

**SOMATOSENSORY EVOKED POTENTIALS IN DIABETES MELLITUS TYPE-2**G. Rekha<sup>1</sup>, G. S. Prema<sup>2</sup>, O. Padmini<sup>3</sup>**HOW TO CITE THIS ARTICLE:**

G. Rekha, G. S. Prema, O. Padmini. "Somatosensory Evoked Potentials in Diabetes Mellitus Type-2". Journal of Evidence based Medicine and Healthcare; Volume 2, Issue 43, October 26, 2015; Page: 7594-7601, DOI: 10.18410/jebmh/2015/1027

**ABSTRACT:** Diabetes mellitus is the most common metabolic disorder affecting majority of population. It is estimated that over 400 million people throughout the world have diabetes. It has progressed to be a pandemic from an epidemic causing morbidity and mortality in the population. Among the many complications of diabetes, diabetic neuropathies contribute majorly to the morbidity associated with the disease. Axonal conduction is affected by elevated levels of protein kinase c causing neuronal ischemia; decreased cellular myoinositol affecting sodium potassium ATPase pump leads to decreased nerve conduction; Somatosensory Evoked Potentials (SSEPs) reflect the activity of somatosensory pathways mediated through the dorsal columns of the spinal cord and the specific somatosensory cortex. Recording of Somatosensory Evoked Potentials in diabetics is done to assess the sensory involvement of spinal cord. Presence of SEPs provides clear evidence for axonal continuity and by using different stimulation sites, the rate of regeneration can be determined. Both onset and peak latencies of all SEP components are prolonged in patients with diabetes. Present study is done to compare somatosensory evoked potentials in diabetics and normal subjects. **MATERIALS AND METHODS:** The present study was undertaken at the Upgraded Department of Physiology, Osmania Medical College, Koti, Hyderabad. The study was conducted on subjects, both male and female in the age group of 45 to 55 years, suffering from type II diabetes excluding other neurological disorders. Non-invasive method of estimation of nerve conduction studies using SFEMG/EP— Electromyography or evoked potential system (Nicolet systems—USA) using surface electrodes with automated computerized monitor attached with printer is used. **RESULTS:** ANOVA showed statistically significant N9 latency (right & left sides). Latencies of all the components of SSEPs were more significant than amplitudes in Diabetic patients multiple linear regression analysis showed statistically significant values for N9 latency, N13 latency, P25 latency, N20 amplitude and P25 amplitude. **DISCUSSION:** Conductive function in the central as well as peripheral somatosensory pathways is affected earlier in diabetes. Increased oxidative stress and mitochondrial dysfunction in diabetic neurons cause nerve dysfunction and decreased neuronal regenerative capacity in sensory, motor and autonomic neurons. In our study significant prolongation of latencies was observed in sensory nerves in diabetic individuals when compared to normals. Multiple regression analysis of N9, N13 & P25 latencies showed significant 'F' values (F value>1). Similar attempts can aid future studies to predict the risk before the onset of diabetic neuropathy.

**KEYWORDS:** Somatosensory Evoked Potentials in (SSEPs); Latencies; Diabetist.

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**INTRODUCTION:** Diabetes mellitus is the most common metabolic disorder affecting majority of population. It is estimated that over 400 million people throughout the world have diabetes. It has progressed to be a pandemic from an epidemic causing morbidity and mortality.

Type 1 diabetes is an autoimmune disease. The most common form is type 2 diabetes which affects about 90 to 95 percent of people. Patients most often show insulin resistance and pancreatic beta cell resistance. Gestational diabetes is seen late in pregnancy. There is 40-60% chance of developing type 2 diabetes in such women after 5-10 years. Existence of family history of diabetes often occurs in such cases.

Among the many complications of diabetes, diabetic neuropathies contribute majorly to the morbidity associated with the disease. Different types of nerves are involved.

**Autonomic Neuropathy:** The autonomic nervous system supplies various organ systems of the body. Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, impaired neurovascular function and hyperglycemic autonomic failure.

