journal homepage: https://jablm.acclmp.com/

Journal of Applied Biochemistry & Laboratory Medicine (2022) 03 (1):22-26

Original Research Article

Nerve Conduction and its Correlations with Blood Sorbitol Dehydrogenase in Diabetic Peripheral Neuropathy

BiswasTuhin Kanti[1], Pandit Srikanta[1], Saha Avijit[2], Bhagat Ajoy[1], Jana Utpalendu[1], Sur Tapas Kumar[2*]

1. Research Unit, J.B. Roy State Ayurvedic Medical College & Hospital, Kolkata
2. Multidisciplinary Research Unit (DHR-ICMR), R.G. Kar Medical College & Hospital, Kolkata

Keywords:
Multiple endocrine neoplasia type 1, Hypercalcemia, Parathyroid adenoma, Renal medullary nephrocalcinosis.

How to cite this article
BiswasTK , Pandit S , Saha A , Bhagat A , Jana U , Sur TK. Nerve Conduction and its Correlations with Blood Sorbitol Dehydrogenase in Diabetic Peripheral Neuropathy. Journal of Applied Biochemistry & Laboratory Medicine 2022; 03 (1):22-26.
Access link for this article
https://jablm.acclmp.com/2022/03/01_22-26.pdf

ABSTRACT

Background: Diabetic peripheral neuropathy (DPN) is one of the most complicated complications for diabetic patients. At present there is no definite treatment for DPN. Early detection can control the progression of DPN. Therefore, this study aims to investigate the relationship between the nerve conduction velocity (NCV) in legs and sorbitol dehydrogenage (SDH) in blood type-2 diabetic patients.

Methodology: The study was conducted among 22 diabetic patients who were suffered in diabetes for >5 yrs and having pain in their limbs. The pain was assessed using tools and glucose (pp), HbA1c and SDH were estimated in blood. NCV was determined by physiograph in legs.

Results: Out of 22 patients, 45% was male and 55% female; with mean age 59.55 yrs and BMI 27.81. The average diabetic neuropathic pain score was 3.41. HbA1c (CI: 8.07-8.47) and SDH (CI: 80.5-86.9) was significantly raised. NCV test exhibited prevalence of DPN was 77% in diabetic patients. Average NCV was 45.85 m/sec in right and 47.34 m/sec in left legs. A strong reverse relationship was noted between NCV and SDH ($r2=-2.71$; $p<0.01$).

Conclusions: The observations of the present study conclude that there are strong, significant opposite correlation between SDH and NCV.

Key words: Nerve Conduction, Sorbitol Dehydrogenase, Glycosylated Haemoglobin, Diabetic Peripheral Neuropathy, Type-2 Diabetes

Abbreviations:
CTN=Common Peroneal Nerve, DPN=Diabetic Peripheral Neuropathy, HbA1c= Glycosylated Haemoglobin, NCV=Nerve Conduction Velocity, PTN= Posterior Tibial Nerve, SDH=Sorbitol Dehydrogenase,

INTRODUCTION

Diabetic peripheral neuropathy (DPN) poses a critical health risk and health care burden to both the individual as well as the society. It is estimated that 35-45% of diabetic patients have suffer by DPN [1]. The hallmark of neuropathies is a progressive damage and loss of nerve fibers, which may affect both somatic as well as autonomic nervous system [2]. Exact prevalence of DPN is not certain and studies suggest their prevalence varying from 10-90% in diabetic patients [3]. Although, the risk of neuropathies in diabetes may arise any time but its risk has been reported to rise significantly with age and the duration of diabetes. Most studies suggest that it is usually developed within 10 years with a peal incidence observed ≥25 years of the disease[4].

DPN is usually affects feet and legs, although hands and arms also may be affected. The spectrum of neuronal damage in DPN varies from mononeuropathy i.e damage to a single nerve, multiple mononeuropathy i.e damage to two or more nerves in different areas or polyneuropathy i.e damage to many nerves. The pathogenesis of DPN is complicated, and the mechanism of this disease remains poorly understood [5]. The major mechanisms of this complication are persistent hyperglycemia leading to glycation of biomolecules, microvascular insufficiency, oxidative and nitrosative stress, defective neurotropism, and autoimmune nerve destruction [6]. The persistent hyperglycemia results in an increased metabolism of glucose by the sorbitol pathway, which is an alternative pathway of glycolysis and significantly increases under the condition of persistent elevation of the blood glucose level. This pathway produces increased amount of sorbitol by sorbitol dehydrogenase (SDH). Sorbitol accumulates intracellularly in the nervous tissues and damages the Schwann cells and promotes nerve fibre degeneration [7].

