



# **A Pilot Study Investigating the effect of Glycemic Control on Electrodiagnostic Parameters in Type II Diabetic Patients**

**Parikshit Ashok Muley<sup>1\*</sup>, Dalia A. Biswas<sup>1</sup> and Avinash Taksande<sup>1</sup>**

<sup>1</sup>*Physiology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi (M), Wardha. India.*

## **Authors' contributions**

*This work was carried out in collaboration among all authors. Author PAM designed the study, wrote the protocol and wrote the first draft of the manuscript. Author DAB gave guidance for the research study protocol and literature searches. Author AT provided the technical support in neurophysiology laboratory and to design research study. All authors read and approved the final manuscript.*

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**Study Protocol**

## **ABSTRACT**

**Background:** Diabetes is a chronic metabolic abnormality due to either decreased secretion of insulin or decreased tissue sensitivity of insulin resulting in elevated blood glucose. Most common complication of diabetes is peripheral neuropathy. In this research project, we will be conducting a pilot study to observe the effect of glycaemic control on physiological functioning of nerve with the help of neurophysiological parameters, independent of duration of diabetes.

### **Objectives:**

- 1) To investigate relationship of quality of glycemic control & severity of neurological changes.
- 2) To find out whether glycemic control acts as an independent risk factor for progression of diabetic neuropathy despite the duration of diabetes.
- 3) To validate the HBA1C at 10 for future longitudinal study to understand the association between glycemic control & progression of neuropathy.

**Methodology:** 60 type II diabetic patients visiting diabetic OPD (Medicine) will participate in the study. The patients will be divided in to 2 groups of Group number 1 with (30 subjects) HBA1C < 10

\*Corresponding author: E-mail: [drparikshit19@yahoo.com](mailto:drparikshit19@yahoo.com);

and Group number 2 having (30 subjects) HBA1C >10. Electrodiagnostic study will be conducted on motor (tibial nerve) and sensory (sural nerve) will be performed in Neurophysiology lab. Neurophysiological parameters data of two groups will be analysed and compared.

**Expected Results:** The pilot study will help to find out whether glycaemic control acts as a separate risk factor for progression of diabetic neuropathy despite duration of diabetes.

**Conclusion:** This pilot study will help to establish the association between quality of glycaemic control and severity of neurological changes. Also, this will help to validate the HBA1C at 10 for further longitudinal study to know whether poor diabetes control is an independent risk factor associated to the severity of neuropathy in type II diabetes.

*Keywords: Diabetes mellitus; glycaemic control; nerve conduction study.*

## 1. BACKGROUND

Diabetes mellitus (DM) is an abnormality related with diminished carbohydrate, fat, and protein metabolism due to either reduction of insulin secretion or reduced sensitivity of the tissues to insulin [1]. Diabetes is a chronic metabolic disease which causes increase level of blood glucose [2]. Hyperglycaemia in diabetes may be because insulin is not being produced at all, is not made at sufficient levels, or its actions are not as effective as it should be. The chronic hyperglycaemia and attended metabolic deregulations may be associated with potential chronic complications which can affect eyes, heart, blood vessels, kidneys and nerves. The most usual complication of diabetes is peripheral neuropathy [3,4]. Diabetic neuropathy affects sensory nerves, motor nerves & autonomic nerves. The prevalence of neuropathy in diabetes ranges from 7% from one year of diagnosis to almost 50% with more than 25 years of diabetes [3]. Diabetic neuropathy is one of the most common micro-vascular complications which is related with foot amputation, ulcer and compromising on the quality of life [5]. It is important characteristics of peripheral nerve dysfunction in diabetes mellitus (DM) [6]. The neuropathic symptoms may not be severe or subclinical but consequent hyperglycaemia causes pathological and functional changes.

