Original article

Effect of glycemic status on peripheral nerve conduction in upper limbs in type 2 Diabetes Mellitus Patients

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ABSTRACT

Background and Aim: The global prevalence of diabetes mellitus (DM) is rising continuously. Diabetic neuropathy being one of the most common complications has been well studied in lower limbs. Similarly it can also affect upper limbs progressively. But exact pathogenesis is not yet known. Comparatively there are very few studies showing relation between upper limb neuropathy and blood glucose levels. Hence, present study was conducted to study the relation between glycemic status & upper limb diabetic neuropathy in type 2 DM.

Methods: 60 type 2 DM male patients were selected from diabetic OPD. 30 were having glycated hemoglobin (Hb A1c) 6%-9% (group B), 30 were having Hb A1c > 9% (group C). They were compared with age and sex matched 30 normal healthy controls (group A). Conduction velocity and amplitude of bilateral ulnar sensory nerve action potential (SNAP) and peroneal compound muscle action potential (CMAP) were recorded. Hb A1c was measured using ion exchange resin method.

Results: Group B and group C had significantly lesser means of amplitude of ulnar SNAP (p<0.05) as compared to group A. Hb A1c had statistically significant negative correlation with amplitude of ulnar SNAP (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 upper limbs worsens with increasing blood glucose levels and may hamper day to day activities. Hence stringent action has to be taken at an early stage to control blood glucose levels.

Keywords: Type 2 Diabetes Mellitus, Diabetic neuropathy, Nerve conduction study, Hb A1c

INTRODUCTION

The global prevalence of diabetes mellitus has grown from 4.7% (108 million) in 1980 to 8.5% (422 million) in 2014. Over the past decade, diabetes prevalence has risen faster in low- and middle-income countries than in high-income countries. Type 2 diabetes mellitus (DM) comprises the majority of diabetic people around the world.[1] Among all the complications, diabetic neuropathy is the most common and troublesome complication of diabetes mellitus leading to great morbidity and high healthcare cost.[2] It is one of the least understood complications, with reported prevalence ranging from less than 5% to approximately 60%.[3] Still, detailed studies are not available because of lack of uniform definition of diabetic neuropathy. In type 1 DM, distal polyneuropathy becomes symptomatic after chronic prolonged hyperglycemia for many years. Conversely, patients with type 2 DM usually present with polyneuropathy within few years of poor glycemic control or even at the time diagnosis. However, the progress of neuropathy can be arrested by early detection and proper intervention.[4]

It is a well known fact that diabetes increases the risk of lower limb neuropathy and amputation because of non-healing, infected foot ulcers.[5,6] Subsequently or simultaneously diabetes can affect upper limbs as well. But, in India there are very
few studies showing association between severity of upper limb neuropathy and glycemic status of the patient. Knowledge regarding upper limb neuropathy and its relation with glycemic status 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 upper limb neuropathy in relation with glycemic status in type 2 diabetic patients.

**AIM & OBJECTIVES:**

To assess and compare the conduction velocities and amplitudes of compound muscle action potentials of ulnar motor nerves and nerve action potentials of ulnar sensory nerves in normal healthy controls and patients with type 2DM of varying blood glucose levels.

**METHODS**

**Study Design:**

An observational analytical study was performed in type 2 DM male patients. All the patients were selected from diabetic OPD of the B. J. Govt. Medical College and Sassoon general hospital, Pune. Study was conducted from August 2010 to July 2012. Approval from Institutional Ethics Committee was obtained. Male patients in the age group of 40-60 years with DM for 0-5 years 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 Hb A1c 6%-9% (i.e. good to moderate diabetic control), Group C: 30 type 2 DM male patients having Hb A1c > 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 B₁₂ deficiency, intake of drugs causing neuropathy, acute complication of diabetes, leprosy, local skin diseases, hypothyroidism, neurodegenerative diseases, neuromuscular transmission disorders and myopathies, autoimmune diseases like SLE, chronic diseases like liver disease, renal failure, airway disease, infections carcinoma and critical illness, permanent pacemaker or other implanted stimulators, familial neuropathy or toxin exposure were excluded from the study.