**Cranial Neuropathy:** Oculomotor neuropathies are most common in diabetes. All the oculomotor muscles innervated by the third nerve are affected, except for the ciliary muscle. This is because the periphery of the nerve which supplies ciliary muscle is less susceptible to ischemic damage as it is closer to the vascular supply. Abducent nerve is also commonly affected but the trochlear nerve involvement is unusual. Mono-neuropathies of the thoracic or lumbar spinal nerves can occur and lead to painful syndromes that mimic myocardial infarction, cholecystitis or appendicitis. Diabetics have a higher incidence of entrapment neuropathies, such as carpal tunnel syndrome.

**Sensorimotor Polyneuropathy:** In diabetic neuropathy, the large diameter sensory fibers degenerate. Such a selective loss is reflected in a reduction in the peak of the compound action potential, a slowing of nerve conduction and a corresponding diminution of sensory capacity.<sup>(1)</sup>

### **Various causes for diabetic neuropathy are:**

Neuronal ischemia is a well-established characteristic feature of diabetic neuropathy resulting from diabetic microvascular injury involving small blood vessels that supply nerves.<sup>(2)</sup> Vascular and neural diseases are closely related. The first pathological change in the microvasculature is vasoconstriction. As the disease progresses, neuronal dysfunction correlates closely with the development of vascular abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia, which contribute to diminished oxygen tension and hypoxia. Vasodilator agents e.g., ACE inhibitors can lead to substantial improvements in neuronal blood flow, with corresponding improvements in nerve conduction velocities.

Elevated intracellular levels of glucose cause a non-enzymatic covalent bonding with proteins, which alters their structure and inhibits their function. Some of these glycosylated proteins are involved in the pathology of diabetic neuropathy and other long term complications of diabetes.<sup>(3)</sup>

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Increased levels of glucose in diabetes cause an increase in intracellular diacylglycerol, which activates protein kinase C. This is associated with changes in blood flow, basement membrane thickening, extracellular matrix expansion, increases in vascular permeability, abnormal angiogenesis, excessive apoptosis and changes in cellular enzymatic activity such as Na<sup>+</sup>-K<sup>+</sup>-ATPase, etc. Studies show that protein kinase c  $\beta$  isoform selective inhibitor normalizes many vascular abnormalities like endothelial dysfunction, renal glomerular filtration rate and prevents loss of visual acuity in diabetic patients.<sup>(4)</sup>

Increased glucose levels activate polyol pathway which is an alternative biochemical pathway. It causes a decrease in glutathione and an increase in reactive oxygen radicals and causes microvascular damage to nervous tissue. The pathway is dependent on the enzyme aldose reductase. Inhibitors of aldose reductase enzyme have demonstrated efficacy in preventing the development of neuropathy.<sup>(5)</sup> Recent studies show that combination of  $\alpha$ -lipoic acid and an aldose reductase inhibitor can be given as monotherapy towards preventing diabetic vascular and neural dysfunction.<sup>(6)</sup>

Excessive activation of polyol pathway leads to high levels of sorbitol which cause reduction in the cellular uptake of another alcohol, myoinositol. This decreases the activity of the plasma membrane sodium-potassium ATPase pump required for nerve function, further contributing to the neuropathy.<sup>(7)</sup> Increased levels of reactive oxygen molecules and decreased levels of nitric oxide and glutathione also occur, as well as increased osmotic stresses on the cell membrane.

Any one of these causes alone can promote cell damage, but in diabetes several act together.

Evoked potentials are the electrical signals generated by the nervous system in response to sensory stimuli. Somatosensory evoked potential (SEP) has been widely used for monitoring the abnormal nerve conduction in various diseases. Auditory, visual, and somatosensory stimuli are used commonly for clinical evoked potential studies. Somatosensory evoked potentials (SEPs) consist of a series of waves that reflect sequential activation of neural structures along the somatosensory pathways. While SEPs can be elicited by mechanical stimulation, clinical studies use electrical stimulation of peripheral nerves, which gives larger and more robust responses.

Recording of Sensory Evoked Potentials in diabetics is done to assess the sensory involvement of spinal cord. Presence of SEPs provides clear evidence for axonal continuity and by using different stimulation sites, the rate of regeneration of nerves can be determined.<sup>(8)</sup>

Present study was undertaken to compare somatosensory evoked potentials in diabetics and normal individuals.

**MATERIALS AND METHODS:** The present study was undertaken at the Upgraded Department of Physiology, Osmania Medical College, Koti, Hyderabad, and period of study being 2012-2013.

