Original Research Paper

Volume-8 | Issue-5 | May-2018 | PRINT ISSN No 2249-555X

Physiology

A STUDY OF SENSORY NERVE CONDUCTION INDICES IN NON INSULIN DEPENDENT DIABETES MELLITUS PATIENTS WITHOUT SYMPTOMS OF PERIPHERAL NEUROPATHY AND ITS CORRELATION WITH GLYCOSYLATED HAEMOGLOBIN.

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ABSTRACT Diabetes mellitus is one of the commonest and major health problems of world and India as well, which predisposes the affected individual to complications like diabetic neuropathy in the long run, causing significant morbidity and mortality. Thus this study was aimed at determining sensory nerve conduction indices in non insulin dependent diabetes mellitus patients (NIDDM) without symptoms of peripheral neuropathy and its correlation with glycosylated haemoglobin. This study was conducted in the Department of Physiology, SMS Medical College, Jaipur on clinically diagnosed 35 NIDDM patients, with disease duration of 5-10 years, aged 30 to 50 years, without signs and symptoms of neuropathy. The present study showed a negative correlation between sensory nerve conduction velocity (SNCV) and HbA1C levels ($r = -0.9014$, $p<0.0001$) in diabetics. Monitoring of HbA1C can be a useful method for early detection of Diabetic Neuropathy, thereby warranting strict glycemic control in patients of NIDDM, which can halt its progression.

KEYWORDS : Diabetes mellitus, polyneuropathy & sensory nerve conduction velocity.

INTRODUCTION

Diabetes Mellitus (DM) seems to be known since the evolution of civilization. Sushrutha (500 BC) an ancient Indian physician had described it as 'Madhumeha (excretion of sweet urine) (DCCT Research Group, 1988; Dowse 1991; Hockaday, 1990; Ramaiya, Swai, McLarty & Alberti, 1991). Diabetes represents a spectrum of metabolic disorder; which has become a major health challenge worldwide. International Diabetes Federation (2011) has reported the global burden of DM to be about 366 million patients in 2011, and 4.6 million deaths due to DM. It is expected to rise to about 552 million by 2030, out of which 439 million would be affected by type-2 DM (Chamnan et al., 2011).

Several risk factors have been reported to be involved in the causation of DM, like genetic, environmental and life style factors (physical inactivity, sedentary lifestyle, obesity, cigarette smoking and alcohol), which account for the variation in incidence of type 2 DM from one geographical region to the other (Chen, Magliano & Zimmet, 2011; Hu et al., 2001; Morbidity and Mortality weekly report, CDC, 2004; Ripsin, Kang & Urban 2009; Zimmet, Alberti & Shaw, 2001).

Insulin resistance is the main etiology behind the type-2 DM (hence called Non-Insulin Dependent Diabetes Mellitus-NIDDM). Eventually there is decreased insulin production culminating into pancreatic beta-cell failure (Kahn, 1994; Robertson, 1995). Alpha cell dysfunction has also been implicated in the pathogenesis of type-2 DM, along with some adipokines (leptin, TNF alpha & adiponectin) responsible for insulin resistance and the impaired functions of beta cells (Fujioka, 2007).

The diabetes is diagnosed as per the guidelines recommended by American Diabetic Association (ADA) guidelines of 1997 or World Health Organization (WHO) National diabetic group criteria of 2006. Patient is termed diabetic if single raised glucose reading with symptoms (polyuria, polydipsia, polyphagia & weight loss), otherwise raised values on two occasions, of either fasting plasma glucose (FPG) ≥7.0 mmol/L (126 mg/dL) or with an oral glucose tolerance test (OGTT), two hours after the oral dose a plasma glucose ≥11.1 mmol/L (200 mg/dL) (Cox & Elelman, 2009). The 1997 ADA recommendations for diagnosis of DM focus on the FPG, while WHO focuses on the OGTT. HbA1c level more than 6.5% is also termed diabetic and levels ≥6.0% and <6.5% have been used to identify those at high risk of developing DM (International Expert Committee, 2009).

Long standing cases of Diabetes mellitus may lead to various complications related to heart, blood vessels, eyes, kidneys and nerves, subsequently leading to heart disease and stroke. Decreased blood supply along with the neuropathies may cause foot ulcers, infection and eventual need of limb amputation. The small vessel damages lead to blindness due to Diabetic retinopathy and also kidney failure. (Azevedo & Alla, 2008).

