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NERVE CONDUCTION VELOCITY AND GLYCATED HAEMOGLOBIN IN PATIENTS OF TYPE 2 DIABETES MELLITUS

Physiology

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ABSTRACT

BACKGROUND: Diabetic peripheral neuropathy (DPN) is one of the most common long term complications of type 2 diabetes mellitus (T2DM).Nerve conduction velocity (NCV) is a reliable indicator of peripheral nerve functions. Glycated haemoglobin (HbA1c) is an indicator of glycaemic control. Impaired glycaemic control is one of the factors that lead to DPN in DM. The aim of this research was to find out the relationship between peripheral nerve functions and glycaemic control in patients of T2DM.

Material and methods: In this observational cross sectional study HbA1c and NCV (for bilateral Sural, Peroneal & Median nerves) were done on 50 eligible T2DM patients and 25 apparently healthy controls. Correlation was studied between HbA1c levels and NCV of the above mentioned nerves.

OBSERVATION:

1. Significant negative correlation was found between HbA1c levels and bilateral Sural nerve conduction velocity.
   - Right sural nerve r= -0.420, p = 0.0001
   - Left sural nerve r= -0.2846, p = 0.0133
2. No significant negative correlation was found between HbA1c levels and NCV of bilateral peroneal motor and bilateral Median sensory &motor nerves.

CONCLUSION: Worsening of glycaemic control is positively correlated to peripheral neuropathy as it adversely effects the peripheral nerve functions.

KEYWORDS

T2DM, Nerve conduction velocity(NCV), HbA_{1c}

INTRODUCTION- Diabetic peripheral neuropathy (DPN) is one the of most common long term complication of DM which is progressive and irreversible, with an incidence rate of about 50 % of all patients with diabetes [1,2,3]. Age, glycated hemoglobin levels, insulin use, male sex, and duration of diabetes independently increase risk of development of peripheral neuropathy.[4]

Several authors have validated that electrophysiological studies (like nerve conduction study) are a reliable indicator of peripheral neuropathy, along with being strongly correlated to the structural changes, least subjective and most reliable single criterion standard [5-8].

The abnormalities in nerve conduction study (NCS) in DPN are manifested as reduced amplitude and slowed nerve conduction velocity (NCV) in both sensory & motor nerves at multiple sites[9,10]. Sensory nerves are more commonly affected in diabetic neuropathy as compared to motor nerves [9,10].

Relationship between DPN and poor glycaemic control has been validated by various authors and studies [4, 11,12]. Patients with impaired glucose tolerance have also shown occurrence of neuropathy .[11]

HbA_{1c} levels are used to assess glycaemic control[13]. HbA_{1c} predicts mean blood glucose concentration over the preceeding 6 to 8weeks [14] .HbA_{1c} is produced as result of glycation of ε-amino group of lysine residues and amino terminals of haemoglobin, by the blood glucose upon entering the erythrocytes[14]. Fraction of HbA_{1c} (out of total haemoglobin) is proportional to blood glucose concentration[14].

Hyperglycaemia damages nerve functions in various ways. Increase in oxidative stress as result of hyperglycaemia is a factor for DPN.[15] .Excess glucose is also diverted to polyol pathway leading to increased production of sorbitol and fructose.[16,17] Sorbitol accumulates inside the nerve cells and causes osmotic stress/imbalance [18] which might also effect metabolism of inositol and Na^+/K^+-ATPase.[19]

In this study we tried to explore the exact nature of the relationship between NCV and HbA_{1c} , as data depicting a significant correlation between NCV of various nerves and HbA_{1c} levels in T2DM patients is limited. This can help in prevention and management of peripheral neuropathy.

MATERIAL AND METHODS

This observational cross sectional study was carried out in the department of Physiology in association with departments of Medicine and Biochemistry, Lady Hardinge Medical College (LHMC) and associated Smt. Sucheta Kriplani Hospital between November 2014 to March 2016.

The ethical clearance was obtained from the Institutional Ethics committee for Human Research. Written and informed consent was taken from all study participants. The study protocol was carried out as per declaration of Helsinki.

Our study consisted of two groups –group I consisting of 50 eligible T2DM patients and group II consisting of 25 apparently healthy controls.

A detailed history taking and examination was done. Age and anthropometric measurements were also recorded.NCV testing was done on all.

Inclusion criteria-

- New or already diagnosed cases of T2DM in the age group of 40-60 years, as per ADA criteria. [20]

Exclusion criteria-

- Type 1 diabetes mellitus
- Pre diabetics as per ADA criteria[20]

The determination of HbA_{1c} was based on latex agglutination inhibition assay in the following way .HbA_{1c} present in the sample competes with the HbA_{1c} agglutinator for antibody binding sites on the latex , therefore slows the rate of agglutination[21]. Increase in absorbance is inversely proportional to the concentration of HbA_{1c} in the sample[21]. Wavelength of 700 nm was used to ascertain the increase in absorbance. This increased absorbance was due to agglutination and a calibration curve was used to estimate the concentration of HbA_{1c} , taking into account the extent of agglutination [21]. The percentage of HbA_{1c} was then calculated using the g/dl HbA_{1c} and total Haemoglobin values[21].The analysis was done by using Randox kits on fully automated analyser Beckman Coulter Au480.

