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Correlation of cardiac autonomic neuropathy in predialysis and dialysis chronic kidney disease patients

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Abstract
Background and Objectives: CKD is one of the major health problems all over the world. Autonomic dysfunction is common in CKD patients but symptomatic autonomic Neuropathy is not that common. Presence of Cardiac Autonomic Neuropathy (CAN) is responsible for silent myocardial infarction and sud+den death in CKD patients. Prolongation of corrected QT (QTc) in electrocardiogram (ECG), lack of heart rate variability (HRV) and postural hypotension (PH) are found to be early indicators of Cardiovascular Autonomic Neuropathy.
Methods: This is a Cross-sectional study done to evaluate the correlation of cardiac autonomic neuropathy among chronic kidney disease patients in pre-dialysis stage and CKD patients in maintenance hemodialysis stage, with the help of prolongation of corrected QT (QTc) in ECG, lack of heart rate variability (HRV) and postural hypotension (PH). A total of 100 patients admitted in KVG Medical College, Sullia satisfying the inclusion and exclusion criteria were studied. They were divided into 2 groups, CKD in predialysis stage and CKD in maintenance hemodialysis stage. The prevalence of CAN was evaluated and compared in the two groups with respect to Heart rate variability, Postural hypotension and QTc interval.
Results: Out of 100 CKD patients, 50 patients were CKD in predialysis stage and 50 patients were CKD on maintenance hemodialysis. Among the predialysis group, 15 patients (30%) had QTc prolongation, 27 patients (54%) had postural hypotension and 49 patients (98%) had lack of heart rate variability. Among the dialysis group, 28 patients (56%) had QTc prolangation, 39 patients (78%) had Postural hypotension and 50 patients (100%) had lack of heart rate variability.
All these values were statistically significant suggesting prevalence of CAN increases as the progression of CKD from predialysis stage to hemodialysis stage.
Conclusions: From the above results we can conclude that the Prevalence of Cardiovascular Autonomic Neuropathy is high in CKD patients and the prevalence of CAN increases as the progression of CKD from predialysis stage to dialysis stage. Hence we suggest all CKD patient should be evaluated with simple bedside tests like postural hypotension, lack of Heart rate variability (HRV), prolongation of QTc in ECG for early detection of CAN, so as to prevent further complications with early intervention and proactive treatment.

Keywords: cardiac autonomic neuropathy, qtc prolongation, heart rate variability, postural hypotension

Introduction
Chronic kidney disease is a growing public health problem, affecting 5-7% of the world's population [1], and the number of clinical cases eventuating in End stage renal disease is increasing at an alarming rate of 3% annually [2].Individuals with Chronic kidney disease are more likely to die of cardiovascular complications than to develop kidney failure because of the high prevalence of cardiovascular disease in this patient population [3, 4, 5]. Therefore the focus recently shifted to optimizing patient care during the phase of Chronic kidney disease before the onset of End stage renal disease [6]. In Chronic kidney disease Patients mortality from cardiovascular disease stratified by age is 10 times higher than in the general population.
Chronic kidney disease patients with cardiovascular autonomic dysfunction consistently have shown an enhanced risk of premature death, suggesting direct detrimental effects on the clinical prognosis of renal failure [7]. Sudden cardiac death is a major cause of cardiac mortality in End stage renal disease patients [8, 9], with the incidence increasing with the stage of renal failure. Therefore Cardio vascular disease prevention and treatment are critical in the management of individuals with Chronic kidney disease.
Cardiac autonomic neuropathy is associated with resting tachycardia, postural hypotension, painless myocardial ischemia or infarction, arrhythmias and sudden cardiac death [10] Cardiac autonomic neuropathy contributes significantly to increased cardiovascular mortality and morbidity in Chronic kidney disease patients [11, 12].