Nerve conduction study (NCS) is a diagnostic modality to measure the conduction velocity of electrical signals in the peripheral nerves. The abnormal findings may be seen when the pathology is in axon, myelin & nodes of Ranvier [7]. In NCS, the nerve potential amplitude correlates with the degree of nerve fibre damage or loss [8]. Thus, NCS help to diagnose the peripheral nerve dysfunction even when the damage to the nerve is subclinical or presymptomatic [5].

Various studies have been done previously, showing the diabetic neuropathy as a common complication of DM [3,4]. The most usual cause of peripheral neuropathy is diabetes related neuropathy [6]. According to an estimate, in majority of diabetics they present either clinical or subclinical neuropathy [6]. In a recent research study done, it suggests that the incidence of neuropathy is 19.1% in type II diabetic patients [9]. It results in frequent hospitalisation as compared to other complications of diabetes. In a study conducted, it was observed that the neuropathy incidence increased from 7.5% during admission to almost to 50% at 25 years follow up [6]. All those studies suggest the duration of diabetes was significant predictors of the severity of neuropathy. Another study observed the result of glycaemic control on morphological severity of diabetic neuropathy by determining fibre density on biopsy of sural nerve [8].

In this research project, we will be conducting a pilot study to observe the effect of glycaemic control on physiological functioning of nerve with the help of neurophysiological parameters, independent of duration of diabetes. We will evaluate peripheral nerve function in diabetic subjects using nerve conduction study in order to correlate between glycaemic control and diabetic peripheral neuropathy.

## 2. AIM AND OBJECTIVES

The pilot study will be done to determine the key risk factor which may be responsible for the development of neuropathic changes in diabetics. The study will primarily be done:

- 1) To investigate relationship of quality of glycemic control & severity of neurological changes.
- 2) To find out whether glycemic control acts as an independent risk factor for

progression of diabetic neuropathy despite duration of diabetes.

- 3) To validate the HBA1C at 10 for future longitudinal study to understand the association between glycemic control & progression of neuropathy.

- Patient presenting with emergency conditions like diabetic keto-acidosis and coma.
- Any other underlying metabolic or endocrine disorders hypo or hyper thyroidism etc.

### 3. METHODS

**a) Study design:** It is a cross section study.

**b) Study setting:** The study will be done in Neurophysiology Lab under department of Physiology of DMIMS campus. Period of study will be from May 2021 to July 2021.

**c) Sample size-** 60 type II diabetic patients (n= 30-HBA1C < 10 and n =30 - HBA1C >10) visiting diabetic OPD (Medicine) will participate in the study.

**d) Eligibility criteria of participants-**

#### Inclusion criteria –

- Patients with age ranging from 35 to 60 years (Male and female)
- Type II Diabetes mellitus patients (The diagnosis of these patients will be confirmed by postprandial serum glucose minimum of 200 mg/dl or fasting glucose at least 140 mg/dl). Blood glucose (Fasting and post prandial levels) will be checked for three times per patient with a gap of 3 days in between tests.
- Those subjects who give valid consent for the study.

#### Exclusion criteria –

- Patients having diagnosed with type I diabetes mellitus.
- Patients with local injuries/lesions at the recording sites that may interfere with the electrophysiological study.
- Other known causes of neuropathy, polyneuropathy, myopathy
- Neuromuscular transmission disorders like myasthenia gravis
- Potential neurotoxic drugs.
- Having lumbosacral pathology, discopathies.
- Patient having diabetic foot / gangrene.

60 sample size of type II diabetics will be studied under following headings:

#### 1. Personal information

- Name
- Age / sex
- Family and occupational history
- Address (Urban/rural)-
- H/s/o other diseases causing neuropathies
- Duration of diabetes
- Enlist the medications to control the glucose level
- Diet – Breakfast, Lunch, Dinner
- Doing any type of exercise- Jogging/walking/swimming/yoga/any other (specify)
- Recently conducted (up to 3 months) blood sugar reports of the patient.

