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Nerve Conduction Study Of Peripheral Neuropathy In Diabetic Kidney Disease Patients And Comparison With Non-Diabetic Chronic Kidney Diesase Patients

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Abstract

Background- Peripheral neuropathy is one of the neurological complication in chronic kidney disease (CKD) leading to significant morbidity. Presence of diabetes mellitus may worsen neuropathy in these patients. However the literature on neuropathy in diabetic renal failure patients is lacking in India.

Aim- The study was performed to assess the impact of diabetes on nerve conduction parameters of peripheral neuropathy in CKD patients and its comparison with that of non-diabetic CKD patients

Methods- 100 adult patients diagnosed with chronic kidney disease were divided into 2 groups each including diabetic CKD and non-diabetic CKD patients. All cases were subjected to nerve conduction study which was performed on median nerve, ulnar nerve, common peroneal nerve, tibial nerve and sural nerve.

Results- Diabetic CKD patients showed more abnormalities in nerve conduction study as compared to non-diabetic CKD patients. These abnormalities were comparable in both dialysis and non-dialysis dependent CKD patients in diabetic group suggesting they were predominantly caused by diabetic neuropathy and were thus not affected by staging of renal failure.

Conclusion- Diabetic CKD patients showed more severity of peripheral neuropathy as compared to non-diabetic CKD patients. Diabetic neuropathy is predominant cause as compared to uremic neuropathy in CKD patients and thus not affected by stage of renal failure.

Keywords: Diabetes, Chronic kidney disease, Neuropathy, Nerve conduction

Introduction

Chronic kidney disease (CKD) is one of the leading causes of chronic disease with 8-16% worldwide prevalence. Diabetes mellitus is the leading cause of end stage renal disease (ESRD) requiring renal replacement therapy. Neurological complications, secondary to the uremic state, largely contribute to the morbidity and mortality in patients with renal failure. Approximately 60% of the population with CKD will encounter neurological complications which affect all the levels of nervous system, including stroke, cognitive dysfunction, encephalopathy, peripheral and autonomic neuropathies, resulting in altered mental state, continued disability, and weakness. Uremic neuropathy is one of the most common neurological complications of uremia. (1)

Peripheral neuropathy in diabetics is attributed to various proposed etiologies including hyperglycemia, accumulation of advanced glycation end products and oxidative stress (2). These metabolic derangements persist in diabetes even after patients develop CKD

and probably continue to play a role in the development of peripheral nerve impairments.

In patients with diabetes on dialysis therapy, symptoms and signs of small fiber involvement can dominate, with patients experiencing severe burning and shooting pain with impaired pain and temperature perception. Commonly, both large and small fibers can be affected in patients with CKD with diabetic peripheral neuropathy (3). In diabetic patients with renal insufficiency under dialysis treatment, the occurrence of severe axonal, length-dependent, sensory, and motor polyneuropathy is common. In such patients it is virtually impossible to ascribe with certainty specific signs or symptoms to any one metabolic disturbance. However, severe symptomatic autonomic disturbances, pains, length-dependent pattern of loss of temperature and pain sensation, which point to predominant involvement of small myelinated and unmyelinated fibers, are more characteristic of diabetic neuropathy. Conversely, prominent motor deficit is in favor of a predominant role of uremia.

The present study was performed to assess the effect of diabetes mellitus on nerve conduction parameters of peripheral neuropathy in CKD patients and their comparison with non-diabetic CKD patients.

Materials And Methods

The study was conducted on 100 adult patients diagnosed with CKD and treated for it in Emergency, Medicine and Nephrology OPD and inpatient wards at Jawaharlal Nehru Medical College (JNMC) and Hospital, Aligarh from December 2018 to December 2020.

The protocol was approved by board of studies and passed by ethical committee of the institution.

Study Design

The study was a cross sectional, observational hospital based study

Inclusion Criteria

1. All patients age ≥ 18 years with CKD on drug therapy
2. All patients age ≥ 18 years with CKD on regular hemodialysis

Exclusion criteria

1. Age less than 18 years
2. Patients with other known cause of peripheral neuropathy
3. Patients on drug therapy known to cause peripheral neuropathy as side effect
4. Electrically sensitive patients
5. Allergy to electrode or contact material (tape/gel)
6. Subjects with reduced levels of consciousness or impaired understanding

The 100 consecutive CKD patients were divided into two groups. Group 1 included 55 diabetic CKD patients while Group 2 included 45 non-diabetic CKD patients. Each group was further subdivided into two subgroups which included dialysis dependent patients and non-dialysis dependent patients.

