International Journal of Research in Medical Sciences
Behera BP. Int J Res Med Sci. 2020 May;8(5):1766-1773
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20201924

Original Research Article

Comparative study of serum electrolytes Na^+, K^+, Ca^{++} in patients of chronic kidney disease in relation to its severity

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Received: 10 March 2020
Accepted: 16 March 2020

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ABSTRACT

Background: Chronic kidney disease (CKD) is a worldwide public health problem. Globally, CKD is the 12th cause of death and the 17th cause of disability, respectively. Yearly incidence of ESRD in India is approximately 150-200 pmp.
Methods: The observational study was conducted in Department of General Medicine, Pandit Raghunath Murmu Medical College Hospital, Baripada between May 2018 and January 2019. 244 patients of Chronic Kidney Disease above 15 years of age satisfying the inclusion and exclusion criteria were included in the study.
Results: Study group constitutes 64.34% (157) of male and 35.66% (87) of female patients with M:F of 1.8:1. The average age of the patients in the study was 55.91±12.49 yrs. 42.21% (103) of the patients were between 46 and 60 years of age. Maximum number of cases (190 cases) (77.87%) are in stage 4 and 5 with e-GFR <30 ml/ min. The average serum electrolytes in this study group for serum sodium, potassium, calcium are 137.31±10.05 mEq/L, 4.12±1.48 mEq/L and 1.10±0.19 mmol/L respectively. When association of hypokalemia with risk factor (known and unknown) is compared, chi-square value found to be 13.664 (p=0.0002) which is statistically extremely significant.
Conclusions: Authors found significant number of cases, more commonly younger patients, presented with atypical manifestations having no specific etiology; the cause may be defect in rennin-angiotensin system or, may be genetic or, may be environmental.

Keywords: Atypical hyponatremia, Atypical hypokalemia, Atypical hypocalcaemia, Chronic kidney disease, Glomerular filtration rate

INTRODUCTION

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR).[1] Chronic kidney disease (CKD) is a universal public health problem, both for the number of patients and cost of treatment involved. Worldwide, CKD is the 12th cause of death and the 17th cause of disability, respectively.[2] Estimated from population data, about 6% of the adult populations in United States have CKD stage 1 and 2; and 4.5% have CKD stage 3 and 4.[1]

Its prevalence is high in India with a study showing 229/million population suffering from end stage renal disease (ESRD).[3] The prevalence of ESRD and patients on renal replacement therapy (RRT) has increased over last twenty years.[4] CKD prevalence has been reported between 0.16% and 0.79% in community-based studies, designed to detect stage 3 CKD or worse; and the real prevalence of CKD is higher than the reported number.[4-6] The ESRD incidences have been reported to be 160-232 per million populations (pmp) and the projected ESRD prevalence was 785–870 pmp.[3,4,7] "Screening and Early Evaluation of Kidney Disease" (SEEK), a community-based voluntary health screening program started in India

in 2006 with tests serum creatinine and urine analysis, reported a very high prevalence of 17.4% of CKD (unpublished and presented in the Annual Conference of the Indian Society of Nephrology) using an abbreviated modified diet in renal disease (MDRD) formula, a glomerular filtration (GFR) estimation formula.[2] In summary, from the database of CKD registry of India, the yearly incidence of ESRD in India is approximately 150-200 pmp with diabetes mellitus as an important cause of CKD in approximately 30-40% of the cases.[8]

Most common causes of CKD include diabetic nephropathy, glomerulonephritis, HTN associated CKD, autosomal dominant polycystic kidney disease (ADPKD) and other cystic and tubulointerstitial nephropathy accounting 90% of the CKD disease burden worldwide.[1]

Decrement in GFR progress to host of excretory, metabolic and endocrine functions abnormalities causing wide range of clinical symptoms of fluid and electrolytes disturbances, hematological- immunologic abnormalities, endocrine metabolic disturbances, cardiovascular pulmonary disturbances and different other systemic abnormalities. Electrolytes disturbances are one of the key features of CKD which become prominent as the disease advances. Hyponatremia, hyperkalemia, hypocalcaemia, hyperphosphatemia are the main electrolytes abnormalities observed.[9]

Authors come across a large number of patients with chronic kidney disease with abnormal serum electrolyte levels in this institution of P. R. M. Medical College, Baripada. All types of abnormalities are noticed hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcaemia etc.

As these being unpublished facts, we want to carry out a study, first of this type in this new college, to see the array of electrolyte abnormalities in this patients of chronic kidney disease and try to find out if any associative cause works.