Cardiac autonomic neuropathy in chronic kidney disease
The autonomic nervous system modulates the electrical and contractile activity of the myocardium via the interplay of sympathetic and parasympathetic activity [13] Cardiovascular autonomic neuropathy, a common form of autonomic dysfunction found in patients with Chronic kidney disease, causes abnormalities in heart rate control, as well as defects in central and peripheral vascular dynamics [14]
Cardiac autonomic neuropathy has been linked to resting tachycardia, postural hypotension, orthostatic bradycardia and orthostatic tachycardia, exercise intolerance, decreased hypoxia-induced respiratory drive, loss of baroreceptor sensitivity, enhanced intraoperative or perioperative cardiovascular liability, increased incidence of

asymptomatic ischemia, myocardial infarction, and decreased rate of survival after myocardial infarction and congestive heart failure [15] Hence this study aims at studying the manifestations of autonomic neuropathy on cardiovascular system in predialysis and dialysis Chronic kidney disease patients, thereby reassessing the need for early recognition and more aggressive management of this disease.

Methodology

Study population

100 Chronic kidney disease patients, 50 in pre-dialysis stage and 50 in maintenance hemodialysis stage, of both gender, attending outpatient department and inpatients of K.V.G Medical College Hospital, Sullia were studied.

Study Duration

This study was conducted for a period of one and a half years from December 2017 to May 2019

Study Design

It is a cross sectional study using random sampling methods to detect cardiovascular autonomic neuropathy in CKD patients and the correlation of cardiac autonomic neuropathy among chronic kidney disease patients in pre-dialysis stage (n=50) and in maintenance hemodialysis stage(n=50).

Methods

Inclusion criteria

- Age 10-70 Years
- Chronic kidney disease patients

Exclusion criteria

- Patients with Valvular heart disease, Ischemic heart disease, cerebro-vascular accident, any Cancer, Demyelinating diseases.
- Patients who were on any drugs that would interfere with the autonomic functions like phenothiazines, tricyclic antidepressants.

After satisfying the inclusion and exclusion criteria, patients were included in the study. Written informed consent was obtained from all the patients participating in the study. Cardiac autonomic imbalance was assessed by detailed history and clinical examination as per annexed proforma. Symptoms suggestive of dysautonomia like light eadedness, postural syncope, pre-syncope, easy fatigability, palpitation, excessive sweating, diarrhoea, constipation were evaluated. Since cardiac autonomic neuropathy is usually associated with other features of autonomic neuropathy this questionnaire was useful in assessing the patients along with the bed side tests. The selected patients were further studied with the 3 bedside cardiovascular reflex tests, namely, Postural hypotension (PH), Heart rate variability (HRV) & corrected QT interval (QTc) in Medical ward by using sphygmomanometer and Electrocardiograph. These tests were performed in 5-8 hours post prandial state and tthese patients were were instructed not to ingest caffeine containing products on the day of study.

Postural hypotension: (PH)

After ensuring the adequate hydration status of the patient, This test was performed by measuring the subject's blood pressure with a sphygmomanometer while he was supine and after one minute of standing. The postural fall in blood pressure was taken as the difference between the systolic pressures in lying and standing position. A difference of more than 20 mmHg is defined as the presence of postural hypotension.

Heart rate variabilty: (HRV)

The subject was asked to breathe deeply at six breaths per minute (Five seconds "inspiration" and five seconds "expiration") for one minute. The average heart rate difference (maximum minus minimum during the respiratory cycle) is calculated while the patient breaths deeply for 1 minute. The results were expressed as the mean of the difference between maximum and minimum heart rates for the six measured cycles in beats per minute.

The variation of heart rates in inspiration and expiration is determined by ECG. The variation of HR during inspiration and expiration of less than 20 beats per minute is accepted as CAN. In addition to respiratory-dependent variations in HR, there are also non-respiratory HR fluctuations (oscillations of RR interval duration on electrocardiogram-ECG) beat to beat in rhythmic oscillations in particular, vagal activity. This phenomenon, when, in balanced state (supine or standing), the system receptors-VMC-respiratory centre effectors and value of HR (duration of R-R interval) oscillates synchronously, is known as heart rate variability.

