction velocity and amplitude of bilateral sural sensory nerve action potential (SNAP) and peroneal compound muscle action potential (CMAP) were recorded. Glycated hemoglobin was measured using ion exchange resin method.

Results: Group B and group C had significantly lesser means of conduction velocity and amplitude of sural SNAP (p<0.001) and peroneal CMAP (p<0.05) as compared to group A. Hb A1c had statistically significant negative correlation with conduction velocity and amplitude of sural SNAP (p<0.001) as well as peroneal CMAP (p<0.001).

Conclusions: This study shows that diabetic patients with higher blood glucose levels are at increased risk of diabetic neuropathy. Diabetic neuropathy in lower limbs worsens with increasing blood glucose levels. Hence stringent action has to be taken at an early stage to control blood glucose levels. Also, patients should be encouraged for regular follow up and strict glycemic control.

Keywords: Type 2 diabetes mellitus, Diabetic neuropathy, Nerve conduction study, HbA1c

INTRODUCTION

Diabetes Mellitus (DM) is one of the most common chronic diseases globally, affecting 8.3% of the world's population and in many countries it is now a leading cause of death, disability and high health care cost. As stated in the findings of The International Diabetes Federation 2014 currently the number of cases of diabetes is estimated to be around 387 million worldwide with largest number in China followed by India.[1] More than 90% of these patients have type 2 DM which usually comes to light in the middle years of life.[2]

Among the complications, diabetic neuropathy is the most common and troublesome complication of diabetes mellitus leading to great morbidity.[3] It can present even at the time of diagnosis. Still, detailed studies have been hampered by lack of uniform definition of diabetic neuropathy. It is one of the least understood complications, with reported prevalence ranging from less than 5% to approximately 60%.[4] It increases risk of amputation 12 times when compared with non-diabetic subjects.[5] However, the progression of neuropathy can be reduced by early detection and intervention.[6]

Presently, in India there are comparatively few studies showing association between severity of neuropathy and glycemic status of the patient. Knowledge regarding relation of glycemic status 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 glycemic status in type 2 diabetic patients.

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. After approval from Institutional Ethics Committee, male patients in the age group of 40-60 years having 0-5 years of duration of diabetes 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 type 2 DM male patients having HbA1c 6%-9% (i.e. good to moderate diabetic control), Group C: 30 type 2 DM male patients having HbA1c > 9% (i.e. poor diabetic control).

Inclusion and exclusion criteria

Inclusion criteria: Normotensive patients taking regular oral hypoglycemic agents as advised by physician, non-smoker, non-alcoholic and non-tobacco chewers were included in the study.

Exclusion criteria: 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.

Estimation of glycated hemoglobin (HbA1c)[7]

Glycated hemoglobin (HbA1c) of all patients was estimated by ion-exchange resin method by the diagnostic glycohemoglobin kit of Asritha Diatech as per the guidelines provided.[7]

Nerve conduction study

Nerve conduction parameters were recorded by using the standard RMS ALERON 401 machine (Recorders and Medicare systems, India) at fixed room temperature of 30^0C using standard procedure.[8, 9, 10] Parameters recorded were conduction velocity and amplitude of sensory nerve action potential (SNAP) of bilateral sural nerves and conduction velocity and amplitude of compound muscle action potential (CMAP) of bilateral peroneal motor nerves.

Statistical analysis

The detailed data was entered into the Microsoft excel 2007 and subsequently analyzed statistically by using Graph pad prism 5 software. Mean of right and left side was taken for each individual parameter and then compared. Values were reported as Mean ± S.D. Comparisons of nerve conduction parameters among groups were done by applying the ANOVA test. Correlation between Hb A1c and mean of each nerve conduction parameter was studied by applying Pearson's correlation coefficient. Significance level was set at p<0.05 and considered as significant.

RESULTS

Difference in means of age, height, weight, body mass index was not statistically significant among three groups and hence these groups were comparable. (Table 1)

Table 1: Descriptive statistics for demographic and baseline parameters among 3 groups (ANOVA test).

	Group A Mean ± SD n = 30	Group B Mean ± SD n = 30	Group C Mean ± SD n = 30	p value
Age (yrs)	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

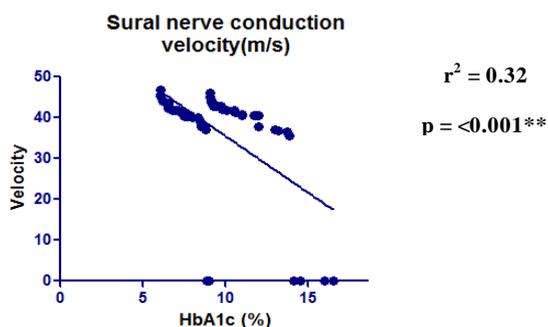* p<0.05 statistically significant ** p<0.001 statistically highly significant

In case of sural SNAP, mean values of conduction velocity were 46.17 ± 3.5 m/s, 38.71 ± 10.76 m/s and 35.68 ± 14.44 m/s for group A, group B and group C respectively. Mean values for amplitude were 21.09 ± 3.77 µV, 15.95 ± 7.10 µV and 13.66 ± 8.28 µV for group

A, group B and group C respectively. This difference in means of conduction velocity and amplitude was significantly lesser in group B and group C than group A (p<0.001). (Table 2)

Table 2: Comparison of conduction velocity (m/s) and amplitude (µV) of sural sensory nerve action potential (SNAP) among 3 groups (ANOVA test).