SNCV is performed by electrical stimulation of a peripheral nerve and recording from a purely sensory portion of the nerve, such as on a finger. Like the motor studies, sensory latencies are on the scale of milliseconds (ms) and amplitudes in the microvolt (μV) range. The SNCV is calculated based upon the latency and the distance between the stimulating and recording electrodes. A decrease in amplitude of compound action potential (sum of all individual nerve action potentials) suggests reduction in the overall number of functioning axons and slow NCV suggests peripheral nerve demyelination either diffuse (demyelinating peripheral neuropathy) or focal (conduction block or pressure on nerves). Thus the present study was designed to evaluate the sensory nerve conduction indices in NIDDM patients without symptoms of peripheral neuropathy and determines its correlation with glycosylated haemoglobin levels.

MATERIAL AND METHODS

The present study was conducted in the Department of Physiology, SMS Medical College, Jaipur after obtaining clearance from institutional ethics committee on thirty five Diabetic patients taken from medical OPD of SMS Hospital, Jaipur, with disease duration of 5-10 years (NIDDM) in age group of 30 to 50 years, without signs and symptoms of neuropathy. Patients suffering from chronic diseases like chronic liver disease, chronic inflammatory demyelinating neuropathy, chronic renal disease, vasculitis, traumatic nerve injuries, any acute or chronic inflammatory illness, myopathy, neuromuscular diseases, inherited neuropathy and neurovascular complications like stroke were excluded from the study. Patients who were on drugs known to cause peripheral neuropathy, alcoholics and/or smokers were also excluded from the study.

Experimental Protocol:

After obtaining written informed consent, the subjects were explained the purpose and outcome of study prior to the commencement of procedure. Instrument was kept out of the view of subject and they

were made to sit comfortably on a chair in a fully relaxed state. Detailed history was obtained and general, physical examination was performed to rule out any disease with its duration. Blood samples were collected for HbA1C and analyzed by Latex Agglutination Inhibition Assay method on instrument Randox I-mola.

Nerve conduction Study:
Total latency, Amplitude and SNCV of right median nerve was assessed using antidromic stimulation of right median nerve on RMS EMG EP - 2 channel , Recorders and Medicare Systems provided by the Department of Physiology, SMS Medical College, Jaipur and analyzed using SALUS software developed by Salus Medical Diagnostics, Hyderabad.

NCS Procedure:
Active electrode: ring electrodes were placed at 2nd digit (index finger).

Reference electrode: ring electrode at 3rd digit (index finger).
Ground electrode: dorsum of hand.

Stimulation was given at 3 cm proximal to distal palmer crease of right hand and latency was measured. The distance between the points of stimulation and active electrode was measured using the measuring tape and SNCV was then measured in m/s by the following formula:

$$\text{Sensory Nerve Conduction Velocity (m/s)} = \frac{\text{Distance in metre (d)}}{\text{Latency in second (t)}}$$

Statistical Analysis:
Analysis was done using SPSS version 17.0 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. Pearson's Correlation Coefficient was used to find the correlation of HbA1c levels with SNCV and statistical significance assigned at $p<0.05$.

RESULTS

Table No. 1 No. of subjects and percentage distribution of subjects of cases in two age groups

Age	Case	
	No. of subjects (n)	Percentage (%) of subjects
30-40 Year	9	25.71
41-50 Year	26	74.29
Total	35	100.00

The Table No. 1 shows the percentage distribution of subjects among 30-40 year and 41-50 year.

Table No. 2 No. of subjects and gender wise percentagedistribution of cases

Gender	Case	
	No. of subjects (n)	Percentage (%) of subjects
Male	20	57.14
Female	15	42.86
Total	35	100.00

Table No. 2 shows the number and percentage of subjects in groups divided on the basis of their gender. The percentage of male subjects was 57.14% (n=20) and the percentage of female subjects was 42.86% (n=15).

Table No. 3 Mean ± SD values of various subject characteristics

	Total No. of Subjects (n)	Mean	Standard Deviation (SD)
Age (Years)	35	43.89	4.55
HbA1c (%)	35	7.93	1.27

Table No. 3 shows the mean ± SD values of height (m), weight (Kg), BMI (Kg/m2) and HbA1c (%) values in case.

Table No. 4 Mean ± SD values of various Sensory Nerve Conduction Indices of median nerve and their Correlation with HbA1c levels

Nerve conduction Indices	Total No. of subjects (n)	Mean	Standard Deviation (SD)	Correlation Coefficient (r)	Significance (p-value)
Latency 1 (ms)	35	3.03	1.66	-0.03526	0.8406
Latency 2 (ms)	35	6.94	2.66	0.2595	0.1322
Duration (ms)	35	3.91	1.34	0.381	0.0240*
Amplitude (µV)	35	20.39	13.57	0.8369	<0.0001*
Area (µVms)	35	27.98	28.50	0.7152	<0.0001*
SNCV (m/s)	35	44.62	12.32	-0.9014	<0.0001*

*p-value<0.05, significant

Table No. 4 shows the mean ± SD values of Latency 1 (ms), Latency 2 (ms), Duration (ms), Amplitude (µV), Area (µVms) and sensory nerve conduction velocity-SNCV (m/s) values along with their correlation with levels of HbA1c (%) using Pearson's Correlation and p-values. The duration, Latency 1, Latency 2 showed a significant positive correlation and the SNCV showed a significant negative correlation.