All patients were subjected to detailed history, general physical examination, and neurological examination. History regarding any previous/concomitant illness, intake of prescriptional as well as recreational drugs, was elicited and recorded. The routine renal and other biochemical investigations including blood urea (mg/dl), serum creatinine (mg/dl), serum uric acid (mg/dl), Hemogram, blood sugar (mg/dl), HbA1c, arterial blood gas analysis, serum sodium, serum potassium, serum corrected calcium, serum phosphorus, serum protein (g/dl), iPTH levels (pg/ml), serum vitamin D, urine routine and microscopy were done as per the standard methods in JNMCH, Aligarh. eGFR was estimated using Cockcroft-Gault equation.

All cases were subjected to nerve conduction studies (NCS) using Nicolet EDX NCS/ EMG/ EP/ IOM system in the clinical neurophysiology unit, Department of Medicine. All tests were performed at constant room temperature to reduce the errors. The nerve conduction studies were performed in all patients on all 4 limbs. Median nerve, ulnar nerve, common peroneal nerve and tibial nerve were assessed for motor conductions. Median nerve, ulnar nerve and sural nerve were assessed for sensory conduction.

Motor nerve conduction study

The recording electrodes were placed on the muscle being tested. The center of the muscle belly over the motor endplate was used for placing the active recording electrode and the reference electrode was placed distally over the tendon of the muscle. The

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nerve that supplies the muscle was used for placing the stimulator where the cathode was placed close to the recording electrode. Current in the range of 20-50 mA was used to achieve supramaximal stimulation. The underlying nerve fibers were brought to action potential as the current was steadily increased from a baseline, usually by 5-10 mA. The summation of all the underlying individual muscle fiber action potentials was represented by the compound muscle action potential (CMAP).

For median nerve motor conduction studies, the recording electrode was placed over the motor point of the abductor pollicis brevis and the reference electrode was placed over the distal interphalangeal joint. Wrist and elbow were sites of stimulation for median nerve. For ulnar nerve motor conduction studies, the recording electrode was placed over the motor point of the abductor digiti minimi muscle with reference electrode over the middle phalanx of digit V. Wrist and below elbow were sites of stimulation for ulnar nerve. For the tibial nerve the electrode was placed over the adductor hallucis muscle. The tibial nerve was stimulated in the popliteal fossa and ankle. For common peroneal nerve the recording electrode was placed over extensor digitorum brevis muscle. The common peroneal nerve was stimulated at the ankle and fibular head.

The latency, CMAP amplitude and conduction velocity were derived for each nerve.

Sensory nerve conduction study

Median sensory nerve conduction study was done antidromically by placing the recording electrode at interphalangeal joint of 2nd digit and stimulation given at wrist. Sensory conduction of ulnar nerve was done antidromically by placing the recording electrode at interphalangeal joint of the fifth digit and stimulation given at wrist. Sural nerve conduction was also done antidromically by stimulating the dorsal aspect of the calf while keeping the recording electrode at the ankle.

The onset and peak latency, sensory nerve action potential SNAP amplitude and conduction velocity of each nerve were recorded.

Statistical Analysis

The data was collected and tabulated using Microsoft Excel 365. The data was analyzed using Social Science (SPSS) version 25.0. Results were expressed as mean $\pm$ SD. All the qualitative variables were analyzed using Pearson chi square test. The variables were compared in two groups using independent sample t test. For all analysis, p-value less than 0.05 was considered as statistically significant.

Results

The mean age of patients in the present study was 55.45 $\pm$ 15.95 years. Majority of patients were of age group 31-60 years in both groups. Males (n=59) outnumbered females (n=41). The mean blood urea, serum creatinine, mean uric acid and mean eGFR were 76.10$\pm$36.27, 5.14$\pm$3.07, 6.59$\pm$1.65 and 17.64$\pm$9.46, respectively.