#### 2. Haematological values-

- Fasting (FBS) blood sugar
- Postprandial (PP) blood sugar
- Glycosylated haemoglobin level (HBA1c)

#### 3. Nerve conduction study parameters

- Motor NCS of Tibial nerve.
- Sensory NCS in Sural nerve.
- Amplitude of Compound muscle action potential in Tibial nerve (CMAP)
- Amplitude of Sensory nerve action potential of Sural nerve (SNAP)

### 2.1 Hematological Values

#### 1) Blood Sugar.

Specimen: Venous blood sample.  
Method to estimate Blood sugar- GOD-POD method  
Normal Range [1]:Fasting – < 120 mg/dl  
Post Meal - < 140 mg/dl.

#### 2) Glycosylated Hemoglobin Level (HbA1c %)

Specimen: Venous blood was collected with EDTA/ Heparin using aseptic techniques.

Name of Method- Immunoturbidity method.

All reagents were stored and stable at 2 - 8°C  
Normal Range [10]:< 6%

## 2.2 Nerve Conduction Study Parameters

Nerve conduction studies will be performed in Neurophysiology department under dept. of Physiology at DMIMS, Wardha on Neuro-soft chrome machine. A written informed consent will be taken from all the subjects after screening through the inclusion and exclusion criteria.

EMG software and USB was installed and the following tests were performed.

- Motor NCS of tibial nerve
- Sensory NCS in sural nerve
- CMAP in tibial nerve
- SNAP of sural nerve

### 1) Tibial motor nerve conduction study

Surface electrodes were used for recording the electrical activity. For tibial motor nerve conduction study, the recording electrode (black coloured) is kept on the muscle belly of abductor hallucis from where the CMAP is measured. The reference electrode (red coloured) is placed distally near the metatarsal head, which is an electrically neutral point. Ground electrode (green coloured) is placed over the dorsum of the foot.

Surface stimulation was used for excitation of nerve at distal(S1) and proximal sites(S2).

S1- Placed behind & proximal to medial malleolus.

S2- In the popliteal fossa, slightly lateral to midline of popliteal fossa.

The distal latency, nerve conduction velocity and CMAP amplitudes are measured following the stimulation.

The normal values of tibial motor nerve conduction are: [11]

CV  $\geq$  41 m/s  
CMAP  $\geq$  4.0 mV

### 2) Sural sensory nerve conduction

Antidromic surface stimulation was performed to assess the sensory nerve conduction in sural nerve. The recording electrode (black) is kept in between lateral malleolus and tendo achillis, while the reference electrode (red) is kept 3 cm distal to recording electrode. Ground electrode

(green) is kept 5 cm proximal to recording electrode on achillis tendon.

Surface stimulation is used for excitation of nerve at only single site.

S1- Distal to lower border of belly of gastrocnemius muscle, roughly at intersection of middle and lower third of the leg, slightly lateral to the midline.

During the recording, the lower limbs are relaxed and laterally placed. The distal latency, nerve conduction velocity & SNAP amplitudes were measured.

The normal values of sural sensory nerve conduction are: [11]