	Group A Mean ± SD n = 30	Group B Mean ± SD n = 30	Group C Mean ± SD n = 30	p value
Conduction velocity(m/s)	46.17 ± 3.51	38.71 ± 10.76	35.68 ± 14.44	< 0.001**
Amplitude(µV)	21.09 ± 3.77	15.95 ± 7.10	13.66 ± 8.28	< 0.001**

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

Figure 1: Correlation of conduction velocity (m/s) of sural SNAP with Hb A1c level (Pearson's correlation coefficient).

$r^2 = 0.32$

$p = <0.001**$
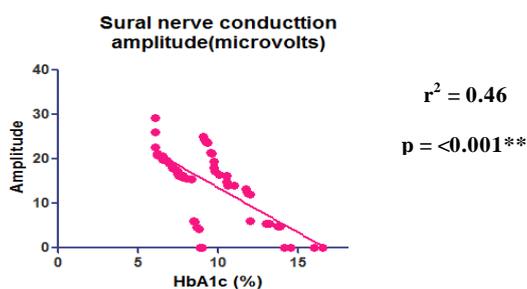
Figure 2: Correlation of amplitude (µV) of sural SNAP with Hb A1c level (Pearson's correlation coefficient).

$r^2 = 0.46$

$p = <0.001**$

Figure 1 and Figure 2 show that conduction velocity ($r^2 = 0.32$) and amplitude ($r^2 = 0.46$) of sural SNAP were negatively correlated with Hb A1c levels, which was statistically highly significant (p<0.001).

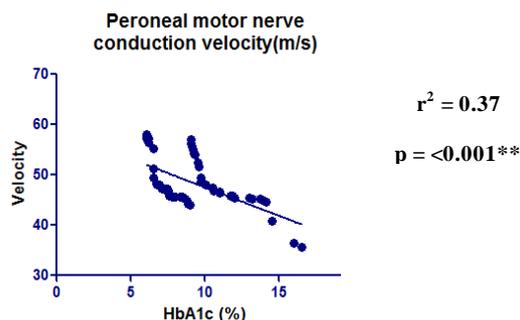In case of CMAP of peroneal motor nerve, mean values of conduction velocity were 48.72 ± 4.48 m/s, 47.76 ±

5.17 m/s and 43.30 ± 8.23 m/s for group A, group B and group C respectively. Mean values for amplitude were 19.39 ± 2.50 mV, 17.33 ± 4.74 mV and 15.65 ± 5.21 mV for group A, group B and group C respectively. Group B and group C had statistically significant (p<0.05) lower means of conduction velocity and amplitude as compared to group A. (Table 3)

Table 3: Comparison of conduction velocity (m/s) and amplitude (mV)) of compound muscle action potential (CMAP) of peroneal motor nerve among 3 groups (ANOVA test).

	Group A Mean ± SD n = 30	Group B Mean ± SD n = 30	Group C Mean ± SD n = 30	p value
Conduction velocity (m/s)	48.72 ± 4.48	47.76 ± 5.17	43.30 ± 8.23	< 0.05*
Amplitude (mV))	19.39 ± 2.50	17.33 ± 4.74	15.65 ± 5.21	< 0.05*

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

Figure 3: Correlation of conduction velocity (m/s) of CMAP of peroneal motor nerve with Hb A1c level (Pearson's correlation coefficient).

$r^2 = 0.37$
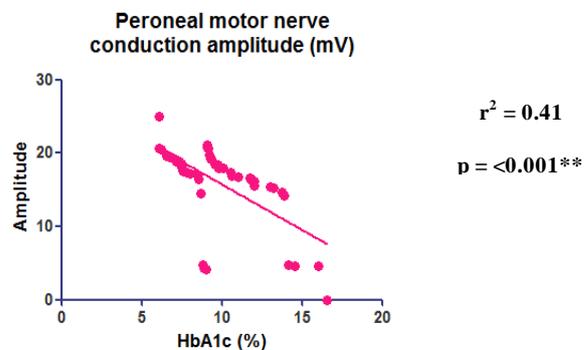
$p = <0.001**$

Figure 4: Correlation of amplitude (mV) of CMAP of peroneal motor nerve with Hb A1c level (Pearson's correlation coefficient)

Figure 3 and Figure 4 show, Hb A1c levels had statistically highly significant (p<0.001) negative correlation with conduction velocity ($r^2 = 0.37$) and amplitude ($r^2 = 0.41$) of CMAP of peroneal motor nerve.

DISCUSSION

Diabetic neuropathy is one of the commonest complications of diabetes, yet its exact pathophysiology is not known. Many different theories have been proposed to identify this mechanism. High blood glucose level is a prominent feature of diabetes and glucose plays a pivotal role in the body's energy metabolism. The axons of peripheral nerves and Schwann cells do not require insulin for glucose transport across cell membrane.[11] So glycemic status is directly reflected in cytoplasmic glucose concentration in peripheral nerves and Schwann cells. It has been postulated that this high glucose concentration may alter neuronal function.