Table 1: Distribution of patients among groups

S.No.	Group	Dialysis/non-dialysis			Ch^2- Value	P- Value
		D	ND	Total		
1	Diabetic	24	31	55	1.98	P > 0.05
2	Non-diabetic	26	19	45		
3	Total	50	50	100		

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Table 2: Electrophysiological properties of diabetic and non-diabetic CKD patients

Median Nerve (Motor)		Diabetic (n=55)	Percentage	Non-Diabetic (n=45)	Percentage	Ch^2-Value	P- Value
Latency	Normal	39	71%	41	91%	3.208	P > 0.05
	Increased	16	29%	4	9%		
Amplitude	Normal	25	45%	32	71%	2.747	P > 0.05
	Decreased	30	55%	13	29%		
Velocity	Normal	44	80%	43	96%	1.53	P > 0.05
	Decreased	11	20%	2	4%		
Ulnar Nerve (Motor)							
Latency	Normal	44	80%	43	96%	1.53	P > 0.05
	Increased	11	20%	2	4%		
Amplitude	Normal	17	31%	30	67%	7.697	P < 0.01
	Decreased	38	69%	15	33%		
Velocity	Normal	31	56%	43	96%	1.53	P > 0.05
	Decreased	24	44%	2	4%		
Peroneal Nerve							
Latency	Normal	25	45%	42	93%	0.104	P > 0.05
	Increased	30	55%	3	7%		
Amplitude	Normal	6	11%	25	56%	0.77	P > 0.05
	Decreased	49	89%	20	44%		
Velocity	Normal	20	36%	40	89%	0.729	P > 0.05
	Decreased	35	64%	5	11%		
Tibial Nerve							
Latency	Normal	34	62%	45	100%	0.008	P>0.05
	Increased	21	38%	0	0%		
Amplitude	Normal	12	22%	35	78%	0.787	P > 0.05
	Decreased	43	78%	10	22%		
Velocity	Normal	16	29%	41	91%	0.109	P > 0.05
	Decreased	39	71%	4	9%		
Median Nerve (Sensory)							
Latency	Normal	14	25%	31	69%	3.602	P > 0.05
	Increased	41	75%	14	31%		

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Amplitude	Normal	32	58%	43	96%	1.53	P > 0.05
	Decreased	23	42%	2	4%		
Velocity	Normal	10	18%	36	80%	0.023	P > 0.05
	Decreased	45	82%	9	20%		
Ulnar Nerve (Sensory)							
Latency	Normal	39	71%	44	98%	1.4	P > 0.05
	Increased	16	29%	1	2%		
Amplitude	Normal	26	47%	45	100%	0.035	P>0.05
	Decreased	29	53%	0	0%		
Velocity	Normal	17	31%	39	87%	0.172	P > 0.05
	Decreased	38	69%	6	13%		
Sural Nerve							
Latency	Normal	4	4%	29	64%	5.607	P < 0.05
	Increased	51	93%	16	36%		
Amplitude	Normal	4	7%	30	67%	7.697	P < 0.01
	Decreased	51	93%	15	33%		
Velocity	Normal	4	7%	30	67%	7.697	P < 0.01
	Decreased	51	93%	15	33%		

