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Pattern of peripheral neuropathy in hemodialysis patients

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Abstract

Around 70 chronic kidney disease patients with or without diabetes who were on hemodialysis (HD) were studied. The study the prevalence of the peripheral neuropathy in CKD patients and its location, severity, type and character of the peripheral neuropathy in both the groups were analyzed. Average age of the study population was 52.90 years with average of diabetics being higher and with peripheral neuropathy was significantly higher. More males in the study at 61.43%, more male diabetics and higher males with peripheral neuropathy but males had 41 % reduced odds of having peripheral neuropathy. Average duration for HD was 21.40 months with no difference between the groups, Higher duration of HD was observed in patients with peripheral neuropathy vice versa increasing duration of hemodialysis it was associated with higher odds of peripheral neuropathy (14% for each additional month) thus more duration more symptoms ad more toxic metabolite damage. 31 (44.29%) diabetics with an average duration of diabetes of 30.65 months and increasing duration of diabetes was associated with higher odds of having peripheral neuropathy (11% additional odds for each additional month) but it didn't affect the symptoms. Proportion of diabetic patients with CKD on HD having neuropathy (80.65%) was significantly higher (P=0.0417) than that in CKD patients on HD without neuropathy (56.42%). Presence of diabetes was associated with >5 times (561%) higher odds of having peripheral neuropathy compared to the non-diabetic CKD patients on Hemodialysis. TCNS score was significantly higher in the peripheral neuropathy group and significantly correlated with symptoms. Average TCNS score for diabetic CKD patients was higher compared to that for non-CKD patients (9.16 vs 7.71) with similar distribution between groups.

47patients (67.143%) who had peripheral neuropathy on NCV where 63% had mild-moderate neuropathy while 36% patients had severe neuropathy. Overall lower limb involvement (25, 53.19%) most common PN while Diabetic patients had higher proportion of generalized neuropathy involvement (48% vs 22.74%) and non-diabetic patients had a higher involvement of the lower limb only (63.63% vs 44%) There was motor involvement only (31, 65.96%) or sensorimotor involvement (16, 34.04%) with no patient with only sensory involvement and similar trend in both groups Presence of diabetes had a higher risk of developing peripheral neuropathy which can be sensorimotor or motor and was associated with significantly raised odds (222% higher odds) Most of the patients had axonal involvement only (45, 95.74%) with no difference between the groups.

Keywords: CKD, Heamodialysis, Neuropathy, NCV

Introduction

Chronic kidney disease (CKD) is an important health concern and its prevalence as per data from international society of nephrology's kidney disease data center study in developed countries is 15% and it's around 17% in Indian population. (1,2) In western countries, diabetes and hypertension comprise over 66% cases of CKD and in India this group comprises of 40-60% of cases of CKD. (3) In India, most common cause of CKD is Diabetes followed by CKD of undetermined etiology followed by Chronic Glomerulonephritis and Hypertensive Nephrosclerosis. (4)

End-stage kidney disease is known to be associated with peripheral neuropathy. Various studies have suggested that incidence of peripheral neuropathy in CKD patients is between 60 to 90% with predominance in dialysis group. (5) Uremic neuropathy in end-stage kidney disease is classically a distal symmetrical length dependent, sensorimotor polyneuropathy which is more common in lower limbs than in upper limbs. Ankle reflex and vibratory sensory loss are the most common clinical signs with a predilection for males. (6) There are many of the postulated theories, one of them is "Middle molecule hypothesis" states that various neurotoxic molecules in middle molecular range of 300-12000 Da like beta 2 microglobulin, parathyroid hormone are found elevated in CKD patients. (7)

Various uremic toxins including guanidine compounds, particularly methyl guanidine, polyamines, my oisotol are involved in pathogenesis of neuropathy. Hyperkalemia also acts as a contributing factor in nerve excitability studies. Hypomagnesemia and hypocalcemia can also contribute to exacerbation of uremic neuropathy. (8) The exact pathophysiology of diabetic neuropathy has not been fully established yet, but it seems to be related with metabolic disturbances, such as hyperglycemia, dyslipidemia, oxidative and nitrosative stress and growth factor deficiencies. (9) Diagnosis of peripheral neuropathy requires careful history and physical examination, which is further augmented by electro diagnostic studies like nerve conduction studies, which also provide information regarding type of fiber involved -motor, sensory or both and pattern of involvement-symmetrical or asymmetrical and pathophysiology - axonal loss versus demyelination. (10)

Thus, the pattern of peripheral neuropathy needs to be evaluated in patients who are undergoing dialysis and understand the characteristics of the neuropathy in both diabetics and non-diabetics.