NCV was tested by SCHWARZER TPAS EMG/NCV/EP neurophysiological measuring system in the proceeding way .Subjects were asked to lie in supine position for median and peroneal nerve testing and in prone position for sural nerve testing.[22]

i.Sensory Nerve Conduction

a. **Sural nerve:** Active electrode was placed between lateral malleolus and tendoachilles[22]. Reference electrode was placed distal to active electrode[22]. Nerve was stimulated 10-16 cm proximal to active electrode at the junction of middle and lower third of leg [22]
b. **Median sensory nerve:** Active electrode was placed 1st interphalangeal joint[22]. Reference electrode was placed 3 cm distal to active electrode. Nerve was stimulated at wrist [22].

ii. Motor Nerve Conduction

a. **Median motor nerve:** Active electrode was placed at abductor pollicis brevis muscle and reference electrode was placed 3cm distal at 1st metacarpophalangeal joint[22]. Stimulation was given 3cm proximal to distal wrist crease and at elbow, near volar crease for brachial impulse .[22]
b. **Common peroneal nerve:** Active electrode was placed over extensor digitorum brevis. Reference electrode was placed over base of little toe[22]. Nerve was stimulated first distally at ankle 2cm distal to fibular neck and then in lateral part of popliteal space.[22]

STATISTICAL ANALYSIS: Statistical evaluation of data was done using Graph Pad Prism software version 6. Mean and Standard error of mean (Mean ± SEM) of the variables were calculated. After testing for normal Gaussian distribution, intergroup comparison was done using unpaired t-test with welsh's correction and Chi square test as per requirement. Correlation was assessed using the Spearman's correlation coefficient.

RESULT

Table 1: Characterstics of the study population in the three groups (Mean ± SEM values)

Groups	I (n=50)	II(n=25)	p value
AGE (yrs)	49.02 ± 0.70	48.36 ± 1.29	0.6552®
BMI (kg/m2)	24.72 ± 0.25	24.46 ± 0.45	0.6189®
SEX	M = 29	M = 14	0.8689#
	F = 21	F = 11	

® Unpaired t-test with welsh's correction, #Chi square test, M -Male, F-Female.

Table 1 illustrates anthropometric characterstics of study population. They were age, BMI and sex distribution matched hence, comparable for study.

TABLE 2: Drugs being received by the T2DM patients. Number of patients on a particular drug is shown by value-

Groups	I (n=50)
Insulin	5
Metformin	43
Glimipride	24
Statins	32
Methyl cobalamin	22

Table 2 shows anti diabetic and other drugs being received by the diabetics of the two groups. Insulin and /or Glimipride were being received in addition to Metformin.

Table 3: Correlation of NCV of Bilateral Sural, Median (Sensory& motor) and Peroneal nerve with HbA1c in all groups (n=75)

Parameters			Correlation with HbA_{1c}
CONDUCTION VELOCITY	SURAL SENSORY NERVE	RT.	r = -0.4200 p = 0.0001***
		LT.	r = -0.2846 p = 0.0133*
	MEDIAN SENSORY NERVE	RT.	r = -0.0114 p = 0.9222
		LT.	r = -0.0773 p = 0.5097
	MEDIAN MOTOR NERVE	RT.	r = -0.1782 p = 0.1260
		LT.	r = -0.0513 p = 0.6617
	PERONEAL MOTOR NERVE	RT.	r = -0.1512 p = 0.1951
		LT.	r = -0.1069 p = 0.3610

Table 3 shows Correlation of NCV of Bilateral Sural, Median (Sensory& motor) and Peroneal nerve with HbA_{1c} in all groups (n=75).

There was-

1. Significant negative correlation between HbA_{1c} levels and bilateral Sural nerve conduction velocity.
2. No significant negative correlation between HbA_{1c} levels and NCV of bilateral Median sensory, Median motor & Peroneal nerve

DISCUSSION In our study it was seen that HbA_{1c} levels and NCV of bilateral Sural sensory nerve had a significant negative correlation. This showed that rising levels of HbA_{1c} had a negative effect on NCV of Sural nerve. Thus, poor glycaemic control is associated with peripheral neuropathy, as per our findings.

Herman et al did a similar study on Egyptian population which showed that Peripheral polyneuropathy was associated with higher HbA_{1c} in a multivariate analysis.[12] As a further matter , in a long term follow up study , a significant reduction in both motor and sensory NCV in the lower limb was found only in the patient group with glycated haemoglobin more than 10%.[23]

Boulton et al did NCV in insulin dependent diabetics and found its similar significant correlation with HbA_{1c} levels, although this was seen with medial and peroneal motor nerves [24]. Moreover, achievement of a better glycaemic control resulted in increased NCV of some nerves as compared to the baseline value.[25]

There were limitations in our study which could have effected the outcome. Majority of the diabetic patients were receiving Metformin which leads to an exacerbation of neuropathy by causing vitamin B12 deficiency [26]. Some of the patients were also receiving Methylcobalamin that might have effected NCV, as evident by studies showing association between neuropathy and Methylcobalamin[27, 28] .Duration of diabetes which is independently associated with peripheral neuropathy in diabetics [4] was also not taken into account .All the patients were from same ethnic background and also the sample size was small.

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