**Estimation of glycated hemoglobin (Hb A1c):**

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. [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°C using standard procedure. [8, 9, 10] Parameters recorded were conduction velocity and amplitude of sensory nerve action potential (SNAP) of bilateral ulnar sensory nerves and conduction velocity and amplitude of compound muscle action potential (CMAP) of bilateral ulnar 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)
In case of ulnar sensory SNAP, mean values for amplitude were 46.26 ± 5.07µV, 41.37 ± 9.01 µV and 40.51 ± 10.35 µV for group A, group B and group C respectively. This difference in means of amplitude was significantly lesser in group B and group C than group A (p < 0.05). Mean values of conduction velocity were 52.57 ± 2.23 m/s, 51.31 ± 2.11 m/s and 50.99 ± 2.45 m/s for group A, group B and group C respectively; but this difference is not statistically significant. (Table 2)
Figure 1 show that amplitude ($r^2 = 0.3$) of sural SNAP were negatively correlated with Hb A1c levels, which was statistically highly significant (p<0.001).
In case of CMAP of ulnar motor nerve, mean values of conduction velocity were 51.89 ± 2.26 m/s, 51.79 ± 2.22 m/s and 51.58 ± 1.90 m/s for group A, group B and group C respectively. Mean values for amplitude were 34.89 ± 8.90 mV, 32.17 ± 10.59 mV and 30.22 ± 8.90 mV for group A, group B and group C respectively. The differences in means of conduction velocity and amplitude were not statistically significant among three groups. (Table 3)

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

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 30</td>
<td>n = 30</td>
<td>n = 30</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>50.4 ± 5.4</td>
<td>51.4 ± 6.5</td>
<td>52.9 ± 5.1</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.6 ± 5.7</td>
<td>166.6 ± 5.6</td>
<td>166.0 ± 4.8</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.4 ± 8.5</td>
<td>66.3 ± 7.2</td>
<td>66.3 ± 7.2</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>23.9 ± 2.9</td>
<td>23.9 ± 2.6</td>
<td>24.1 ± 2.6</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

* p<0.05 statistically significant ** p<0.001 statistically highly significant
Table 2: Comparison of conduction velocity (m/s) and amplitude (µV) of ulnar sensory nerve action potential (SNAP) among 3 groups (ANOVA test):

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± SD</th>
<th>n = 30</th>
<th>Group</th>
<th>Mean ± SD</th>
<th>n = 30</th>
<th>Group</th>
<th>Mean ± SD</th>
<th>n = 30</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conduction velocity (m/s)</td>
<td>52.57 ± 2.23</td>
<td>51.31 ± 2.11</td>
<td>50.99 ± 2.45</td>
<td>&gt; 0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amplitude (µV)</td>
<td>46.26 ± 5.07</td>
<td>41.37 ± 9.01</td>
<td>40.51 ± 10.35</td>
<td>&lt; 0.05*</td>
<td></td>
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</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± SD</th>
<th>n = 30</th>
<th>Group</th>
<th>Mean ± SD</th>
<th>n = 30</th>
<th>Group</th>
<th>Mean ± SD</th>
<th>n = 30</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conduction velocity (m/s)</td>
<td>51.89 ± 2.26</td>
<td>51.79 ± 2.22</td>
<td>51.58 ± 1.90</td>
<td>&gt; 0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amplitude (mV)</td>
<td>34.89 ± 8.90</td>
<td>32.17 ± 10.59</td>
<td>30.22 ± 8.90</td>
<td>&gt; 0.05</td>
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</tbody>
</table>

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

Figure 1: Correlation of conduction velocity (m/s) of ulnar SNAP with Hb A1c (%) level (Pearson’s correlation coefficient):

\[ r^2 = 0.3 \]
\[ p = <0.001** \]
DISCUSSION

Diabetes mellitus is a disease which affects various target organs at random. It is not known that when and at what stage of disease the complications will occur. Mechanisms leading to diabetic peripheral neuropathy are multifactorial. Higher prevalence of diabetic neuropathy in lower limbs is a well known fact.[5, 6] Subsequently it can also affect upper limbs. But exact pathophysiology of diabetic neuropathy is not known. Various theories have been put forth to identify this mechanism. Hyperglycemia is a prominent feature of diabetes and glucose plays a key role in energy metabolism of body. Transport of glucose across peripheral nerve axons and Schwann cells membranes do not require insulin.[11] So blood glucose level is directly reflected in cytoplasmic glucose concentration in peripheral nerves and Schwann cells. It has been hypothesized that high glucose concentration may cause alterations in neuronal function.

Nerve conduction studies are one of the most sensitive indices to assess severity of neuropathy.[12] Motor axons are assessed by motor nerve conduction by selectively recording muscle responses on nerve stimulation. Sensory axons are assessed by sensory nerve conduction studies by recording electrical activity from peripheral nerves.[13] These tests are used to find the location of lesions. It can also describe the type and severity of the pathophysiology and can detect subclinical functional alterations. 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, 13] Clinically, amplitude is more important, since most neuropathies are caused by damage to the nerve's axon.[14]

In the present study 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) were included. All the participants were in the age group of 40-60 years. Their sensory-motor nerve conduction in bilateral ulnar nerves was recorded. We found that amplitude of ulnar SNAP was significantly lesser in diabetic patients with good to moderate control as well as in patients with poor control (p<0.05) (Table 2). But the reduction in ulnar sensory nerve conduction velocity was not statistically significant among three groups. This suggests that, axonopathy is the main contributor of upper limb diabetic neuropathy.