Corrected QT interval (QTC)

QT interval is measured on an ECG recorded at rest and corrected for the cardiac cycle Length (QTc). The QTc is calculated by the equation of Bazett:QTc = [QT interval/√RR interval]. A QTc interval more than 440 Millisecond is considered prolonged and as an indicator of CAN.

Results

Age distribution

Table 1: Age distribution

Age group		Group		Total
		Predialysis[a]	Dialysis	
<40	Count	8	6	14
	%	16.0%	12.0%	14.0%
40 - 45	Count	6	8	14
	%	12.0%	16.0%	14.0%
45 -50	Count	1	5	6
	%	2.0%	10.0%	6.0%
50 - 55	Count	6	8	14
	%	12.0%	16.0%	14.0%
55 - 60	Count	10	5	15
	%	20.0%	10.0%	15.0%
60 - 65	Count	10	10	20
	%	20.0%	20.0%	20.0%
>65	Count	9	8	17
	%	18.0%	16.0%	17.0%
Total	Count	50	50	100
	%	100.0%	100.0%	100.0%

a. x2=5.249 p=0.512 ns

Among the Predialysis group 30% patients were below 50 years of age, 70% of them were above 50 years of age.

Among the dialysis group 38% patients were below 50 years of age, 62% of them were above 50 years of age.

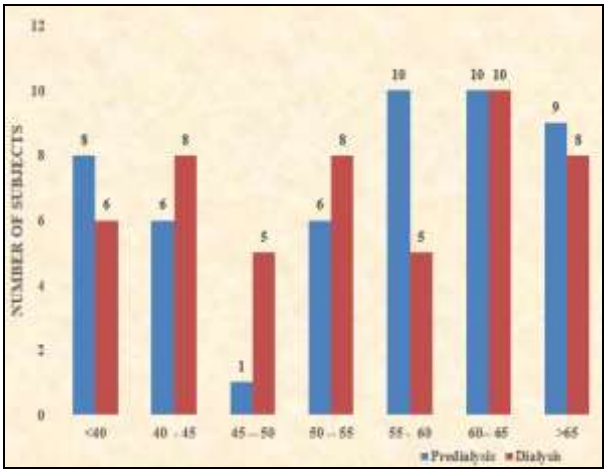

Fig 1: Age distribution

Gender distribution

Table 2: Gender distribution

Gender		Group		Total
		Predialysis[a]	Dialysis	
Male	Count	33	29	62
	%	66.0%	58.0%	62.0%
Female	Count	17	21	38
	%	34.0%	42.0%	38.0%
Total	Count	50	50	100
	%	100.0%	100.0%	100.0%

a. x2=0.679 p=0.41 ns

Among predialysis group 33 patients were male, 17 patients were female. Among dialysis group 29 patients were male, 21 patients were female.

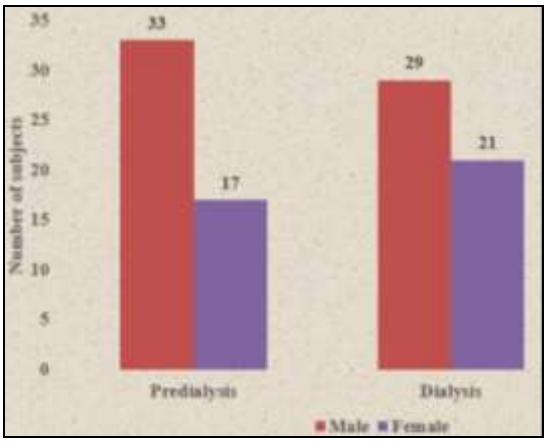

Fig 2: Gender distribution

Symptoms
Postural giddiness

Table 3: Postural giddiness among predialysis and dialysis group

Postural giddiness		Group		Total
		Predialysis[a]	Dialysis	
Yes	Count	8	25	33
	%	16.0%	50.0%	33.0%
No	Count	42	25	67
	%	84.0%	50.0%	67.0%
Total	Count	50	50	100
	%	100.0%	100.0%	100.0%

a. x2=13.071 p<0.001 vhs

Among predialysis group 8(16%) patients complained of giddiness on standing. Among dialysis group 25(50%) patients had symptom of giddiness on standing, 25 (50%) patients did not. P value is <0.01 and the result is statistically significant. Postural giddiness was more common in dialysis group compared to predialysis group.