Aims and objectives

1. To evaluate the pattern of peripheral neuropathy in patients undergoing haemodialysis.

2. To study peripheral neuropathy characteristics and severity in diabetic and non-diabetic CKD patients.

Materials and methods

Study Design & Methodology

- A cross sectional study was carried out which was include patients undergoing hemodialysis for at least 3 months.
- An informed written consent from the patient and/or legal guardian was taken from all the patients included in the study.
- A detailed history, examination and laboratory investigations was done on all patients involved in this study. Peripheral neuropathy was assessed clinically by Toronto clinical neuropathy score and classified as

1. Sensory
2. Motor
3. Mixed
4. Autonomic

Further evaluation was be done by nerve conduction studies.

Study Duration: Study was carried out for 18 months.

Study Site: Medicine and Nephrology Ward at Shri Mahant Indiresh Hospital, Patel Nagar, Dehradun

Study Population: Subjects comprised of all CKD patients undergoing heamodialysis for at least 3 months.

Inclusion Criteria

1. All cases of CKD patients undergoing dialysis for at least 3 months.

Exclusion Criteria

Common diseases and factors that can contribute to peripheral neuropathy.

1. Autoimmune disease like SLE, RA
2. Sarcoidosis
3. Multiple myeloma
4. HIV and chronic infections
5. Primary neurological disease
6. Vitamin B12 deficiency
7. History of chemo or radiotherapy
8. Established Diabetic for <3 years

Statistical Analysis: Appropriate sample size were taken and the data thus obtained was analyzed with SPSS version 20 for its statistical significance and various statistically tests like Fisher's exact test, chi square, Mann Whitney test and logistic regression analysis for both univariate and multivariate analysis were used.

Result

The study was done on 70 chronic kidney disease patients with or without diabetes who were on heamodialysis (HD) in the Department of Internal Medicine at the Shri Guru Ram Rai Institute of Medical & Health Sciences, Patel Nagar, Dehradun. The data was collected and analyzed under the following sections.

1. Section A. Overall results
2. Section B. Comparisons based on Status of diabetes in CKD patients
3. Section C. Comparisons based on Peripheral Neuropathy in CKD patients
4. Section D. Predictor/Risk factors for Peripheral Neuropathy in CKD patients
5. Section E. Comparison based on Symptoms in CKD patients

Total Number of patients	70

Section A. Overall: Data of total 70 chronic kidney disease patients who were undergoing heamodialysis were included in the study.

Age: The average age of the study population was 52.90 years (St. dev = 13.18). The median age was 56 years.

Table 1: Age related parameters of the study population

Age related parameters	Value/Parameter
Mean	52.90
Standard deviation	13.18
Median	56.00
Quartile 1	49.00
Quartile 3	62.00

Gender: The proportion of males (43, 61.43%) was higher in the study than females (27, 38.57%).

Table 2: Gender related parameters of the study population

Gender related parameters	Number of patients	Percentage
Male	43	61.43
Female	27	38.57
Total	70	100.00

Figure. Gender related parameters of the study population

Duration of Haemodialysis: The average duration for which the patients were on haemodialysis was 21.40 months (St. Dev – 8.38). The median duration for which the patients were on haemodialysis was 20.00 months

Table 3. Haemodialysis duration related parameters of the study population

Duration of haemodialysis	Value/Parameter
Mean	21.40
Standard deviation	8.38
Median	20.00
Quartile 1	15.00
Quartile 3	28.00

Diabetes status: Thirty-one patients (31, 44.29%) had diabetes in the study.

Table 4: Status of diabetes

Status of diabetes	Number of patients	Percentage
Yes	31	44.29
No	39	55.71
Total	70	100.00

Figure. Status of diabetes

Duration of diabetes: The average duration of diabetes in the study was 30.65 months with a median of 32 months.

Table 5: Duration of diabetes

Duration of diabetes	Value/Parameter
Mean	30.65
Standard deviation	5.17
Median	32.00
Quartile 1	29.00
Quartile 3	34.00

Toronto clinical nephropathy score (TCNS): The average TCNS score for the study population was 8.36 with standard deviation of 4.07. The median score was 8.

Table 6: Toronto clinical nephropathy score (TCNS) related parameters

Toronto Clinical Neuropathy Score (TCNS)	Value/Parameter
Mean	8.36
Standard deviation	4.07
Median	8.00
Quartile 1	5.00
Quartile 3	12.00

TCNS Score based classification: Most of the patients in the study had severe nephropathy (26, 37.14%) based on clinical signs and symptoms assessed by the TCN score system. 20 patients each (20, 28.57%) had no or mild nephropathy symptoms and signs.

Table 7: TCNS Score based classification

TCNS Based Category	Number of patients	Percentage
No	20	28.57
Mild	20	28.57
Moderate	4	5.71
Severe	26	37.14
Total	70	100.00

Figure. TCNS Score based classification

Peripheral neuropathy status based on Nerve conduction velocity test: 47 patients (67.143%) had peripheral neuropathy on NCV.