Also, ulnar SNAP was negatively correlated with Hb A1c levels, which was also statistically highly significant (p<0.001) (Figure 1). This finding highlights the role of glycated haemoglobin in causation of diabetic neurapathy.

We also found that reduction in conduction velocity and amplitude of CMAP of ulnar motor nerve was statistically not significant in control group and in diabetic patients (Table 3).

In present study, we found that the reduction in means of amplitude of ulnar SNAP is statistically significant among three groups. But it is not significant in case of amplitude of ulnar CMAP as well as ulnar motor nerve conduction velocity .This suggests that sensory nerve conduction is affected earlier than motor nerve conduction. Tesfaye S [15], Kasznicki J [16], Andreassen CS et al [17] also observed that no patient had motor involvement without sensory involvement. The first clinical sign of sensory loss in upper limb is loss of vibration and pinprick sensation in hands which gradually extends into arms. The distal motor symptoms include impaired
fine hand coordination and difficulty with day to day tasks.

Tkac I et al. [12] in their study recorded median motor and median sensory nerve amplitudes and conduction velocities. They found that raised glycated haemoglobin contributed greatly to reduction in sensory SNAP amplitudes. We observed similar findings in present study. But they also found significant reduction in conduction velocity as well. We do observed slight reduction in conduction velocity, but it was not statistically significant. This difference in results could have appeared because mean age of duration of diabetes in their study was 12.5 years and in present study we have considered patients having diabetes duration between 0 to 5 years. Partanen J et al. [13] in their study on type 2 DM patients also found that, sensory amplitude of median nerves were lowered in long term poorly controlled diabetics indicating that chronic hyperglycemia had significant contribution in development of diabetic peripheral neuropathy and axonal degeneration predominates in upper limb neuropathy. These findings were confirmed in our study. Lee SS et al. [18], Valensi P et al. [19], DCCT research group [20] and Ugoya SO et al. [2] in their respective studies also highlighted the significance of hyperglycemia in causation of diabetic neuropathy. On the contrary, Bagai K et al. [6] in their study observed that in type 2 DM patients, axonal injury was more common in legs while demyelinating injury was more common in arms. This difference need to be investigated in large scale study.

Novella SP et al. [21] observed that patients having abnormal glucose metabolism have higher frequency of painful neuropathy than those without painful symptoms. Hence they pointed out the significance of considering undiagnosed hyperglycemia in patients with neuropathy.

Fraser DM et al. [22] in their study observed that, in spite of satisfactory glycemic control patients treated with oral hypoglycemic agents didn’t show improvement in motor nerve conduction velocity. They attributed this to prolonged previous hyperglycemia which might be asymptomatic and led to permanent nerve damage. To confirm this finding, a longitudinal study is needed.

Chronic hyperglycemia causes nonenzymatic glycosylation of nerve cell proteins which damages nerves and hence prevent the transmission of signals across nerve cell membranes. [23] High blood glucose levels lead to increase in advanced glycation end products (AGEs). AGEs induce endothelial cells and monocytes to increase cytokine production. [24] Increase in sorbitol concentration via polyol pathway may lead to osmotic swelling and cell damage. [25] Myo-inositol is a constituent of plasma membrane involved in ionic transport and transmission of nerve impulses. Hyperglycemia causes reduction in carrier mediated myo-inositol transport system by competitive inhibition [26] and hampers nerve conduction. Perineurial and endoneurial vasculitis of blood vessels causes abnormal cytokine production, which in turn causes activation of more inflammatory signaling pathways leading to lesions of blood vessels and ischaemic changes in nerves. [27] Alteration in Na⁺/K⁺ ATPase pump, increased oxidative stress are some other proposed mechanisms. [28] Thus both metabolic as well as ischaemic mechanisms might be responsible for all changes observed in our study.

Though the hyperglycemia may be essential to develop the complications of diabetes, susceptibility to tissue damage may vary among patients with similar levels of glycemic exposure. Hence a multipronged approach is needed while treating diabetic neuropathies. Nerve conduction
studies should be performed in patients even at the
time of diagnosis and at regular treatment intervals
to assess nerve functions. Definitely, prolonged and
constant optimal glycemic control remains the boon
in prevention of neuropathy in type 2 DM patients
throughout lifetime.

In conclusion, type 2 diabetic patients with poorly
controlled blood glucose levels have higher risk of
developing diabetic neuropathy. Along with lower
limbs, diabetic neuropathy in upper limbs also
worsens with increasing blood glucose levels. This
can greatly hamper day to day activities of the
patient and may also deteriorate the performance of
professionals who need great precision in upper
limbs like musicians, painters, weavers etc. Hence
strict action should be taken right from the
diagnosis of diabetes to control blood glucose
levels and to prevent diabetic peripheral
neuropathy. Also, patients should be encouraged
for regular follow up and strict glycemic control.

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