International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

A Study of Nerve Conduction in Newly Diagnosed Type 2 Diabetes Mellitus

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Abstract: ***Background: Neuropathy is one of the most common complications of type 2 diabetes mellitus (T2D) which can cause sensory deficit, neurological disorder, limb ulcers resulting in amputation. Hence, judicious neurological examinations at appropriate time intervals to determine nerve conduction velocity (NCV) are of prime importance to avoid catastrophic consequences like amputations. Aim: The present study aimed to investigate NCV in newly diagnosed asymptomatic diabetes patients and compare the results with age- and sex-matched healthy controls. Material and Methods: The present study was an observational case-control study in 50 T2D out-patient and 50 healthy controls aged 31-60 years who offered informed consent during the year 2015 to 2017. In all patients, neurological examination, NCV, and F wave latencies of tibial and peroneal were examined and recorded. The data obtained were analyzed using MS-excel and Minitab software. RESULTS: The results showed that even in the newly diagnosed participants there is impairment in F wave latency as compared to controls and there is a positive correlation with fasting blood glucose (FBG), (r=0.76 to 0.78; P=0.00). Both sensory NCV of superficial peroneal and sural nerve and motor nerve conduction of tibial and peroneal nerve has a negative correlation with FBG (r=-0.68 to -0.74; P=0.00). The sensory nerve is more impaired than the motor. Impairment is bilaterally symmetrical and features are primarily suggestive of axonal neuropathy. CONCLUSION:This signifies that even in asymptomatic patients; neuropathy might have already set in with severity directly proportional to FBG. Hence, it would be prudent at the time of diagnosis of T2D itself to perform NCV to would ensure early diagnosis and optimize BG levels.***

Keywords: Type 2 diabetes, neuropathy, nerve conduction velocity, fasting blood glucose, sensory and motor nerves

1. Introduction

Type 2 diabetes mellitus (T2D), the most common endocrine disorder is characterized by metabolic abnormalities and in the long run with micro-and macrovascular complications that are associated with significant morbidity and mortality.[1] Diabetic neuropathy (DN) is one of the most common and troublesome complications of T2D leading to great morbidity and resulting in a huge economic burden for diabetes care. Studies have found that one of three diabetic patients has DN.[2] The most important diagnostic criteria for DN, also corroborated by experts, are irregularities in nerve conduction velocity (NCV), the increased threshold of sensory nerves, and instabilities in autonomic system function tests. Among electro-diagnostic tests, NCV determination is one of the important diagnostic tests, since it is both sensitive and reproducible.[1] DN is a progressive complication leading to diabetic foot but with a prolonged asymptomatic stage mostly necessitating amputation.[4] It is therefore important to identify DN in the asymptomatic stages. Early identification along with glycaemic control are the key factors for preventing DN. The American Academy of Neurology recommends at least one of the five criteria for diagnosing DN: Symptoms, Signs, Electrodiagnostic tests, Quantitative sensory tests, and Autonomic testing.[5]

The development of neuropathy correlates with the duration of diabetes and glycaemic control. Both myelinated and unmyelinated nerve fibers are lost.

Several studies document clinical and subclinical signs of DN even before neurological impairment and symptom development.[6,7]These cases substantiate the importance of early and intensive glycemic control as the most important preventable risk factor in the development of DN. Some patients with DN are asymptomatic but electrophysiological or nerve biopsy can reveal impairment of peripheral nerves.[8,9]Considering the importance of early recognition of signs of the onset of DN, we conducted this case-control study to look for changes in NCV in asymptomatic newly diagnosed T2D patients, to obtain the correlation of NCV changes with fasting blood glucose (FBG) and to Correlate motor nerve conduction (MNC), sensory nerve conduction (SNC) & F wave Changes in newly diagnosed T2D patients.

2. Material and Methods

The present research was a case-controlled study in 100 participants with and without diabetes in a 1:1 ratio. The study was conducted for a period of two years from December 2015 to November 2017. Participants more than 30 years of age, with T2D for less than a year with asymptomatic (absence of unsteadiness in walking, numbness, burning, aching pain, or tenderness in legs or feet, pricking sensation) with DN Symptom Score (DNS) of '0' willing to participate were included in the study along with age- and sex-matched healthy volunteers.

Patients with any neurological problems due to other diseases that may affect the nerve function, such as renal failure, systemic lupus erythematosus, hepatic failure, and unwillingness to provide consent were excluded.