Qtc prolongation

Table 4: Qtc prolongation in predialysis and dialysis group

QTc prolongation		Group		Total
		Predialysis	dialysis	
Yes	Count	15	28	43
	%	30.0%	56.0%	43.0%
No	Count	35	22	57
	%	70.0%	44.0%	57.0%
Total	Count	50	50	100
	%	100.0%	100.0%	100.0%

a. x2=6.895 p=0.009 hs

Among predialysis group 15 patients (30%) had qtc prolangation, 35 patients (70%)did not have qtc prolongation.
Among dialysis group 28 patients (56%) had qtc prolangation, 22 patients (44%) did not.
p value is 0.009 The results are statistically significant.

Postural hypotension

Table 5: Postural hypotension in predialysis and dialysis group

PH			Group		Total
			Predialysis[a]	Dialysis	
PH	Yes	Count	27	39	66
		%	54.0%	78.0%	66.0%
	No	Count	23	11	34
		%	46.0%	22.0%	34.0%
Total		Count	50	50	100
		%	100.0%	100.0%	100.0%

a. x2=6.417 p=0.011 sig

Among predialysis group 27 patients (54%) had postural hypotension, 23 patients (46%) did not had postural hypotension. Among dialysis group 39 patients (78%) had PH and 11 patients (22%) did not p value 0.011 The results are statistically significant.

Heart rate variability

Table 6: Heart rate variability in predialysis and dialysis group

HRV		Group		Total
		Predialysis[a]	Dialysis	
Yes	Count	49	50	99
	%	98.0%	100.0%	99.0%
No	Count	1	0	1
	%	2.0%	0.0%	1.0%
Total	Count	50	50	100
	%	100.0%	100.0%	100.0%

a. x2=1.01 p=0.315 ns

Among predialysis group 49 patients (98%) had lack of heart rate variability.
Among dialysis group 50 patients (100%) had lack of heart rate variability.

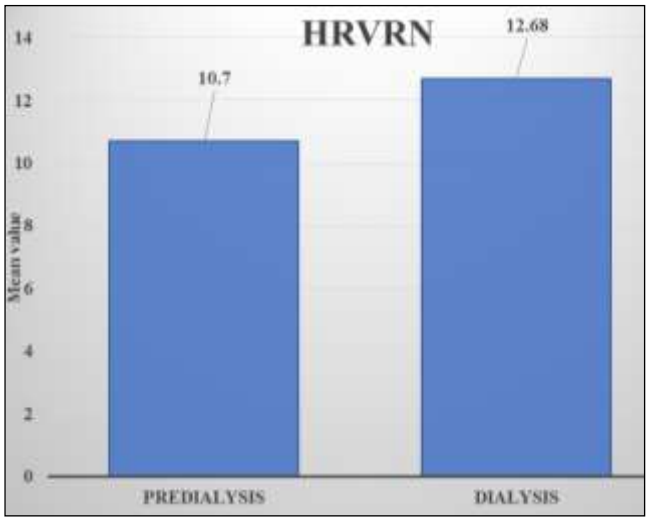

Fig 3: HRVRN during breathing

Table 7: Comparison of mean heart rate variability in predialysis and dialysis group

CKD	N	Mean	Std. Deviation	T
Predialysis	50	10.740	3.735	2.722
Dialysis	50	12.680	3.383	p=0.008 hs

Mean Heart Rate Variability in predialysis group was 10.740, among dialysis group it was 12.680 p=0.008 and the results are statistically significant.