METHODS

The observational study was conducted in Department of General Medicine, Pandit Raghunath Murmu Medical College Hospital, Baripada. The patients of chronic kidney disease who had attended to the department of general medicine OPD and who were admitted to department of general medicine, Pandit Raghunath Murmu Medical College Hospital, Baripada between May 2018 and January 2019 were enrolled in this study.

Inclusion criteria

- All patients of Chronic Kidney Disease above 15 years of age satisfying the following criteria were included in the study. Criteria for diagnosis of Chronic Kidney Disease were as given by- National kidney foundation: K/DOQI clinical practice guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification.[10]

CKD is defined as the presence, for at least 3 months, of evidence of kidney damage with an abnormal GFR or alternatively, by a GFR $\leq$60 ml/min /1.73m^2 BSA.[10]

Kidney damage is evidenced by,

- Proteinuria >300mg/day OR
- Pathological abnormality found in histopathological study OR
- Renal imaging study (USG) showing bilateral contracted kidneys <9.0 cm with thinned parenchyma and reduced corticomedullary differentiation.

Exclusion criteria

- Patients aged below 15 years of age
- Patients on haemodialysis

Among 244 CKD patients were included in the study. The study population was divided into three groups.

- Group A → Patients with mild CKD (n=109) (S. Creatinine =1.5-3.0 mg/dl).
- Group B → Patients with mild to moderate CKD (n=85) (S. Creatinine =3-6.0 mg/dl).
- Group C → Patients with advanced CKD (n=50) (S. Creatinine >6.0 mg/dl).

Investigations

All patients had undergone thorough clinical examination and laboratory investigations like complete blood counts, serum urea and creatinine, serum sodium, serum potassium, serum calcium, serum chloride, blood sugar and urine analysis. Ultrasonography of abdomen was done on every patient. The eGFR was calculated according to the CKD- EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, 2009. e-GFR was graded G1, G2, G3a, G3b, G4 and G5 as per the KDIGO 2012 guidelines.[1]

Statistical analysis

The statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 21.0. Univariate analysis was used in description of demographic characteristics of the study population. Discrete variables were presented as frequency and percentages. Continuous variables were presented as means and standard deviation (SD) for unpaired data; Student t-test was used to compare mean values (for two groups). Pearson's correlation was used to determine association between eGFR and other variables. Chi-square test with Yate's correction, two tailed Fisher's test was used to determine the significant associations

between categorical variables. p value <0.05 was considered statistically significant and <0.001 was considered as statistically extremely significant.

RESULTS

During the study period, 244 patients with chronic kidney disease attended to Medicine OPD and admitted in medicine ward of PRM MCH, Baripada, fulfill inclusion and exclusion criteria. All the cases were studied for the clinical presentation, risk factors and laboratory parameters.

The sex distribution among 244 patients with chronic kidney disease which constitutes 64.34%(157) of male and 35.66%(87) of female with M: F of 1.8:1. The age range was from 20 to 95. The average age of the patients in the study was 55.91±12.49 years. The average age of the male patients in the study was 55.75±13.06 years. The average age of the female patients in the study was 56.21±11.44 years (Figure 1).

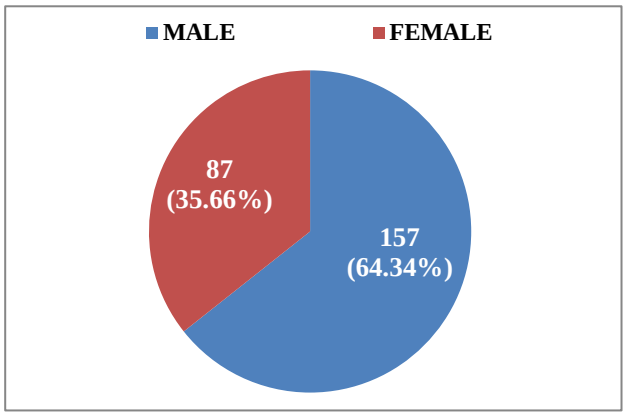

Figure 1: Sex distribution.

Age distribution of the chronic kidney disease patients in this study group; 42.21%(103) of the patients were between 46 and 60 years of age followed by 28.69%(70) of the patients were between 46 and 60 years of age; majority being in the middle age group which is a worrisome issue (Table 1).