*Correspondence:
drtapaskumarsur@gmail.com
Dr. Tapas Kumar Sur, Research Scientist II, Multidisciplinary Research Unit (DHR-ICMR),R.G. Kar Medical College & Hospital, Kolkata.

The diagnosis of DPN is mainly based on the characteristic symptoms [8]. A nerve conduction study is a good tool to identify DPN. Studies are commonly performed on upper and lower limbs on motor and sensory nerves [9]. However, as the observations of nerve conduction changes are non-specific, other disorders which may be superimposed on DPN must be excluded [10]. The hallmark abnormality evident in diabetes mellitus using the nerve conduction study is a significant reduction in both the velocity and amplitude of motor or sensory action potentials due to axonopathy caused by the DPN [11].

Treatment options for DPN are limited, but first step is to maintain glucose level within the normal range. Besides glucose lowering therapy, alternative management systems like use of antidepressants, anticonvulsants, opioid analgesics, antiarrhythmics and NMDA receptor antagonists are commonly used although each of them has side effects of their own [12-14]. Hence, early detection can be helpful to restrict the progression of DPN. Therefore, this study aims to investigate the relationship between sorbitol dehydrogenase (SDH) and nerve conduction velocity (NCV) in type 2 diabetic patients with DPN.

METHODOLOGY

This cross sectional observational study was conducted at Research Unit, J B Roy State Ayurvedic Medical College and Hospital, Kolkata on diabetic neuropathic pain after receiving Institutional Ethical permission. Participants of either gender, aged between 40-75 years, suffering from diabetes for more than 5 years and with complaints of neuropathic pain, were enrolled. Diabetics with foot ulcers or deformed or contracted foot or any congenital deformities and serious neurological complications were excluded in this study.

After receiving the written consent, all participants were clinically diagnosed by valid questionnaire for Pain Assessment and Diabetic Neuropathic Score [15-16]. Postprandial glucose and glycosylated haemoglobin (HbA1c) were estimated spectrophotometrically and Sorbitol dehydrogenase (SDH) in blood was estimated using ELISA. Nerve conduction velocity test in both legs was conducted by applying electrophysiological method using physiograph.

Summary statistics comprised of means and standard deviation (SD). Statistical analysis was done using one sample t-test and confidence interval (95%) of the difference for the parametric data. Bivariate analysis by Person's correlation (2-tailed) covariance to compare the association between SDH and NCV was done. The level of significance for all analysis was taken as $p<0.05$.

RESULTS

Table 1 shows the clinical parameters of selected diabetic patients (mean postprandial blood glucose 234.73 mg/dl and HbA1c 8.27%). In this study, 22 patients (45% male and 55% female) suffered in type-2 diabetes for more than 5 years (average 11.73 years) were selected. Their mean age was 59.55 years and BMI was 27.81. The mean systolic blood pressure was observed 134 mm of Hg and diastolic pressure 85.5 mm of Hg. 10-point pain score by Mosby showed all patients experienced pain in their limbs (CI: 6.7-7.8). Nevertheless, the average diabetic neuropathic pain score was 3.41 in 0-4 scale (CI: 3.08-3.73).

Table 1. Diabetic patients

	Results	P value* (95%CI)**
Total patients	22	-
Male	10	-
Female	12	-
Age (yrs)	59.55±4.64	<0.001 (57.4-61.6)
Diabetes duration (yrs)	11.73±3.55	-
Body mass index	27.81±2.08	<0.001 (26.8-28.7)
Systolic blood pressure (mm Hg)	134±13.43	<0.001 (128-139)
Diastolic blood pressure (mm Hg)	85.5±7.14	<0.001 (82.3-88.7)
Pain score	7.33±1.28	<0.001 (6.7-7.8)
Diabetic neuropathic pain score	3.41±0.73	<0.001 (3.08-3.73)
Blood glucose pp (mg/dl)	234.73±39.64	<0.001 (217-252)
HbA1c (%)	8.27±0.45	<0.001 (8.07-8.47)
Sorbitol dehydrogenase (ng/ml)	83.78±7.20	<0.001 (80.5-86.9)

Mean ± SD; *One sample t-test; **95% Confidence Interval in parenthesis; significant level $p<0.05$;

Table 2 shows 77% incidences of mild to moderate DPN among the selected patients examined by physiograph. The incidences of nerve conduction velocity were slow in 81.8% CPN and 91% in PTN. The amplitude of sensory nerve conduction in legs was drastically reduced even at early age of diabetic patients.