Table 8: Peripheral neuropathy status based on Nerve conduction velocity test

Peripheral Neuropathy	Number of patients	Percentage
Yes	47	67.143
No	23	32.857
Total	70	100

Figure. Peripheral neuropathy status based on Nerve conduction velocity test

Patterns of neuropathy – Neuropathy localisation - Most of the patients had either lower limb involvement only (25, 53.19%) or generalised involvement of both upper and lower limbs (17, 36.17%). Only 5 patients had only upper limb involvement (5, 10.64%).

Table 9: Patterns of neuropathy – Neuropathy localisation

Neuropathy localisation	Number of patients	Percentage
Upper limb only	5	10.64
Lower limb only	25	53.19
Generalised	17	36.17
Total	47	100.00

Figure. Patterns of neuropathy – Neuropathy localization

Patterns of neuropathy – Neuropathy type - Most of the patients had either motor involvement only (31, 65.96%) or sensorimotor involvement (16, 34.04%).

Table 10: Patterns of neuropathy – Neuropathy type

Neuropathy type	Number of patients	Percentage
Sensory	0	0.00
Motor	31	65.96
Sensorimotor	16	34.04
Total	47	100.00

Figure. Patterns of neuropathy – Neuropathy type

Patterns of neuropathy – Neuropathy Characterisation Most of the patients had axonal involvement only (45, 95.74%). Only two patients had demyelinating neuropathy (2, 4.26%).

Table 11: Patterns of neuropathy – Neuropathy Characterisation

Neuropathy characterisation	Number of patients	Percentage
Axonal	45	95.74
Demyelinating	2	4.26
Mixed	0	0.00
Total	47	100.00

Figure. Patterns of neuropathy – Neuropathy Characterisation

Diabetes and Peripheral Neuropathy comparison - The proportion of diabetic patients with CKD on HD having neuropathy (80. 65%) was significantly higher (P = 0. 0417) than that in CKD patients on HD without neuropathy (56. 42%).

Table 12: Diabetes and Peripheral Neuropathy comparison

Peripheral Neuropathy and Diabetes	Non-Diabetic	Diabetes +	Grand Total	P Value

No Peripheral Neuropathy	17 (43.58 %)	6 (19.35 %)	23	0.0417
Peripheral Neuropathy +	22 (56.42 %)	25 (80.65 %)	47	
Grand Total	39	31	70	
Test		Fisher's exact test		
P value		0.0417		
P value summary		*		
One- or two-sided		Two-sided		
Statistically significant (P < 0.05)?		Yes		

Figure. Diabetes and Peripheral Neuropathy comparison

Section B. Comparisons based on Status of diabetes in CKD patients

Age related parameters comparison - The average age of CKD patients with diabetes was higher than the non-diabetic patients (55.32 vs 50.97 years). The difference was not statistically significant (P=0.0733).

Table 13. Age related parameters comparison

Age related comparison	Non-Diabetic	Diabetes +	Grand Total	P Value
Average of Age (In Years)	50.97	55.32	52.9	0.0733
St. Dev.	11.38	13.95	13.18	

Gender related parameter comparison - The proportion of males amongst diabetic CKD patients was higher than in the non-diabetic patients (67.75% vs 56.42%). The difference was not statistically significant (P=0.4589).

Table 14: Gender related parameter comparison

Gender related comparison	Non-Diabetic	Diabetes +	Grand Total	P Value
Females	17 (43.58%)	10 (32.25 %)	27	0.4589
Males	22 (56.42%)	21 (67.75 %)	43	
Grand Total	39	31	70	

Haemodialysis duration comparison - The duration of haemodialysis was similar across both the groups of patients (21.79% vs 20.90%) with no statistically significant difference (P=0.5981).

Table 15: Haemodialysis duration comparison

Duration of haemodialysis related comparison	Non-Diabetic	Diabetes +	Grand Total	P Value
Average of Duration of HD (in months)	21.795	20.903	21.4	0.5981
St. Dev.	9.01	7.33	8.38	

TCNS Score comparison - The average TCNS score for diabetic CKD patients was higher compared to that for non-CKD patients (9.16 vs 7.71). The difference was not statistically significant (P=0.1457).

Table 16: TCNS Score comparison

TCNS comparison	Non-Diabetic	Diabetes +	Grand Total	P Value
Average of Toronto Clinical Neuropathy score - Total score (out of 19)	7.7179	9.1613	8.3571	0.1457
St. Dev.	2.15	4.92	4.07	

TCNS Based category wise distribution - The distribution of patients across the two patient subgroups was similar with no statistically significant difference.

Table 17: TCNS Based category wise distribution

TCNS Based Category	Non-Diabetic	Diabetes +	Grand Total	P Vale
No	14 (35.80)	6 (19.35)	20	0.1327
Mild	12 (30.76)	8 (25.80)	20	0.6617
Moderate	2 (5.12)	2 (6.45)	4	0.8014
Severe	11 (28.20)	15 (48.38)	26	0.0848
Grand Total	39	31	70	

Patterns of neuropathy – Neuropathy localisation-based comparison - Diabetic patients had higher proportion of generalised neuropathy involvement (48% vs 22.74%). Non-diabetic patients had a higher involvement of the lower limb only (63.63% vs 44%). The differences were not statistically significant.