For all the asymptomatic patients attending the outpatient department, careful methodical examination of the central nervous system was conducted for recording the physical signs. Information regarding the patients' symptom and risk factors were obtained from family members or caregivers. All patients were subjected to nerve conduction tests. Velocities in the tibial nerve, peroneal nerve, superficial peroneal nerve, and sural nerve were obtained.

Motor and sensory nerve conduction studies were conducted in lower limbs using bipolar surface electrodes in 50 patients with T2D without symptoms of neuropathy referred to our neurophysiology lab for NCS and 50 healthy volunteers. NCS was performed with RMS EMG EP MARK II machine and the temperature of the lab was maintained at 21-23ºC.

Normally distributed continuous variables are expressed as means ± standard deviations. Meanwhile, categorical variables are described as frequencies and percentages. The data obtained was organized into MS excel and the statistical analysis was performed by using MS-Excel and Minitab software. The unpaired t-test was used to determine the significance or p values between the means.

The correlation is represented as the correlation coefficient (or "r"). It ranges from -1.0 to +1.0. The closer r is to +1 or -1, the more closely the two variables are related. If r is close to 0, it means there is no relationship between the variables. If r is positive, it means both variables are directly proportional to each other. If r is negative, it means variables have an inverse correlation.

3. Results

The baseline characteristics of the study population are shown in **Table 1** Clearly, the total cholesterol (p=0.005) and FBG (P=0.00) levels were significantly higher in the diabetic group compared to the control. **Table 1**

Table 1: Baseline Characteristics

Characteristics	Diabetics (N=50)	Control (N=50)
Gender (Male/Female)	28/22	28/22
Age (years)	47.46±6.28	44.64±6.55
31-40 Male Female	 6 (21.4%) 4(18.1%)	 9(32.2%) 6(27.2%)
41-50 Male Female	 13(46.4%) 11(50%)	 10(35.6%) 11(50%)
51-60 Male Female	 9 (32.2%) 7(31.9%)	 9(32.2%) 5(22.8%)
Fasting blood glucose (mg/dl)	183.44 ± 37.17	88.02 ± 11.11
Total cholesterol (mg/dl)	205.3±27.2	188.9±30.1

Normally distributed continuous variables are expressed as means ± standard deviations. Categorical variables are described as frequencies and percentages.

The observations indicate a significant delay in the conduction velocity in the **peroneal, tibial, superficial peroneal, and sural nerve** in either side in the patients with T2D compared to the control group. **Table 2**

Table 2: Nerve conduction study in patients with Type 2 Diabetes and control

Subjects	Peroneal		Tibial		Superficial peroneal		Sural	
	Left	Right	Left	Right	Left	Right	Left	Right
Diabetics	48.49 ± 2.98	48.44± 2.80	48.51 ± 3.09	48.47 ± 2.96	47.76 ± 3.19	47.42 ± 2.62	48.32 ± 3.00	48.06 ± 2.86
Controls	49.83 ± 1.18	49.81 ± 1.28	48.69 ± 1.57	49.80 ± 1.47	49.55 ± 0.98	49.39 ± 1.12	50.66 ± 1.19	50.73 ± 1.33
t value (p value)	2.95 (0.004)	3.15 (0.002)	2.39 (0.019)	2.84 (0.006)	3.79 (0.000)	4.89 (0.000)	5.15 (0.000)	5.98 (0.000)

Data is represented as Mean±SD

The results show that there is a significant prolongation of F wave latency in the peroneal and tibial nerve of both rights and left sides in patients with T2D as compared to controls. **Table 3**

Table 3: F wave study in diabetics and non-diabetics

Subjects	Peroneal		Tibial	
	Left	Right	Left	Right
Diabetics	51.94 ± 8.97	50.68 ± 6.30	51.66 ± 6.06	51.26 ± 6.08
Controls	42.98 ± 2.68	43.06± 2.67	44.74 ± 2.67	44.86 ± 2.72
t value (p value)	6.7 6.77(0.00)	7.88 (0.00)	7.39 (0.00)	6.79 (0.00)

Data is represented as Mean±SD

The motor nerve conduction was negatively correlated with FBG, which means that they are inversely related, viz increase in FBG leads to decrease in the conduction velocity in Superficial Peroneal and Sural nerves. **Table 4**

The F wave latencies were positively correlated with FBG, which indicates that an increase in FBG increases the F wave latencies in the Peroneal and Tibial nerves. **Table 4**