Table 8: Comparison of various factors in predialysis and dialysis group

	Group	N	Mean	Std. Deviation	T
SBP(Supine)mmHg	Predialysis	50	128.000	9.806	1.101
	Dialysis	50	125.560	12.231	p=0.274 ns
DBP supine	Predialysis	50	83.920	5.965	1.506
	Dialysis	50	81.960	7.004	p=-0.135 ns
SBP(standing)mmHg	Predialysis	50	110.200	16.078	3.985
	Dialysis	50	121.280	11.312	<0.001 vhs
DBP standing	Predialysis	50	75.080	8.093	2.053
	Dialysis	50	78.080	6.426	p=0.043 sig
RR	Predialysis	50	16.160	1.845	1.756
	Dialysis	50	16.840	2.024	p=0.082 ns

Systolic blood pressure at supine position was measured in both the study groups. The mean SBP was found to be 128mmhg and 125.560mmhg among the 2study groups respectively, which was not statistically significant. Mean SBP on standing was 110.2 in CKD predialysis group and 121.280mmhg in dialysis group.

P value <0.001 and the result was found to be statistically significant. Diastolic blood pressure at supine position was measured in both the study groups. The mean DBP was found to be 83.920mmhg and 81.960mmhg among the 2study groups respectively, which was not statistically significant. But again in the standing position the mean DBP was 75.080 in CKD predialysis group and 78.080mmhg in dialysis group.

P value 0.043 and difference was found to be statistically significant.

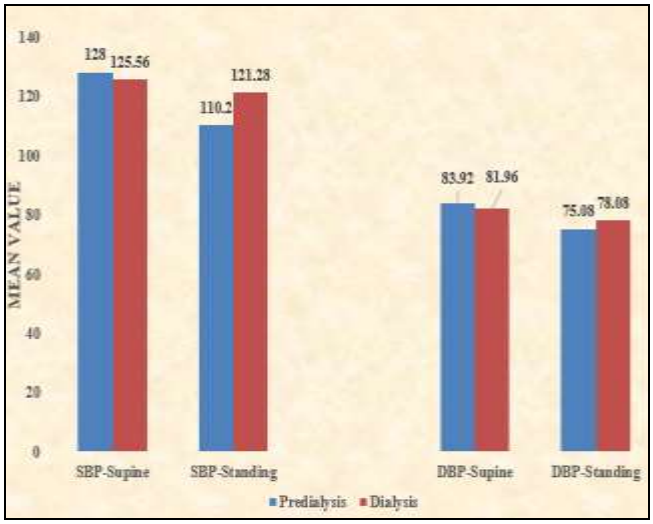

Fig 4: Comparison of Mean SBP & DBP between Predialysis and Dialysis patients

Discussion

Age

Majority were in age group of 60-65 years, in pre-dialysis group majority were in age group of 55-65 years and in dialysis group it was 60-65 years. The difference was not significant statistically. Mean was 54.2±13.2 years. The study by Obinna Onodugo *et al* [16], had majority in the age group of 20-29 years which is younger than the current study and the study by Preeti Chandra *et al*[17] had mean age of 59.5±14.7, this is higher than our study.

Gender

In the current study there were majority males (62%). In the pre-dialysis group there were 66% and in dialysis group 58%. The difference was not significant statistically.The study by Obinna Onodugo *et al* [16], had majority females while in the current study it was males and The study by Preeti Chandra *et al* [17] and the study by Thapa L [18] had majority male patients this is similar to the current study. but the percentage was higher in the current study (62%).The study by H. Makimoto *et al* [19] had 53% males which is less than the current study.

Postural giddiness

Postural giddiness was present only among 33%, among that 16% had in pre-dialysis group and 50% among dialysis group. The difference was statistically significant.The study by H. Makimoto *et al*. [20] had seen that sympathovagal balance was not affected by CKD.

QTc prolongation

QTc prolongation was present among 43%, in the predialysis group it was 30% and in dialysis group 56%. The difference was significant statistically.

Postural Hypotension

Postural Hypotension was present among 66% patients, in the predialysis group it was 54% and in dialysis group its 78%.

The difference was significant statistically. The study by Obinna Onodugo *et al* [16], had orthostatic hypotension among 13.8% while in our study it was 64% and the study by Beata Januszko-Giergielewicz [21] had 37% patients with hypotension while in our study it was more.