Figure-1 Sural nerve in Diabetic CKD

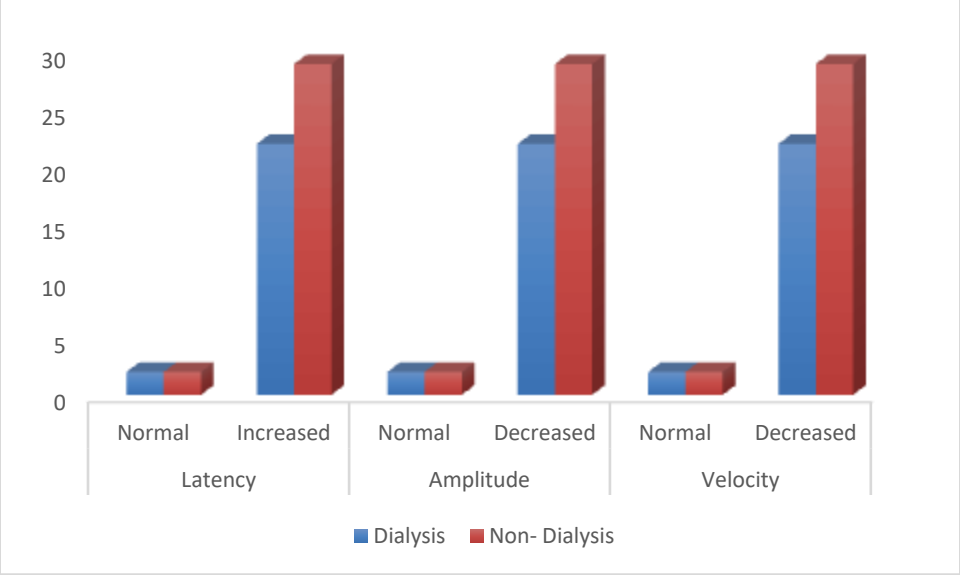

Figure-2 Sural nerve in Non-diabetic CKD

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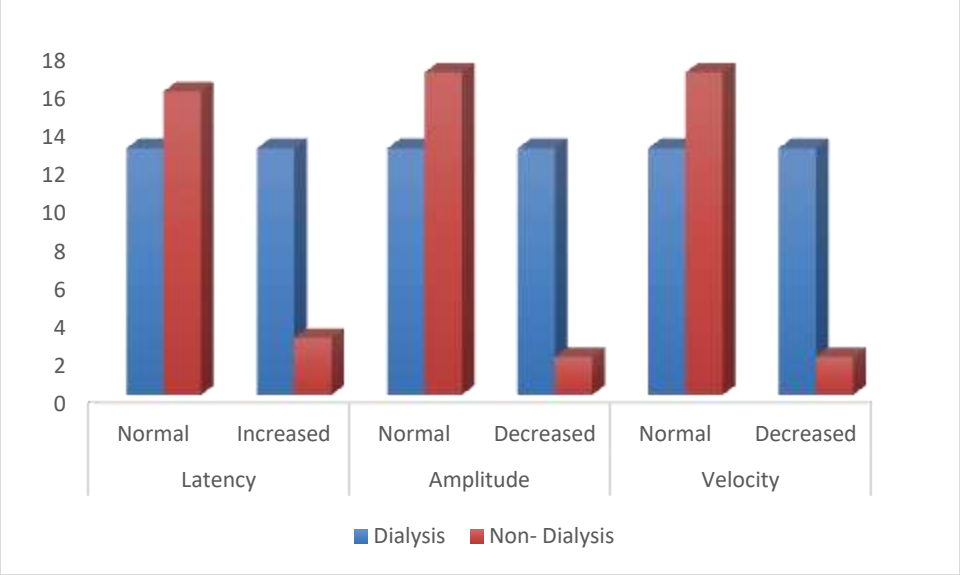

On analyzing nerve conduction abnormalities (Table 2) it was found that in most of the diabetic patients there was depressed median nerve (motor) amplitude (55% of total patients), depressed ulnar (motor) nerve amplitude (69%), depressed common peroneal nerve amplitude (89%), depressed tibial nerve amplitude (78%), depressed tibial nerve velocity (71%), prolonged sural nerve latency (93%), depressed sural nerve SNAP amplitude (93%) and decreased sural nerve velocity (93%).

In non-diabetic CKD patients (Table 2) it was found that most patients had depressed peroneal nerve amplitude (44%), depressed sural nerve amplitude (33%), increased sural nerve latency (36%), and depressed sural nerve velocity (33%).

Sural nerve is the most affected nerve in both groups.

On comparing sural nerve properties among dialysis dependent and non-dialysis dependent CKD patients in both groups separately (Figures 1&2) it was found that the abnormalities (increased latency, depressed amplitude and decrease conduction velocity) were more in dialysis dependent in non-diabetic group.

Discussion

Diabetic polyneuropathy has a lifetime prevalence of ~50% and carries with it the risk of ulcers and falls (4). The progression of diabetes to advanced stages of CKD is associated with the progression of multiple other micro and macrovascular complications including diabetic neuropathies. Diabetic peripheral neuropathy is associated with high morbidity, poor quality of life and high risk of lower-extremity amputation in patients with renal failure, especially those on dialysis. Early recognition and treatment of patients with diabetes and feet at risk for ulcers and amputations can delay or prevent adverse outcomes(5). The risk of ulcers or amputations is increased in people who have CKD, especially patients on dialysis.