Table 18: Patterns of neuropathy – Neuropathy localisation-based comparison

Neuropathy localisation	Non-Diabetic	Diabetes +	Grand Total	P Value
Upper limb only	3 (13.63)	2 (8)	5	0.6337
Lower limb only	14 (63.63)	11 (44)	25	0.1831
Generalised	5 (22.74)	12 (48)	17	0.0752
Grand Total	22	25	47	

Patterns of neuropathy – Neuropathy type-based comparison - The distribution of patients across both the groups was similar with no statistically significant difference.

Table 19: Patterns of neuropathy – Neuropathy type-based comparison

Neuropathy type	Non-Diabetic	Diabetes +	Grand Total	P Value
Sensory	0	0	0	-
Motor	14 (63.63)	17 (68)	31	0.6337
Sensorimotor	8 (36.37)	8 (32)	16	0.7197
Grand Total	22	25	47	

Patterns of neuropathy – Neuropathy characterisation-based comparison - The neuropathy character was similar across both the groups with no statistically significant difference. The two cases of demyelinating neuropathy were seen in the non-diabetic group.

Table 20: Patterns of neuropathy – Neuropathy characterisation-based comparison

Neuropathy characterisation	Non-Diabetic	Diabetes +	Grand Total	P Value
Axonal	20 (90.90)	25 (100)	45	0.6019
Demyelinating	2 (9.10)	0	2	0.1397
Mixed	0	0	0	-
Grand Total	22	25	47	

Section C. Comparisons based on Peripheral Neuropathy in CKD patients

Age related comparison - The average age of patients with peripheral neuropathy was significantly higher than those without neuropathy (55.19 years vs 48.22 years, P=0.0334).

Table 21: Age related comparison

Age related comparison	No Peripheral Neuropathy	Peripheral Neuropathy +	Grand Total	P Value
Average of Age (In Years)	48.22	55.19	52.90	0.0334
St. Dev.	9.34	13.62	13.18	

Mann Whitney test	
P value	0.0334
Exact or approximate P value?	Exact
P value summary	*
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column I, N	1838, 647
Mann-Whitney U	371

Figure. Age related comparison

Gender related comparison - The proportion of males was higher in the patients with peripheral neuropathy (42.55% vs 30.43%). The difference in gender distribution was not statistically significant (P=0.435).

Table 22: Gender related comparison

Gender related comparison	No Peripheral Neuropathy	Peripheral Neuropathy +	Grand Total	P Value
Females	7 (30.43)	20 (42.55)	27	0.435
Males	16 (69.7)	27 (57.45)	43	
Grand Total	23	47	70	

Haemodialysis duration related comparison - The duration of haemodialysis was higher in the peripheral neuropathy group (23.915 vs 16.261 months). The difference was statistically significant (P<0.0001).

Table 23: Haemodialysis duration related comparison

Duration of haemodialysis related comparison	No Peripheral Neuropathy	Peripheral Neuropathy +	Grand Total	P Value
Average of Duration of HD (in months)	16.261	23.915	21.4	<0.0001
St. Dev.	6.12	9.35	8.38	
P value		0.0001		
Exact or approximate P value?		Exact		
P value summary		***		
Mann-Whitney U		245.5		

Figure. Haemodialysis duration related comparison

TCNS Score comparison - The average TCNS score was significantly higher in the peripheral neuropathy group compared to the patients with no peripheral neuropathy (10.234 vs 4.52, P<0.0001).

Table 24: TCNS Score comparison with peripheral Neuropathy

TCNS comparison	No Peripheral Neuropathy	Peripheral Neuropathy +	Grand Total	P Value
Average of Toronto Clinical Neuropathy score - Total	4.5217	10.234	8.3571	<0.0001

score (out of 19)				
St. Dev.	1.26	5.11	4.07	
P value		<0.0001		
Exact or approximate P value?		Exact		
P value summary		****		
Significantly different (P < 0.05)?		Yes		
One- or two-tailed P value?		Two-tailed		
Sum of ranks in column K, P		2098, 387		
Mann-Whitney U		111		

Figure. TCNS Score comparison

Duration of diabetes comparison in patients with peripheral neuropathy -Diabetic CKD patients with neuropathy were associated with higher duration of diabetes mellitus compared to the those without neuropathy (31.28 months vs 28 months, P=0.5631).