Heart Rate Variability

Heart Rate Variability was present among 99% patients. In pre dialysis group it was 98% and 100% in dialysis group. The difference was significant statistically.

The study by Obinna Onodugo *et al* [16], had variability of heart rate among 80% while in our study in predialysis group it was 98%. The study by Obinna Onodugo *et al*, had statistically significant results and the study by Yu-Hsiang Chou [22], in their study found that heart rate variability increased with severity of CKD this is similar to the current study.

SBP (supine)

Mean SBP (supine) was 128±9.08 among predialysis group and in dialysis group it was 125.5±12.23, difference was not statistically significant. The study by Carlos Alberto de Oliveira *et al.* [23] had mean SBP in the CKD group to be 150.3 ± 23.4 mmHg while in our study in the predialysis group it was 128±9.08 which was much less. The study by H. Makimoto *et al* [19] had mean SBP of 126 ± 19 this is comparable to the current study.

DBP (supine)

Mean DBP (supine) was 83±5.9 in predialysis group and in dialysis group it was 81.9±7.0, difference is not statistically significant.

- The study by Carlos Alberto de Oliveira *et al* [23], had mean DBP in the CKD group to be 93.6 ± 17.0 mmHg while in our study in the predialysis group it was 83±5.9 which was much less. This could be because all patients in the above mentioned study were hypertensive.
- The study by Yoshihiro Matsumoto [20] had mean DBP of 83 ± 15 it was comparable to the current study and the study by H. Makimoto *et al*. [98] had mean DBP of 70 ± 12 this is less in comparision to the current study.

SBP (standing)

Mean SBP (standing) was 113±15.0 in predialysis group and in dialysis group it was 118±13.6, difference was statistically significant.

- The study by Carlos Alberto de Oliveira *et al* [23], saw for variability in SBP on tilting of predialysis patients and normal controls, they found that the variability was no significant in predialysis group. However in the current study Mean SBP on standing in both groups the results are statistically significant.

DBP (standing)

Mean DBP (standing) was 76.3±7.7 predialysis group and in dialysis group it was 76.8±7.12, difference was statistically significant.

QT interval

Mean QT interval was 361.0±37.9 in predialysis group and in dialysis group it was 357±59, difference was statistically significant.

QTc interval

Mean QTc interval was 433±35.5 in predialysis group and in dialysis group it was 446.8±44.37 and difference was statistically significant.

- The study by Yoshihiro Matsumoto [20] had mean QTc interval at 1 year after dialysis to be 437, this is comparable to the current study predialysis values. The mean of QTc at 7years after dialysis was 445ms and this is comparable to the dialysis group of the current study. The difference was statistically significant similar to the current study.

Mean variability

Mean variability of heart rate was 11.98±3.86 in predialysis group and in dialysis group it was 11.180±3.403, difference was statistically significant.

- The study by Carlos Alberto de Oliveira *et al* [23], saw for variability in heart rate on tilting of predialysis patients and normal controls, they found that the variability was significant in predialysis group. Similar findings are seen in the current study and the study by Preeti Chandra *et al* [17], saw that lower heart rate variability was associated with greater cardiovascular risks.

Conclusion

The Prevalence of Cardiovascular Autonomic Neuropathy is high in CKD patients. A significant correlation is present between QTc prolongation, lack of heart rate variability, postural hypotension in CKD predialysis stage and maintenance dialysis stage patients.The prevalence of CAN increases as the progression of Chronic Kidney Disease from predialysis stage to maintenance dialysis stage.So Heart rate variation (HRV) is the earliest manifestation in CAN patients and autonomic features that are associated with sympathetic nervous system dysfunction (postural hypotension) is relatively late complications.

- Simple bed side tests like postural hypotension, prolongation of QTc, lack of heart rate variability, should be performed in every CKD patient, for early detection of CAN.
- All these tests are bed side tests which are easy, cheap and safe and can be performed in any centre. Hence all CKD patients should be evaluated with simple bedside tests for early detection of CAN, so as to prevent further complications with early intervention and proactive treatment.

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