The study was conducted on 34 Diabetic patients (21 Males & 13 Females) and 32 Controls (19 Males & 13 Females) with a mean height 5 feet 3 inches. The mean age of Diabetic individuals was 51.18 $\pm$ 3.04 years whereas the mean age of Non-diabetic individuals was 49.63 $\pm$ 8.95 years. Duration of diabetes was 10 years. Prior to study, ethical guidelines were followed and consent was taken.

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**Inclusion Criteria:** Patients with type 2 diabetes with 10 years duration.

**Exclusion Criteria:** Non-diabetic neuropathies.

**METHODS:** Non-invasive method of estimation of nerve conduction studies using SFEMG/EP—Electromyography or evoked potential system (Nicolet systems—USA make) using surface electrodes with automated computerized monitor attached with printer.

**PROCEDURE:** This study was conducted on patients using 3-channel with normal averaging technique. The procedure was explained to the patient and consent taken. Patient was asked to sit comfortably on a chair and instructed to gently close his/her eyes while relaxing all the head and neck muscles during the recording. Patient is asked to count the number of stimuli so as to get proper recordings. Electrodes of the 3 channels were placed on the patient at appropriate sites after its proper abrasion.

Surface EEG electrodes are used. Fz is used as the reference in most montages.

**Equipment:** Single fiber electromyography (Nicolet system) is used for the recording of Evoked potentials.

**MEASUREMENTS:** For upper limb SEPs, the AEEGS guidelines include identification of the obligate components N9, N13, P14, N18, and N20. Measurement of the N9-N20, N9-P14, and P14-N20 interpeak intervals is specified; interpeak intervals involving the N13 component are listed as options. The N9-P14 interpeak interval measures neural conduction from the brachial plexus to the lower medulla, P14-N20 from the lower medulla to primary somatosensory cortex, and N9-N20 from the brachial plexus to primary somatosensory cortex. The N13 component reflects activity within the lower cervical spinal cord.<sup>(9)</sup>

**Latency:** latency in evoked potential wave is usually stated in milliseconds (1000th of a second). In EP studies, the wave form peak is most commonly used as the measurement point. The time separation between 2 peaks is termed 'inter-wave latency' or 'inter-peak latency'.

**Amplitude:** Amplitude in EP wave is usually stated in millionth of a volt.

**ACTIVE RECORDING ELECTRODES ARE PLACED AS FOLLOWS:**

- 1st channel-over the contralateral C3/C4' scalp region (2cm posterior to C3 or C4)
  - 2nd channel-over the C5/C2 cervical spinous process (referred to as C5S or C2S and located relative to the prominent C7 spinous process with the neck flexed.
  - 3rd channel-at Erb's point (2-3 cm above clavicle in the angle between it and posterior border of the clavicular head of the Sternocleidomastoid muscle ipsilaterally.
- Inactive recording electrodes of the 3 channels were placed on Fz position on the scalp.

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**Ground Electrode:** is placed between stimulating and recording electrodes relatively closer to the former. We have used a band around the forearm.

**Stimulation Electrode:** using surface disk electrodes placed between the tendons of pmaris longus and flexor carpi radialis, i.e., at the supinated wrist, median nerve was stimulated. Stimuli of 0.2-0.3 milliseconds duration were given at 4-7 Hz. The intensity of the current was adjusted till a visible twitch was produced, to ensure the application of threshold stimulus.

**Data collection and interpretation:** Recommended filter settings are 5-30 Hz. An analysis time of 25-40msec is recommended to average 1000 sweeps. Measurement is made of peak latency ofN20 and P25 (channel 1), N13 (channel 2) and N9 (channel 3).

The patient was subjected to acupuncture mode of treatment followed by subsequent recording of the SEPs using the same method as mentioned above, i.e., before and after the acupuncture procedures, SEPs were recorded.

The data was subjected to appropriate statistical analysis.

**RESULTS:** The table given below shows the comparison of means of the SSEP components recorded in Right & Left upper limbs of Diabetic patients and Controls.