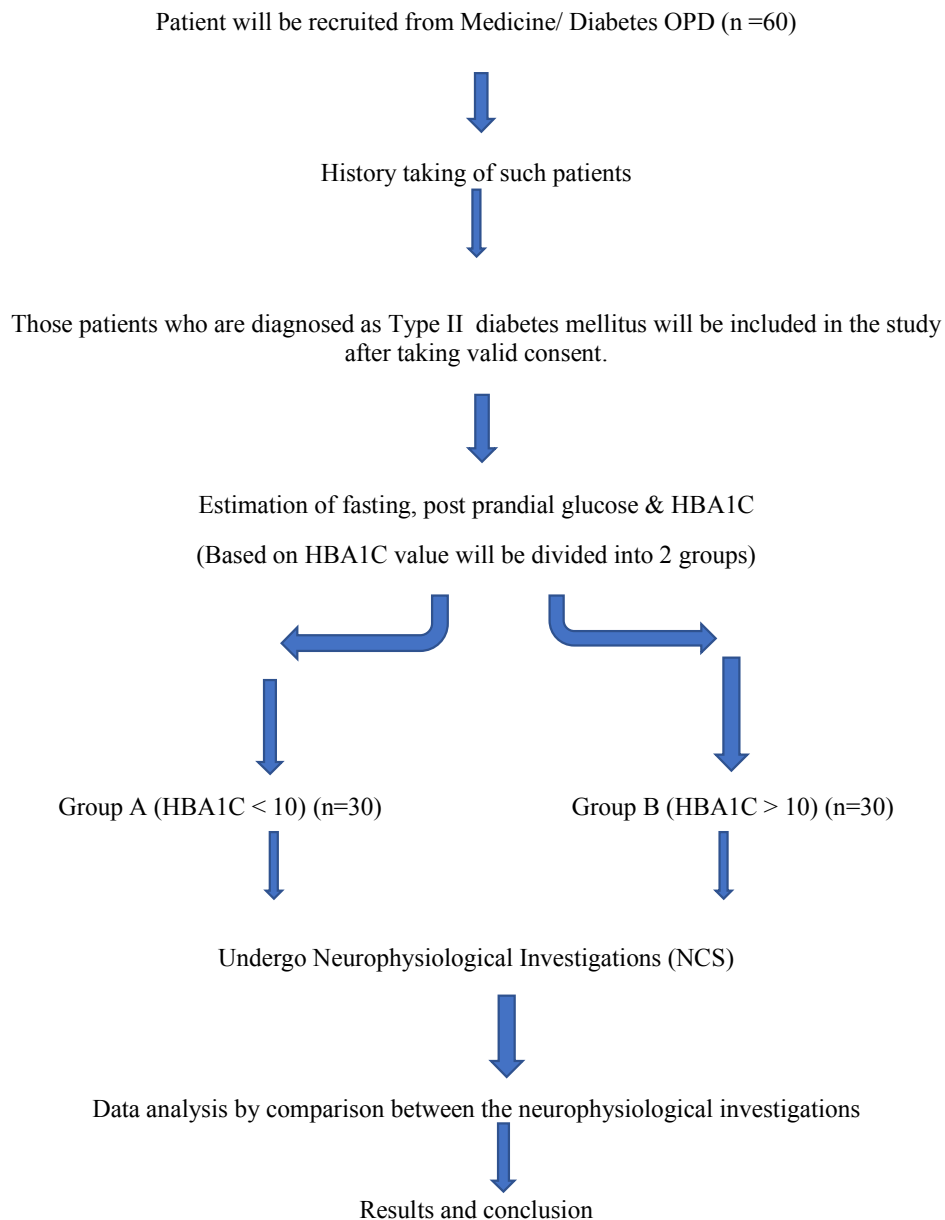
CV  $\geq$  40 m/s  
SNAP  $\geq$  6.0  $\mu$ V

The data of motor and sensory nerve conduction study will be collected. All tests will be performed by same investigator and under constant room temperature.

Improper electrode placement, inaccurate measurements, and failure to monitor and control limb temperature influence the results [12]. Limb temperature is particularly important in the evaluation of neuropathy. Cooling reduces conduction velocity and increases amplitude, a combination of findings atypical for most pathologic processes. Thus temperature of the room was maintained at a 25°C (constant level) while taking observations.

## 2.3 Statistical Analysis

In this pilot study, effect glycemic control over the motor as well as sensory nerve conduction will be evaluated. The total sample size in the study project will be 60 patients by using purposive sampling and as duration of study is small. Accordingly, patients will be divided according to the HBA1c values, and the cut off value will be 10. Thus, the total sample size is 60 which will be divided into 2 groups i.e. Group A having HBA1c < 10 (n= 30) and Group B having HbA1c > 10 (n =30). This cut off value was derived from a study made by Satoshi Kuwabara [13] in 2005 where he found significant improvement in both motor & sensory nerve conduction parameters, four weeks after giving intensive insulin treatment. Statistical method – SPSS 24.0 version, Graph Pad Prism 7V , Chi- square test, students unpaired t test ( 2 sided).