Table 25: Duration of diabetes comparison in patients with peripheral neuropathy

Duration of diabetes comparison	No Peripheral Neuropathy	Peripheral Neuropathy +	Grand Total	P Value
Average of Duration of diabetes mellitus (In months)	28	31.28	30.645	0.5631
St. Dev.	4.39	6.2	5.17	

Table 26: Duration of haemodialysis and NCV based neuropathy severity - As the duration of haemodialysis increased, the proportion of patients with severe neuropathy increased. The difference in proportion was however, not statistically significant.

Duration of Haemodialysis	Mild moderate	Mild moderate (%)	Severe	Severe (%)	P value
Up to 12 months	5	16.67	0	0.00	0.0781
>12-24 months	10	33.33	7	41.17	0.5949
More than 24 months	15	50	10	58.82	0.5646
Grand Total	30	100	17	100	

Table 27: Distribution of patients as per the NCV based neuropathy severity -63% patients had mild-moderate neuropathy while 36% patients had severe neuropathy.

	Mild moderate	Severity	Grand Total
NCV Based neuropathy Category (Mild-Mod=1, Severe=2)	30	17	47
Percentage	63.83	36.17	100.00

Section D. Predictor/Risk factors for Peripheral Neuropathy (on NCV) in CKD patients

Univariate analysis: A univariate logistic regression analysis for predictors/risk factors of peripheral neuropathy in CKD patients on HD was done.

Age: Increasing age was associated with higher odds (4% higher odds for every year of age) of having peripheral neuropathy in the patients.

Table 28: Predictors/risk factors of peripheral neuropathy in CKD patients on HD – Age

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1a	Age (Years)	0.04	0.02	4.065	1	0.044	1.041

	Constant	-1.376	1.058	1.693	1	0.193	0.252

Gender: Males were associated with reduced odds of having peripheral neuropathy (41% lower odds compared to females). The odds were not statistically significant (P=0.33)

Table 29: Predictors/risk factors of peripheral neuropathy in CKD patients on HD – Gender

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1a	Gender (Male1 Female0)	-0.527	0.541	0.948	1	0.33	0.591
	Constant	1.05	0.439	5.715	1	0.017	2.857

Duration of haemodialysis: Increasing duration of haemodialysis was associated with higher odds of peripheral neuropathy (14% higher odds for each additional month of haemodialysis).

Table 30: Predictors/risk factors of peripheral neuropathy in CKD patients on HD – Duration of HD

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1a	Duration of HD (in months)	0.139	0.042	10.831	1	0.001	1.149
	Constant	-2.031	0.819	6.15	1	0.013	0.131

Status of diabetes: Presence of diabetes was associated with significantly raised odds (222% higher odds, P=0.036) of peripheral neuropathy in CKD patients on Haemodialysis.

Table 31: Predictors/risk factors of peripheral neuropathy– Diabetes status

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1a	Status of Diabetes (Yes1No0)	1.169	0.558	4.397	1	0.036	3.22
	Constant	0.258	0.323	0.637	1	0.425	1.294

Duration of diabetes: Increasing duration of diabetes was associated with higher odds of having peripheral neuropathy (11% additional odds for each additional month of diabetes).

Table 32: Predictors/risk factors of peripheral neuropathy– Duration of diabetes

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1a	Duration of diabetes (months)	0.109	0.084	1.71	1	0.191	1.116
	Constant	-1.839	2.494	0.54	1	0.461	0.159

Multivariate analysis: A multivariate analysis of the risk factors for peripheral neuropathy was done. After controlling for age, gender and duration of haemodialysis, it was seen that presence of diabetes was associated with >5 times (561%) higher odds of having peripheral neuropathy compared to the non-diabetic CKD patients on Haemodialysis.

Table 33: Predictors/risk factors of peripheral neuropathy in CKD patients on HD – Multivariate

	B	S.E.	Wald	df	Sig.	Exp (B)	95% C. I. for EXP(B)	
							Lower	Upper
Age (Years)	0.051	0.026	3.861	1	0.049	1.052	1	1.107
Gender (Male1 Female0)	-1.084	0.743	2.129	1	0.145	0.338	0.079	1.45
Duration of HD (months)	0.169	0.05	11.279	1	0.001	1.185	1.073	1.308
Status of Diabetes (Yes1No0)	1.889	0.763	6.131	1	0.013	6.61	1.482	29.473
Constant	-5.268	1.83	8.289	1	0.004	0.005		

Section E. Comparison based on Symptoms in CKD patients

Table 34: Gender and number of symptoms

	Female (Diabetes +)	Female (Diabetes -)	Male (Diabetes +)	Male (Diabetes -)	P Value
Median	1.50	1.00	4.00	1.50	0.602
Quartile 1	1.00	1.00	1.00	1.00	
Quartile 3	3.75	2.00	4.00	4.00	
Mean	2.30	1.76	2.95	2.27	
Standard deviation	1.57	1.20	1.56	1.45	

The average and median number of symptoms were higher in the diabetes patients across both the genders but the difference was not statistically significant.