Table 2. Diabetic peripheral neuropathy incidences

	Motor Nerve Conduction Velocity (m/sec)				Sensory Nerve Conduction Amplitude (µV)	
	Common Peroneal Nerve (CPN)		Posterior Tibial Nerve (PTN)		Sural Nerve	
	Incidences	Value	Incidences	Value	Incidences	Value
40-59 yrs (N=11)	3 (27.2%)	>50 m/sec[a]	3 (27.2%)	>50 m/sec[a]	0	>5 µV[a]
	8 (72.8%)	<50 m/sec[b]	8 (72.8%)	<50 m/sec[b]	11 (100%	<5 µV[b]
>60 yrs (N=11)	2 (18.2%)	>50 m/sec[a]	1 (9%)	>50 m/sec[a]	5 (45.5%)	>2 µV[a]
	9 (81.8%)	<50 m/sec[b]	10 (91%)	<50 m/sec[b]	6 (54.6%)	<2 µV[b]

a=normal value; b=abnormal value (DPN)

Figure 1shows NCV in motor and sensory nerves in legs of diabetic patients. The average value of NCV in right and left CPN was 45.85 and 47.34 m/sec respectively; while, PTN showed 45.98 m/sec in right and 44.25 m/sec in left legs. The normal reference value of NCV in motor nerves is >50 m/sec. The amplitude of sensory nerve conduction (SNC) in sural nerves was decreased to 2.14 µV in right and 2.31 µV in left legs. Moreover, a reverse relationship was noted between NCV and SDH (r^2=-2.71).