Table 4: Correlation between FBG and MNC, SNC and F wave

Parameters		Diabetics		Control	
MNC		r value	p value	r value	p value
Peroneal	Right	-0.72	0.000	0.02	0.917
	Left	-0.74	0.000	-0.03	0.852
Tibial	Right	-0.71	0.000	-0.08	0.574
	Left	-0.73	0.000	-0.12	0.422
SNC		r value	p value	r value	p value
SUP	Right	-0.71	0.000	0.02	0.880
	Left	-0.68	0.000	-0.16	0.260
Sural	Right	-0.74	0.000	-0.07	0.643
	Left	-0.73	0.000	0.03	0.865
F wave latency		r value	p value	r value	p value
Peroneal	Right	0.76	0.000	0.16	0.279
	Left	0.40	0.004	0.17	0.239
Tibial	Right	0.78	0.000	0.06	0.685
	Left	0.78	0.000	0.04	0.768

MNC- motor nerve conduction, SNC-sensory nerve conduction

Further diabetic patients were grouped based on the FBG levels as Group 1 -greater than 200 (N=16; 32%), Group 2- less than 200 mg/dl (N=34; 68%), and subgroup analysis was performed. The mean FBG in Group 1, Group 2, and Controls was 225.5 ± 20.7, 163.6 ± 24; and 88.0 ± 11.1 mg/dl, respectively. **Table 5**

Table 5: Comparison of Group 1, Group 2 and Control

Parameter	Nerve	Side	Group 1	Group 2	Control	p value		
			Mean ± SD			Group 1 vs 2	Group 2 vs Control	Group 1 vs Control
MNC	Tibial	R	45.29 ± 2.47	49.97 ± 1.75	49.80 ± 1.47	0.000	0.648	0.000
		L	45.17 ± 2.66	50.09 ± 1.72	49.68 ± 1.57	0.000	0.276	0.000
	Peroneal	R	45.74 ± 2.84	49.71 ± 1.68	49.81 ± 1.28	0.000	0.761	0.000
		L	45.43 ± 2.87	49.93 ± 1.67	49.83 ± 1.18	0.000	0.759	0.000
SNC	Superficial peroneal	R	44.96 ± 1.92	48.57 ± 2.06	49.39 ± 1.12	0.000	0.040	0.000
		L	44.84 ± 2.16	49.14 ± 2.62	49.55 ± 0.98	0.000	0.380	0.000
	Sural	R	45.37 ± 2.06	49.33 ± 2.24	50.73 ± 1.33	0.000	0.002	0.000
		L	45.49 ± 2.20	49.65 ± 2.33	50.66 ± 1.19	0.000	0.024	0.000
F Wave	Tibial	R	57.00 ± 2.48	48.56 ± 5.35	44.86 ± 2.72	0.000	0.001	0.000
		L	57.31± 2.52	49.00 ± 5.38	44.74 ± 2.67	0.000	0.000	0.000
	Peroneal	R	56.44 ± 3.01	47.97 ± 5.58	43.06 ± 2.67	0.000	0.000	0.000
		L	57.13 ± 2.66	49.50 ± 9.85	42.98 ± 2.68	0.000	0.001	0.000

MNC- motor nerve conduction, SNC-sensory nerve conduction

There is a significant delay in conduction velocity of diabetics with FBG > 200 mg/dl as compared to diabetics with FBG level < 200 mg/dl as well as controls and it was bilaterally symmetrical for the tibial, peroneal, superficial peroneal, and sural nerves. While there was no significant delay in conduction velocity of diabetics with FBG less than 200 mg/dl and controls in the tibial and peroneal nerves; the superficial peroneal and sural nerves did show a significant delay in nerve conduction even in those with FBG < 200 mg/dl. This data thus implies that the sensory nerve conduction is affected in diabetics even FBG level < 200 mg/dl as compared to motor nerve conduction. The study found that there is a significant prolongation of F wave latencies of tibial and peroneal nerves in diabetics, regardless, of whether the FBG was less than or greater than 200 mg/dl as compared to control.

4. Discussion

The present study focused on a group of newly diagnosed diabetic patients who were neurologically normal. Recommendations for standardized classification of DN made by the American Diabetic Association and Academy of Neurology include measurement of at least one parameter of nerve conduction studies. The subclinical DN has been defined as the presence of nerve lesions attributable to diabetes mellitus in the absence of abnormal clinical data but detectable through electrophysiological studies. In our study, the cases are newly diagnosed diabetic patients in whom nerve conduction velocities and F Wave latencies were affected. This suggests that the early ill-effects of T2D on the peripheral nerves are primarily in form of axonal neuropathy.