**Fig. 1. flowchart of the study processing**

### 3. KEY RESULTS

The pilot study will help to find out whether glycemic control act as independent risk factor for progression of diabetic neuropathy despite the duration of diabetes. This will help to establish the correlation ship between quality of glycaemic control and severity of neurological changes. Also, being pilot study, it will help to validate the HBA1C at 10 for future longitudinal study to understand the co-relationship in glycemc control and neuropathic complications

### 4. DISCUSSION

The pilot study will be done to determine the glycaemic control as the key risk factor which may be accountable for progression of neuropathic changes in diabetics. Various studies were conducted to determine the association of glycaemic control and diabetic neuropathy.

Kuwabara et al [13] investigated acute modifications in various parameters of NCS

associated with glycaemic control. The result suggested that glycaemic control quickly changes the nerve conduction [13]. Mackel et al [14] studied the median nerve conduction in diabetes patients. The results suggested disruption of the axonal recovery process in them may be due to membrane potential fluctuations [14]. Shaw et al [15] performed a study which assessed neuropathy disability score in type 1 DM subjects. The neuropathic severity score was related to increasing glycated haemoglobin [15].

Tkac et al [16] examined the electrophysiologic severity of diabetic neuropathy. NCS were done on sensory & motor nerves of upper & lower limb. Glycated haemoglobin was significantly related to both sensory nerve conduction velocity and amplitude [16]. Morkrid et al [17] completed study to find prevalence of peripheral neuropathy in type 2 DM. Peripheral neuropathy was assessed using the Neuropathy Score. It was observed that prevalence of peripheral neuropathy is of 19.7% [17].

Stolar et al [18] studied the association between glycaemic control and complications in type 2 DM. It was observed that microvascular complications were associated with haemoglobin A1C (HbA1c) [18]. Akaza et al [5] investigated whether glycaemic variability is associated with diabetes peripheral neuropathy (DPN). They studied glycaemic variability by mean amplitude of glycaemic excursions in continuous glucose monitoring and found that glycaemic variability is independent risk factor for DPN [5].

Few of the studies related to Type-II diabetes were reported [19-21]. Rathi et al [22] reported nerve conduction studies of peripheral motor and sensory nerves in the subjects with prediabetes [22]. Shrivastava *et.al.* reported on assessment of Mean Platelet Volume (MPV) in subjects with Type 2 Diabetes Mellitus [23]. Ashfaque *et al* reported about assessment of self-care practices among type 2 diabetes patients [24]. Jankar *et al* reported on Association of Urinary Albumin with HbA1c Levels in Subjects of Type 2 Diabetes Mellitus [25].

## 5. LIMITATIONS

In present pilot study, we will evaluate electro diagnostic parameters on the basis of glycaemic control with the help of HbA1c level. The study will be limited in the manner that the data obtained for the study will be cross-sectional.

Thus, further longitudinal study may be required for further evaluation. The study factor will be restricted to glycaemic control by (HbA1C) and its relation to diabetic neuropathy. We will not be able to evaluate glycaemic variability using continuous glucose monitoring in this study. Similarly, we will be conducting the study in Type II DM patients only. This may restrict the study to observe the effect of glycaemic control on neuropathy in Type I DM patients. The age restrictions in the inclusion criteria (from 35 to 60 years) may limit the evaluation of patients with severe diabetes complications.

## 6. CONCLUSION

This pilot study will help to establish the association between quality of glycaemic control and severity of neurological changes. Also, this will help to validate the HbA1C at 10 for further longitudinal study to know whether poor diabetes control is an independent risk factor associated to the severity of neuropathy in type II diabetes.

## CONSENT

A written informed consent will be taken from all the subjects after screening through the inclusion and exclusion criteria.

## ETHICAL APPROVAL

As per international standard or university standard written ethical will be taken by the author(s).

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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