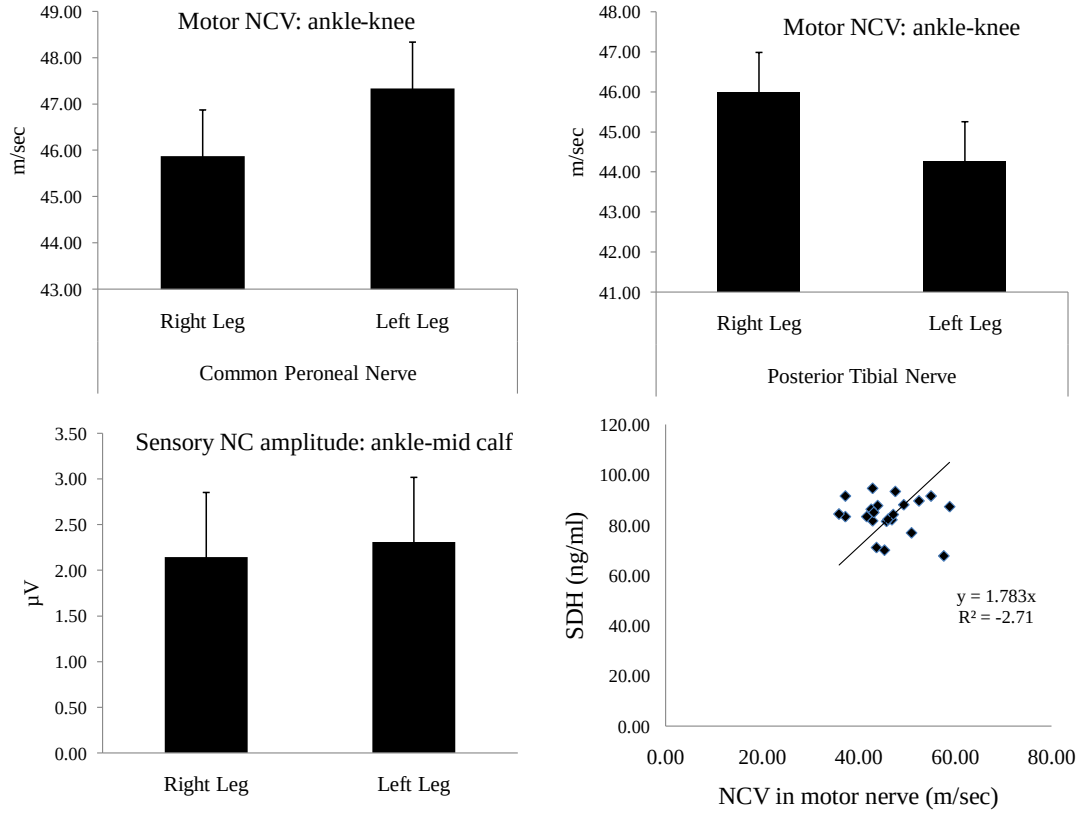

Fig 1. Nerve conduction velocity (NCV) and it's correlation with sorbitol dehydrogenase (SDH) in blood

The Pearson correlation (2-tailed) was measured for clarifying the strength of the liniar relationship between SDH and NCV sub-sets in Table 3. Negative significant correlation was noted between SDH and NCV sub-sets ($p<0.01$).

Table 3. Correlation between SDH and NCV in DPN

	Pearson Correlation					
	Nerve Conduction Velocity and Amplitude					
	CPN Right	CPN Left	PTN Right	PTN Left	SNC Right	SNC Left
SDH	-0.339					
		-0.117				
			-0.561*			
				-0.410		
					-0.186	
						-0.036

*Correlation is significant at the 0.01 level (2-tailed); Bivariate analysis;

DISCUSSION

Diabetic peripheral neuropathy (DPN) causes pain or loss of feeling in the toes, feet, legs, hands, and arms. Feet and legs are likely to be affected before hands and arms. Symptoms of DPN include numbness or insensitivity to pain/temperature; a burning/prickling sensation; sharp pains/cramps and extreme sensitivity to touch [17]. DPN starts in the toes and gradually moves proximally [18]. The pain can be assessed symptomatically using different validated visual analogue scales. In the present study, two pain scales were used – Mosby® 10-point Pain Rating Scale and 5-point Diabetic Neuropathic Scale (DNS**)** to identify DPN in patients. Both the scales have been validated using standard clinical methods [15-16]. In the present screening, average Mosby Pain Score was 7.33 and DNS score was 3.41 considering the possibility of DPN in the diabetic patients, who were diagnosed for >10 years (average 11.73 years).

Motor nerve conduction and sensory nerve conduction studies are important for the diagnosis of DPN. It can distinguish localization, severity and progression of neuropathy. Motor nerve conduction studies are affected in a small subset of DPN. Unilateral NCV changes are particularly found in the entrapped segment of the nerve as entrapment neuropathies are common in diabetic patients[1,11,19]. In the present study, motor and sensory nerve conduction studies were examined in lower limbs. Most of the patients showed bilateral radiculopathy. It has been observed that NCV was significantly slow in lower limbs particularly in CPN and PTN in ankle-knee indicating DPN due to axonopathy. Moreover, the neuropathy incidences were increased with advances in ages. Likewise, the amplitude of sensory nerve conduction in legs was also affected in ankle-calf muscle of diabetes patients. The prevalence of DPN in the present study was observed 77%, similar to previously reported study [1,20].

It is well known that polyol pathway hyperactivity activates several inter related metabolic imbalances and considered as main reason for DPN. Sorbitol dehydrogenase or SDH (EC 1.1.1.14) is responsible for accumulation of sorbitol from glucose and therefore, high sorbitol level exhibited in diabetic patients [7]. The increased SDH accounts for NAD-redox imbalances, which enhances advanced glycation end products (AGEs), but depleted myo-inositol and taurine and the activity of protein kinase C and Na^+–K^+-ATPase and ultimately leads to demyelination or nerve damages in type 2 diabetes [21-22]. But till date there is little information about the correlation between NCV and SDH in DPN. The present study confirmed the elevation of SDH among the diabetic patients with postprandial blood glucose >230 mg/dl and HbA1c >8%. In other studies, elevation of SDH in DPN was also reported [23-24]. Moreover, a significant and strong inverse correlation was observed between NCV and SDH of diabetic patients.

CONCLUSION

The diagnosis and prognosis of DPN could not be determined by a single test. The present study concludes that there are strong and opposite correlation between SDH and NCV, which should be considered during the diagnosis, prognosis and treatment management of DPN. Further multi-centric studies with large population are still needed to confirm the present findings.

Acknowledgment: Nil.

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