Nerve conduction studies are primarily considered as one of the most sensitive indices to assess severity of neuropathy.[12] 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.[13] 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.[14] Amplitude depends on number and size of underlying nerve axons or muscle fibres and indicate their functioning. Decrease in amplitude suggests axonal degeneration, whereas decrease in conduction velocity suggests demyelination.[8,9,15] Clinically, amplitude is more important, since most neuropathies are caused by damage to the nerve's axon.[16]

The present study included 30 type 2 DM male patients with good to moderate diabetic control (group B), 30 type 2 DM male with poor diabetic control (group C) and 30 non diabetic control subjects (group A). Their ages were ranging from 40-60 years. Their sensory-motor nerve conduction in sural and peroneal nerves was recorded.

We found that conduction velocity and amplitude of sural SNAP were significantly lesser in diabetic patients with good to moderate control as well as in patients with poor control (p<0.001) (Table 2). These parameters were negatively correlated with Hb A1c levels, which was also statistically highly significant (p<0.001) (Figure 1 and Figure 2).

Diabetic patients with good to moderate control as well as poor control had statistically significant (p<0.05) lower means of conduction velocity and amplitude of CMAP of peroneal motor nerve as compared to controls (Table 3). Also, Hb A1c levels had statistically highly significant (p<0.001) negative correlation with conduction velocity and amplitude of CMAP of peroneal motor nerve.

We observed decrease in conduction velocity as well as decrease in amplitude of sural SNAP. It suggests that, axonopathy as well as demyelination, both contribute to the development of diabetic neuropathy.

Tkac I et al[12] in their study found that mean of amplitude of sural SNAP was 45.0 ± 13.5 µV in patients with good to moderate control and 36.8 ± 15.5 µV in poorly controlled patients. This difference was statistically significant (p < 0.05). They also found significant reduction in sural nerve conduction velocity in both diabetic groups. In their study also sural nerve conduction velocity (r = -0.39, p<0.001) and amplitude (r = -0.36, p<0.001) were negatively correlated with glycated hemoglobin.

Dutta A et al[17] in their study on type 2 DM patients also found that, high blood glucose levels had some contribution in development of diabetic peripheral neuropathy. They also found significant correlation between diabetic peripheral neuropathy and blood glucose levels. These findings were confirmed in our study. Ugoya SO et al[18], Valensi P et al[19], Perkins BA et al[20], Partanen J et al[21] also got similar results in their study.

Bagai K et al[22] observed that in type 2 DM patients, axonal injury was more common in legs while demyelinating injury was more common in arms.

Said G et al[23] in a clinicopathological study, observed progressive centripetal degeneration of axons in sural nerve biopsy specimens.

Novella SP et al[24] found that patients having neuropathy with painful symptoms had higher frequency of abnormal glucose metabolism than those without painful symptoms. Hence they pointed out the need to consider undiagnosed abnormal glucose metabolism in patients with neuropathy.

Fraser DM et al[25] in their study found that patients treated with oral hypoglycemic agents did not show improvement in motor nerve conduction velocity despite satisfactory glycemic control. They attributed this to a previous longer period of asymptomatic hyperglycemia leading to metabolic upset. A longitudinal study is needed to confirm this finding.

Hyperglycemia causes increase in advanced glycation end products (AGEs), which induce monocytes and endothelial cells to increase cytokine production. They also activate matrix metalloproteinases which damage nerve fibers.[26] Nonenzymatic glycosylation of nerve cell proteins damages nerves, thereby preventing the nerve cells from transmission of signals in response to stimuli.

Glycosylation of myelin may form products that are recognized and degraded by macrophages leading to demyelination.[27,28] Oxidative stresses in neurons and supporting glial cells can lead to oxidative injury. The target cell organelle that is specifically affected is mitochondrion, which is the site of production of reactive oxygen species in hyperglycemic neurons. Deregulation of proteins that control mitochondrial function leads to apoptosis and degeneration.[29,30]

Since exact pathogenesis of diabetic neuropathy is not clear, a multipronged approach should be used while treating diabetic neuropathies and to prevent further complication like diabetic foot. A lot of clinical trials are going on about various pharmacologic agents. Currently treatment of diabetic neuropathies is directed to prevent their progress, to reduce symptoms and to prevent neuropathic complications. To design a treatment for diabetic neuropathy, a detailed longitudinal study is needed to enlighten on underlying pathogenesis. Definitely, optimal glycemic control remains the core treatment in type 2 DM patients throughout lifetime.

In conclusion, this study shows that diabetic patients with higher blood glucose levels are at increased risk of diabetic neuropathy. Diabetic neuropathy in lower limbs worsens with increasing blood glucose levels. This can lead to serious complications in future viz. diabetic foot. Hence stringent action has to be taken at an early stage to control blood glucose levels to prevent diabetic neuropathy. Also, patients should be encouraged for regular follow up and strict glycemic control.

ACKNOWLEDGEMENTS

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