SSEP COMPONENTS ms/jiv	RIGHT UPPER LIMB		LEFT UPPER LIMB	
	DIABETIC	CONTROL	DIABETIC	CONTROL
N9 Latency	9.99 +/- 0.96	9.6 +/- 0.74	9.73 +/- 0.98	9.38 +/- 0.09
N9 Amplitude	-2.73 +/--1.47	-3.82 +/--2.21	-2.27 +/--1.84	-3.37+/--1.73
N13 Lat	13.37+/-0.91	12.87+/-0.52	13.28+/-0.91	12.8+/- 0.81
N13 Amp	-0.932+/-0.49	-1.22 +/--0.53	-0.85 +/- 0.49	-1.12+/-0.56
N20 Lat	19.26+/-1.12	18.41/-1.68	18.98+/- 0.08	18.69+/-1.32
N20 Amp	-0.81 +/--0.65	0.84 +/- 0.69	-0.69 +/- 0.54	-0.74 +/- 0.48
P25 Lat	23.77+/- 1.76	23.11+/-2.06	23.09+/- 1.56	22.95 +/- 2.2
P25 Amp	3.77 +/--13.15	1.32+/-0.08	1.37 +/--0.91	1.25 +/- 0.82

ANOVA shows statistically significant N9 latency (right & left sides).Significant "F" values were obtained with N9 Latency (Right & Left), N13 Latency (Right).

Multiple linear regression analysis shows statistically significant values for N9 latency (right & left), N13 latency (right & left), P25 latency (right), N20 amplitude (right) and P25 amplitude (left).

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**DISCUSSION:** An onset of neuropathy before or simultaneously with the manifestations of the diabetes, as well as the frequent occurrence of asymptomatic changes in sensory conduction support the evidence that the neuropathy may develop concomitantly with and as an integral part of the metabolic disturbance rather than as a consequence of the vascular complications of diabetes. Hyperglycemia causes increased sorbitol which in turn decreases uptake of myoinositol by the cells. This is known to cause myoinositol related defect in the sodium-potassium ATPase pump of the cell. Sodium-potassium ATPase pump normally generates transmembrane sodium and potassium potentials necessary for nerve impulse conduction and the concentration gradient for sodium to aid in the uptake of substrates by the cell. Thus a defect in the pump causes biochemical and structural abnormalities in diabetic neuropathy.

Increased oxidative stress and mitochondrial dysfunction in diabetic neurons cause nerve dysfunction and decreased neuronal regenerative capacity in sensory, motor and autonomic neurons.

Conductive function in the central as well as peripheral somatosensory pathways is affected earlier in diabetes. Electrophysiological studies have revealed a number of different abnormalities in relation to latencies and amplitudes in diabetic neuropathy.

Electrophysiologic neuropathy (EPN) score shows positive correlation between significant P value (<0.001) and duration of diabetes.<sup>(10)</sup>

Laser evoked potentials show involvement of small diameter sensory fibers in parallel with large diameter sensory fibers in diabetic polyneuropathy.<sup>(11)</sup>

In patients with diabetic neuropathy when sensory potentials in the median nerve, motor conduction in the lateral popliteal and median nerves, and electromyographic findings in distal and proximal muscles were compared with the severity of symptoms and signs, sensory potentials were the most sensitive indicators of subclinical involvement indicating that sensory fibers are affected earlier than motor fibers.<sup>(12)</sup>

Effects of aging cannot be ignored in diabetics. Aging affects nerve conduction in the central and peripheral somatosensory pathways. The peak Central Conduction Time (CCT) is more affected than the onset CCT. Studies show increase in onset to peak duration of the N20-P20 by 0.8 secs between 4<sup>th</sup> and 7<sup>th</sup> decades.<sup>(13)</sup>

In our study, Multiple Linear Regression Analysis and ANOVA showed significant correlation between latencies of nerve conduction velocities in diabetic and non-diabetic subjects. Significant prolongation of latencies was observed in diabetic individuals. Multiple regression analysis of N9, N13 & P25 latencies showed significant 'F' values (F value>1).

**CONCLUSION:** Our study is an attempt at reestablishing the fact that sensory nerve conduction abnormalities occur earlier than motor nerve conduction in diabetics. Studying independent component analysis of wave forms of SSEPs opens a new arena in science of signal processing. Similar attempts can aid future studies to predict the risk before the onset of diabetic neuropathy.

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