Table 1: Age distribution (years).

	n	%
15-30	8	3.28%
31-45	51	20.90%
46-60	103	42.21%
61-75	70	28.69%
>75	12	4.92%
Total	244	100%

Figure 2 show 36.07% CKD cases had determined etiology like hypertension (32.38%), diabetes (2.87%), adult polycystic kidney disease (1.23%), obstructive nephropathy (1.23%) and medullary sponge kidney (0.41%); and rest of the 63.93% cases had undetermined etiology.

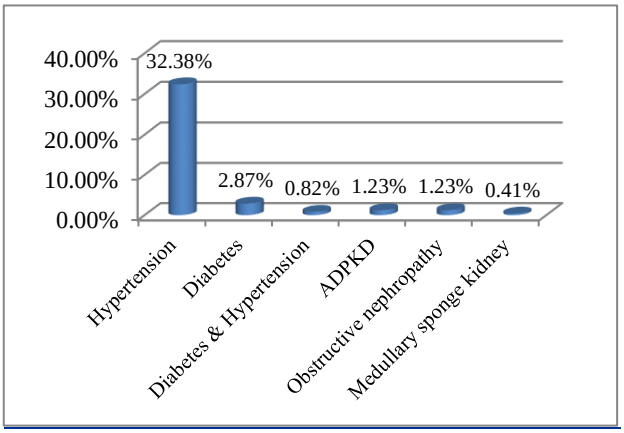

Figure 2: Etiology of chronic kidney disease.

Table 2 shows 77.87% (190 cases) of the patients in this study group belong to stage 4 and stage 5 chronic kidney diseases.

Table 2: Chronic kidney disease stage based on eGFR.

	n	%
Stage 1 (eGFR > 90 ml/min)	0	0.00%
Stage 2 (eGFR 60-89 ml/min)	0	0.00%
Stage 3a (eGFR 45-59 ml/min)	6	2.46%
Stage 3b (eGFR 30-44 ml/min)	48	19.67%
Stage 4 (eGFR 15-29 ml/min)	104	42.62%
Stage 5 (eGFR <15 ml/min)	86	35.25%
Total	244	100%

Serum urea levels in chronic kidney disease patients (Figure 3). Figure 4 shows, 109(44.67%) patients belong to mild CKD (group-A), 85(34.84%) patients belong to moderate CKD (group-B), 50(20.49%) patients belong to severe CKD (group-C) in this study group. Hyponatremia are seen in 34.84% compared to hypernatremia in 17.21% in this study group (Figure 5). Hypokalemia is seen in 36.89% compared to hyperkalemia in 18.03% in this study group (Figure 6). Hypocalcaemia is seen in 70.08% compared to hypercalcemia in 7.38% in this study group (Figure 7). Hypochloremia is seen in 36.89% compared to hyperchloremia in 21.31% in this study group (Figure 8).

On comparing various indices between the three groups of chronic kidney disease patients, there is a significant decrease in hemoglobin (p=0.0397 [A vs. B], p=0.0001 [A vs. C, B vs. C]), and a rise in blood urea (p=0.0001) and serum creatinine (p=0.0001). There is significant increase (p<0.05) in systolic and diastolic blood pressure, comparing between mild to severe CKD patients. On comparing different serum electrolyte parameters between three groups of chronic kidney patients, authors observed significant increase in serum potassium

(p=0.0433 [A vs. B], p=0.0001 [A vs. C, p=0.0047 [B vs. C]), and chloride level (p<0.05) (Table 3). The average serum electrolytes in this study group for serum sodium, potassium, calcium, chloride are 137.31±10.05 mEq/L, 4.12±1.48 mEq/L, 1.10±0.19 mmol/L and 98.01±10.42 mEq/L respectively.

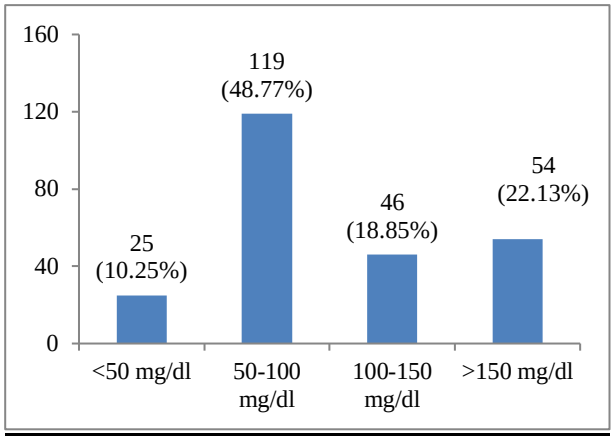

Figure 1: Urea levels (mg/dL) in CKD patients.