Table 35: Diabetes status-based correlation of HD and number of symptoms

The duration of hemodialysis was positively corelated with the number of symptoms across both diabetic and non-diabetic patients. The correlation was not significantly different amongst the two groups.

Table 35: Symptoms and HD duration

Duration of HD	Foot Pain +	%	L/L Numb +	%	L/L Tingling +	%	L/L Weakness +	%	U/L Numb +	%
Up to 12 months	7	15.22	0	0.00	8	13.79	2	8.33	2	6.25
>12-24 months	19	41.30	2	40.00	24	41.38	8	33.33	11	34.38
More than 24 months	20	43.48	3	60.00	26	44.83	14	58.33	19	59.38
Grand Total	46	100.00	5	100.00	58	100.00	24	100.00	32	100.00

The proportion of patients with any particular symptom having a higher duration of hemodialysis (>12 months) was much higher than those with less than 12 months of HD duration.

Table 36: TCNS score and symptoms

Patients with foot pain had a higher average TCNS score (9.96 vs 5.29). The difference was statistically significant (P<0.0001).

Foot pain	Present	Absent	P value
Average of Toronto Clinical Neuropathy score – Total score (out of 19)	9.96	5.29	<0.0001
St Dev	2.35	1.20	

Patients with lower limb numbness had a higher average TCNS score (14.20 vs 7.91). The difference was statistically significant (P<0.0001).

Table 37: With duration of haemodialysis: The duration of haemodialysis was positively correlated with number of symptoms (r=0.39). The results were statistically significant (P=0.0008).

Lower limb numbness	Present	Absent	P value
Average of Toronto Clinical Neuropathy score - Total score (out of 19)	14.20	7.91	<0.0001
St Dev	3.52	3.20	

Patients with lower limb tingling had a higher average TCNS score (9.31 vs 3.75). The difference was statistically significant (P<0.0001).

Table 38: With duration of diabetes: There was no statistical correlation between the duration of diabetes and the number of symptoms.

Lower limb tingling	Present	Absent	P value
Average of Toronto Clinical Neuropathy score - Total score (out of 19)	9.31	3.75	<0.0001
St Dev	2.56	1.33	

Patients with lower limb weakness had a higher average TCNS score (12.88 vs 6.00). The difference was statistically significant (P<0.0001).

Table 39: With age in years: Age of patients was positively correlated with number of symptoms (r=0.16). The results were not statistically significant (P=0.176).

Lower Limb weakness	Present	Absent	P value
Average of Toronto Clinical Neuropathy score - Total score (out of 19)	12.88	6.00	<0.0001
St Dev	4.26	1.27	

Patients with Upper limb numbness had a higher average TCNS score (12.09 vs 5.21). The difference was statistically significant (P<0.0001).

Table 40: With TCNS score: TCNS Score was very highly correlated with the number of symptoms (r=0.9256). Number of symptoms are a part of TCNS score-based assessment and therefore this positive correlation was observed.

Upper limb numbness	Present	Absent	P value
Average of Toronto Clinical Neuropathy score - Total score (out of 19)	12.09	5.21	<0.0001
St Dev	3.49	1.24	

The difference was statistically significant (P<0.0001).

Discussion

Chronic kidney disease (CKD) is characterized by reduction in the functional capacity of kidney along with structural abnormalities that may lead to reduced kidney size, fall in GFR, proteinuria, uremia, electrolyte imbalances, hematological abnormalities and endocrinopathies (17). The importance of CKD which include primary renal disease or secondary to any systemic illness have been well established globally. There are many theories which state a multifactorial pathogenesis of CKD. In western countries, diabetes and hypertension comprise over 66% cases of CKD and in India this group comprises of 40-60% of cases of CKD (3). In the diabetics, structural changes in renal parenchyma include thickening of glomerular basement membrane, loss of endothelial fenestrations, mesangial matrix expansion, and loss of podocytes with effacement of foot processes leading to CKD over the time.

Diabetic neuropathies are the most widespread chronic complications of diabetes. The prevalence of neuropathy in diabetics with CKD patients varies and can be as high as 50% of all dialysis patients. This heterogeneous group of conditions comprising of mainly diffuse, mono and radiculopathy affects different parts of the nervous system and has varied presentations. Increased oxidative stress due hyperglycemia cause DNA damage, endoplasmic reticulum stress, mitochondrial dysfunction, cellular injury, and irreversible damage leading to neuropathy. In Diabetics after overt nephropathy development, a substantial number of patients will progress to end-stage renal disease (ESRD) with reported rates of 4% to 17% at 20 years and approximately 16% at 30 years from time of initial diagnosis of DM. Uremic neuropathy denotes peripheral neuropathy that is due to the extended effects of the spectrum of uremia. Some of the few identified toxins are middle molecules, guanidine compounds, parathyroid hormone, myoinositol and so on (7,8). They are implicated but are not established causes of peripheral neuropathy in patients of CKD.