In the current study, of a total of 100 age- and sex-matched participants were included, 50 were recently diagnosed T2D patients without any neurological symptoms and the remaining were controls without T2D. Compared to the study by Prasad Neelambala et al, our study population was relatively younger and FBG higher, since we included newly diagnosed patients.[10] Our patient demographics and FBG levels are fairly similar to those included in the study by Ram Babu Singh et al since it had also included newly diagnosed patients.[11]

In our study, the age range was 35-60 years with maximum patients in the age range of 41 to 50 years. In the study by Adgaonkar et al, in which the age range was 21 to 70 years and maximum patients aged between 51 to 70 years.[12] The DN is most common after the 5th decade of life. Shaw et al. showed an incidence of peripheral neuropathy was 17.6% between the age group of 20-40 years and 56.8% between 40-70 years.[13] Kasturi et al. found that the incidence of

neuropathy was more in patients over 40 years of age (60 out of 70 patients) with a duration of disease over two years (78.33%).[14] Thus, it is common that peripheral neuropathy, in general, was common in middle age and elderly diabetics.[15] Nevertheless, it can sometimes occur in younger diabetics and may be absent in older ones.

Our observations regarding conduction velocities for motor nerves agreed with those reported by Prasad Neelambala et al and Kimura et al, but unlike the former study we additionally also tested the conduction velocity of sensory nerves (Superficial and sural nerve). Our study found that there is a significant decrease in conduction velocity of the superficial peroneal nerve and sural nerve of both sides in diabetics.

The results for the correlation between FBG and NCV for peroneal and tibial were also like those reported by Prasad Neelambala et al.[10] Our additional testing showed that sensory nerves (superficial nerve and sural nerve) also showed results like motor nerves. The F wave latency and their correlation with FBG also confirmed that NCV positively correlated with FBG.

The results obtained from subgroup analysis found that conduction velocities were significantly decreased in diabetic patients with FBG more than 200 mg/dl in peroneal, tibial, superficial, and sural nerves as compared to those with less than 200 mg/dl and controls. Except in the left superficial peroneal nerve, there was a significant delay in conduction velocity. Unlike, NCV, the F wave latencies were significantly prolonged regardless of FBG more or less than 200 mg/dl compared to the control group. Our results are slightly comparable to those reported by Kanavi Roopa SheKhaRappa et al. However, this study had used HbA1c instead of FBG, and only ulnar NCV was tested. [16] While we tested both motor and sensory in the lower limb nerves.

From the evaluation of the data obtained through our study, we suggest that practically the most useful nerves for electrophysiological study in diabetic patients were the motor and sensory nerves in the lower extremity. The nerve dysfunction in the lower extremity must be correlated with the length of the nerves.

The decreased delivery of slowly transported proteins (structural proteins) to the axons may be the cause of reduced axon ability. The key event in the development of neurological irregularities in diabetes is an impairment of the axonal transport, subsequently leading to the abnormality of the transport of structural proteins. Primary axonal degeneration is known to occur in patients with T2D even at the time of diagnosis of the metabolic disturbance. A decrease in the transport of structural proteins in diabetic patients might well be an explanation of these structural axon changes.[17] Thus, axonal transport maintains the anatomic and functional integrity of the nerve. The interruption of axoplasmic flow in the long nerve is more prominent than in short nerves.

Conduction abnormalities are more frequent in large myelinated fibers in the early stage of diabetes but there is also prominent involvement in small myelinated and unmyelinated fibers especially in the lower extremity. Thus, nerve length might be an important factor in the early dysfunction of the nerve. In our study, we found that the somatic large fibers could be affected in an early stage of diabetes.

This study shows that there exists grade 1a neuropathy as per ADA guidelines for DN, in newly diagnosed T2D patients, and severity increases with initial FBG levels. This signifies that even in asymptomatic patients; neuropathy might have already set in with severity directly proportional to FBG. Hence, it would be prudent at the time of diagnosis of T2D itself to perform NCV along with retinal and renal investigations, which together contribute to diabetic triopathy. This would ensure early diagnosis of microvascular complications like DN and initiation of optimal control of blood sugar levels.

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