Although there are numerous studies on peripheral neuropathy in CKD , the data comparing nerve conduction abnormalities of peripheral neuropathy in diabetic and non-diabetic CKD patients is sparse in literature.

In the present study, nerve conduction parameters were compared in diabetic and non-diabetic groups to study the impact of diabetes on peripheral neuropathy in CKD patients. Higher percentage of diabetic CKD patients showed electrophysiological abnormalities as compared to non-diabetic patients. This observation was also found in a previous study by Jasti et al (6). In our study, electrophysiological parameters differentiating diabetics and non-diabetics were median nerve motor amplitude, ulnar nerve motor conduction velocity and amplitude, common peroneal nerve motor conduction velocity, latency and amplitude, tibial nerve motor conduction velocity and amplitude, median nerve sensory latency, amplitude and velocity, ulnar nerve sensory conduction velocity and amplitude, and sural nerve latency amplitude and conduction velocity. As peripheral neuropathy depends more on glycemic control, in addition to

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uremia, diabetic CKD patients showed more severity of peripheral neuropathy.

Depressed amplitude was the most common abnormality in both groups suggesting axonal neuropathy to be predominant.

In contrast to previous Indian studies like Jasti et al. (6) and Aggarwal et al. (7) who did nerve conduction studies on pre-dialysis CKD patients and excluded those on hemodialysis, this study was conducted on both dialysis-dependent and non-dialysis dependent CKD patients.

The nerve conduction abnormalities were compared separately among dialysis dependent and non-dialysis dependent patients in both groups to study the effect of CKD stage on severity of neuropathy. Dialysis dependent patients had lower mean eGFR (10.82 ± 4.03) and thus had advanced stage of renal failure as compared to non-dialysis group (24.46 ± 8.34). The sural nerve abnormalities were comparable in both dialysis and non-dialysis patients in diabetic group (Figure 1) suggesting they were predominantly caused by diabetic neuropathy and were thus not affected by staging of renal failure. However, in non-diabetic group these abnormalities were more predominant in dialysis dependent patients than non-dialysis dependent patients suggesting that neuropathy tends to worsen with advanced stage of CKD (Figure 2). Thus, patients who are on maintenance dialysis have more prevalence of peripheral neuropathy when compared to predialysis patients.

Tight control of blood glucose levels is the optimal treatment for prevention of diabetic neuropathy in CKD. A comprehensive foot evaluation should be performed at least annually to identify risk factors for ulcers and amputations. The examination should include inspection of the skin, assessment of foot deformities, neurological assessment (10-g monofilament testing with at least one other assessment: pinprick, temperature, vibration), and vascular assessment including pulses in the legs and feet (8). Nerve conduction studies play a major role in detecting subclinical neuropathy. It can also help in monitoring the progress of neuropathy during a long period, particularly if the patient is asymptomatic. The use of specialized therapeutic footwear is recommended for high-risk patients with diabetes including those with severe neuropathy, foot deformities, ulcers, callous formation, poor peripheral circulation, or history of amputation.

Early reports investigating the effects of hemodialysis on uremic neuropathy suggested that some patients with mild neuropathy recovered completely with adequate dialysis(9). More frequent and prolonged dialysis is capable of halting further deterioration and in some, even improvement in conduction velocities has been reported. The neuropathy appears to be reversible by renal transplantation. Renal transplantation remains the only known cure for uremic neuropathy, with clinical improvement in sensory and, to a lesser extent, motor function occurring within a few days of transplantation (10).

Conclusion

Diabetic CKD patients showed more severe nerve abnormalities as compared to non-diabetic patients. Both groups showed predominantly axonal neuropathy. Sural nerve was most affected in both the groups. Nerve conduction abnormalities were almost similar in dialysis dependent and non-dialysis dependent patients among diabetics suggesting diabetic neuropathy to be predominant cause as compared to uremic and thus not affected by stage of renal failure. In non-diabetics, nerve conduction abnormalities were more prominent in dialysis dependent as compared to non-dialysis dependent patients suggesting increased prevalence of neuropathy with advancement of CKD stage.

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