In this study we have studied the prevalence and pattern of neuropathy among the patients of CKD undergoing Hemodialysis. We have used TCNS as a screening tool and NCV to confirm the presence, location and character of the peripheral neuropathy in this study. It was attempted to understand pattern and risks of neuropathy in diabetes or non-diabetic CKD patients.

Age

Age is an independent risk factor for CKD as well as diabetes mellitus (DM). Additionally, CKD can occur in any age group. (22)

In our study average age of the study population was 52.90 years (St. dev = ±13.18), where the average age of CKD patients with diabetes was higher than the non-diabetic patients (55.32 vs 50.97 years) and with peripheral neuropathy was significantly higher than those without neuropathy (55.19 years vs 48.22 years, P=0.0334). (Table 13 & 21)

In our study increasing age was associated with higher odds (4% higher odds for every additional year of age) of having peripheral neuropathy while age of the patients was positively correlated with number of symptoms (r=0.16). (Table 28)

Thus the mean age among the current study and previous studies in India had a lower mean than other international studies pretending the higher prevalence of CKD among the young patients especially in diabetic subgroup.

Gender

The proportion of males (43, 61.43%) was higher in the study than females (27, 38.57%). A study by Hari et al on 100 patients in Haryana state also had around 68% males while 32% were females. (11) (table 2)

In our study, the proportion of males amongst diabetic CKD patients was higher than in the non-diabetic patients (67.75% vs 56.42%) while females were higher in non-diabetic CKD subgroup (43.58% vs 32.25%) but this comparison was not statistically significant. Similarly, there were more males than females with peripheral neuropathy overall (42.55% vs 30.43%). (Table 14 & 22) This is in concordance with study by Raskin and Fishman that states, males develop peripheral neuropathy more frequently than females. (21)

Although the reason behind this disparity in gender is not well established in renowned literatures.

Duration of hemodialysis

In the work illustrated by Rathna Kumar, enrolling 74 patients of CKD, the average duration for which the patients were on hemodialysis was 21.40 months (S.D.: ±8.38) with the duration of CKD varying from 3 months to 7 years (84 months).

Our study also showed that the duration of hemodialysis was positively correlated with number of symptoms (r=0.39) and was statistically significant (P=0.0008) and the proportion of patients with any particular symptom having a higher duration of hemodialysis (>12 months) was much higher than those with less than 12 months of HD duration. As the duration of hemodialysis increased, the proportion of patients with severe neuropathy increased. The difference in proportion was however, not statistically significant. (Table 34)

The duration of hemodialysis was positively correlated with the number of symptoms across both diabetic and non-diabetic patients in our study. (Table 35)

Therefore, more the duration of hemodialysis more the prevalence of peripheral neuropathy was observed as there is more damage to nerves due the various toxic compounds known or unknown.

Diabetes

The most common cause of CKD in India and abroad is Diabetes mellitus. Indian study by Agarwal and colleagues highlighted that the most witnessed cause of CKD in population of India is diabetes. DM, hypertension and glomerulonephritis combined comprise three-fourth of the causes of CKD in adult population.

There were Thirty-one patients (44.29%) who had diabetes in our study with an average duration of diabetes being 30.65 ± 5.17 months (SD) with a median of 32 months. (Table 4,5)

In our study Diabetic CKD patients with neuropathy were associated with higher duration of diabetes mellitus compared to the those without neuropathy (31.28 months vs 28 months, P=0.5631). (Table 25)

Our study showed that presence of diabetes was associated with significantly higher odds (222% higher, P= 0.036) of peripheral neuropathy. Similarly increasing duration of diabetes was associated with higher odds of having peripheral neuropathy (11% additional odds for each additional month of diabetes). However, there was no statistical correlation between the duration of diabetes and the number of symptoms. (Table 31) Even Bashi et al in their diabetic clinic showed that there was a strong correlation between diabetic peripheral neuropathy and

nephropathy (P<0.01), in patients with type 2 diabetes mellitus.

If the duration of DM is longs-enough and level of glycaemia are high enough to result in diabetic complications thus longer duration of diabetes will lead to nephropathy culminating into ESRD and along with neuropathy.