Figure 1. Correlation between HbA1c levels & Latency 1

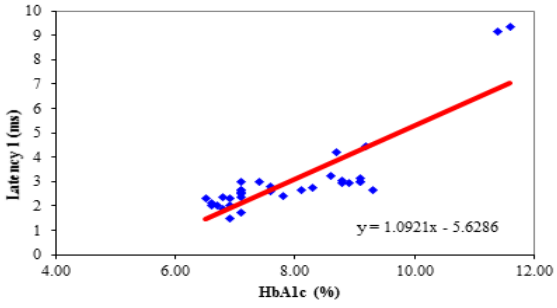


Figure 2. Correlation between HbA1c levels & Latency 2

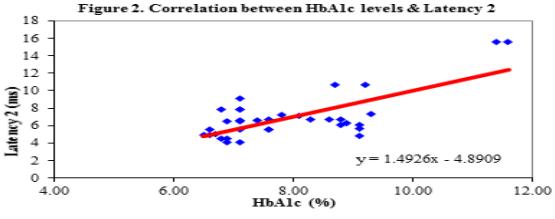
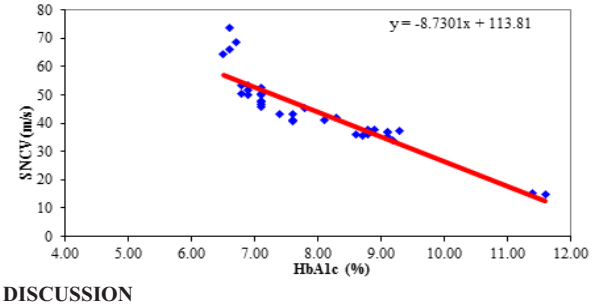


Figure 3. Correlation between HbA1c levels & SNCV of Median Nerve



DISCUSSION

One of the commonest associated complications in Diabetes Mellitus is diabetic polyneuropathy, involving the peripheral nervous system, which can be evaluated by Nerve conduction studies, which is a very sensitive, specific, reproducible, and objective tool to assess the degree of damage. In the present study a significant negative correlation was found between the sensory nerve conduction velocity and the levels of glycosylated hemoglobin, suggestive of long standing hyperglycemia contributing to the progression of diabetic polyneuropathy (Table No. 4, Figure 3). Similar results were also observed in the study of Roopa, Vedavathi & Venkatesh (2011), where an inverse correlation between NCV and levels of HbA1c was seen in ulnar nerve that provides a supportive piece of evidence for results of this study (Roopa, Vedavathi & Venkatesh, 2011). HbA1c is the glucose bound hemoglobin, which can be used to monitor the long-term control of diabetes mellitus, reflecting average blood glucose level over the past 3 months. The hyperglycemia triggers the cascade by excessive glucose being metabolized into sorbitol and fructose, and both activate advanced glycation end products (AGEs), resulting in molecular oxidative stress (Chung, Ho, Lam & Chung, 2003). Excessive AGEs formation on peripheral nerve components, primarily axons, and a significantly higher level of circulating AGE-immune complexes in patients with both distal diabetic polyneuropathy and proximal neuropathy, contribute to Diabetic neuropathy (Mišur et al., 2004).

Oxidative stress within the soma triggers withdrawal of the longest (typically most distal) nerve axons from their distal terminals without cellular death (Souayah et al., 2009).

El-Salem, Ammari, Khader & Dhaimat (2009) found HbA1c as the most important factor predicting higher risk of subclinical neuropathy and suggested that nerve conduction studies abnormalities commonly exist in diabetic patients in the subclinical stages of polyneuropathy, and are highly correlated to HbA1c levels. Thus this study also supports the findings of the present study (El-Salem, Ammari, Khader, & Dhaimat, 2009). Sonawane et al. (2017) also suggested greater risk of diabetic neuropathy with higher blood glucose levels in their study, that showed negative correlation between NCV of sural nerve and the levels of HbA1c (Sonawane et al., 2017).

CONCLUSION

The halt in the progression of polyneuropathy will surely improve the disease outcome and improve the overall prognosis, thus it should be detected by NCS like studies as early as possible. The present study shows a negative correlation between SNCV and HbA1C levels in patients. Monitoring of HbA1C can be a useful method for early detection of Diabetic Neuropathy and hence reduced mortality, morbidity and the overall economic burden. This study also warrants the strict glycemic control in patients of NIDDM so as to lower the HbA1C levels which can retard the development of Diabetic neuropathy.

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