Tcns score

The TCNS score was used to screen and grade the severity of peripheral neuropathy. The average TCNS score for the study population was 8.36 with SD of ± 4.07. The median score was 8. Most of the patients in the study had severe neuropathy (26, 37.14%) based on clinical signs and symptoms assessed by the TCN score system. 20 patients each (20, 28.57%) had no or mild neuropathy. (Table 6 & 7)

In our study the average TCNS score for diabetic CKD patients was higher compared to that for non-CKD patients (9.16 vs 7.71) and in our study it showed that the diabetics have more severity of peripheral neuropathy with TCN score but the distribution among the grades of severity is similar between diabetics and non-diabetics, thus indicating towards a more profound effect of diabetes on neuropathy, although the data was not statistical significance. (Table 16)

As predicted in our study the average TCN score was significantly higher in the peripheral neuropathy group compared to the patients with no peripheral neuropathy (10.234 vs 4.52, P<0.0001). (Table 24)

On comparison of TCN score and symptoms our study showed that patients with foot pain (9.96 vs 5.29), lower limb numbness (14.20 vs 7.91), lower limb tingling (9.31 vs 3.75), lower limb weakness (12.88 vs 6.00) and Upper limb symptoms (12.09 vs 5.21) had a higher average TCN score. The difference was statistically significant (P<0.0001). The data indicated lower limb numbness followed by lower limb weakness being most common manifestations as the peripheral neuropathy progresses which is similar to studies by Hari et al. (11) (Table 37).

The average number of symptoms were higher in the diabetes patients across both the genders but the difference was not statistically significant. (Table 34)

In our study TCN Score was very highly correlated with the number of symptoms (r=0.9256). Number of symptoms are a part of TCN score-based assessment and therefore this positive correlation was observed as expected. (Table 41)

Peripheral neuropathy

There were 47 patients (67.143%) who had peripheral neuropathy on NCV where 63% patients had mild-moderate neuropathy while 36% patients had severe neuropathy. Similar study was conducted by Krishnan et al in 2005 and reported 91% peripheral neuropathy in chronic kidney disease which was higher than ours. (18) (table 27) According to Tilki et al peripheral neuropathy was seen in 97.6% of chronic kidney disease patients on hemodialysis, which was 86.8% according to Janda K et al and 60% according to Bolton et al. The prevalence of neuropathy in our study fell in between the range of previous studies. (20)

While in our study the proportion of diabetic patients with CKD on HD having neuropathy (80.65%) was significantly higher (P=0.0417) than that in CKD patients on HD without neuropathy (56.42%) indicating a potential additive risk of hyperglycemia in uremic neuropathy. (Table 12)

Location of peripheral neuropathy

Most of the patients had either lower limb involvement only (25, 53.19%) or generalized involvement of both upper and lower limbs (17, 36.17%). Only 5 patients had

only upper limb involvement (5, 10.64%). (Table 9) In our study Diabetic patients had higher proportion of generalized neuropathy involvement (48% vs 22.74%). Non-diabetic patients had a higher involvement of the lower limb only (63.63% vs 44%). (86) Both diabetic and uremic neuropathy present as distal symmetrical peripheral neuropathy involving predominantly lower limbs indicating a length dependent neuronal damage as a common pathophysiology.

Since diabetic subgroup had more generalized type of neuropathy, this association might arise due to augmented or synergistic effect of uremia and hyperglycemia in these patients, thus necessating further studies in this arena.

Type of pn

Santos et al had a 92 % generalized involvement in 27 patients out of which 25 patients had neuropathy which was higher than our study. The distribution of patients across both the groups was similar with no statistically significant difference in our study and it was seen that presence of diabetes was associated with >5 times (561%) higher odds of having peripheral neuropathy compared to the non-diabetic CKD patients on Hemodialysis but Santos et al showed that diabetic patients when compared with non-diabetic patients had 6.7 times the risk of having sensorimotor neuropathy and diabetic patients alone had 3.094 times more risk to have sensorimotor neuropathy than sensory neuropathy. Thus our study shows that presence of diabetes had a higher risk of developing peripheral neuropathy which can be sensorimotor or motor and was associated with significantly raised odds (222% higher odds, P=0.036). (Table 4 and 33)

Character of pn

Most of the patients had axonal involvement only (45, 95.74%). Only two patients had demyelinating neuropathy (2, 4.26%) that too in non-diabetic group only. (Table11) The neuropathy character was similar across both the groups with no statistically significant difference. (Table 20)

In our study factors that showed to be the risk factors for development of peripheral neuropathy were age, duration of hemodialysis, presence of diabetes and its duration on univariate analysis while multivariate analysis showed diabetes as an independent risk factor for development of peripheral neuropathy in CKD patients. On the other hand, symptoms positively correlated with age, TCN score, duration HD and not with diabetes.

Therefore, our study gives information not only on the type, severity and pattern of the neuropathy among patients of CKD and also throws light on the effect of the diabetes on uremic neuropathy.

Thus in future, other risk factors of CKD and patterns and type of neuropathy needs to be studied to further validate the study.

Conclusion

Peripheral neuropathy in patients of chronic kidney disease on hemodialysis is influenced by both diabetes, uremia and duration of dialysis. More duration of HD more the peripheral neuropathy which was already observed in previous studies, in this study diabetic patients had more severe type of PN, higher TCNS score and more generalized neuropathy. Presence of diabetes and its increasing duration was associated with higher odds of developing peripheral neuropathy. Motor and axonal involvement was more commonly seen in the entire study with more number of males but males had reduced odds having neuropathy.

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