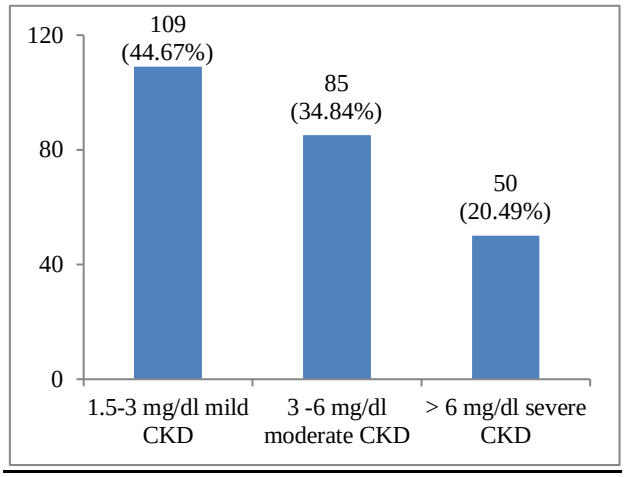

Figure 4: Creatinine levels (mg/dL) in CKD patients.

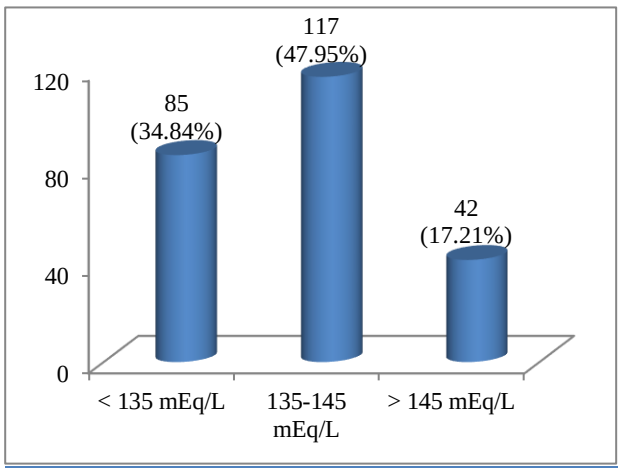

Figure 5: Serum sodium levels (mEq/L) in CKD patients.

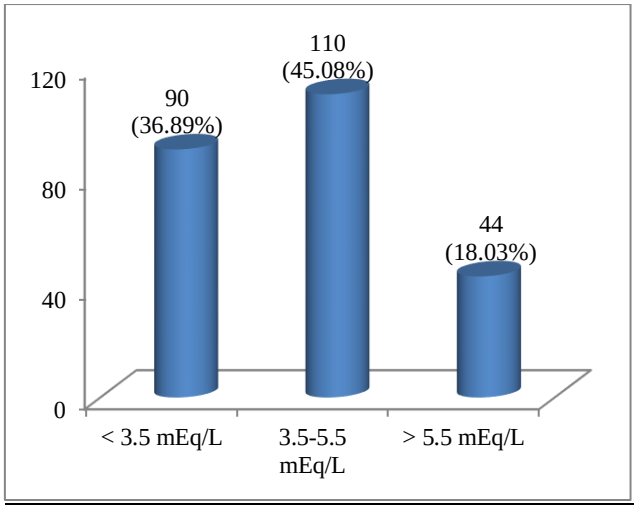

Figure 6: Serum potassium levels (mEq/L) in CKD patients.

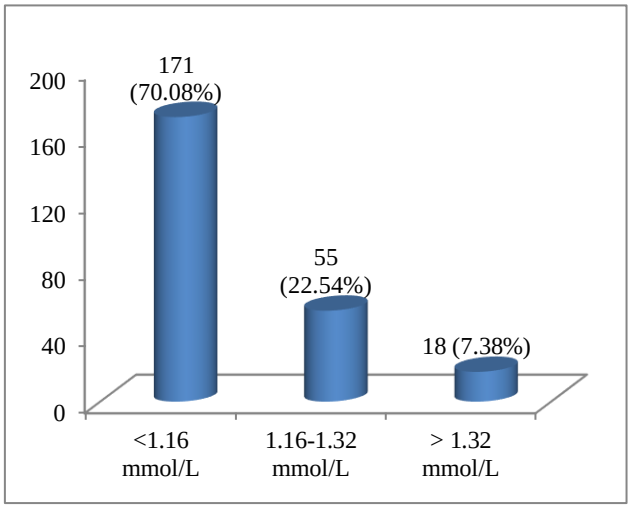

Figure 7: Serum ionized calcium levels (mmol/L) in CKD patients.

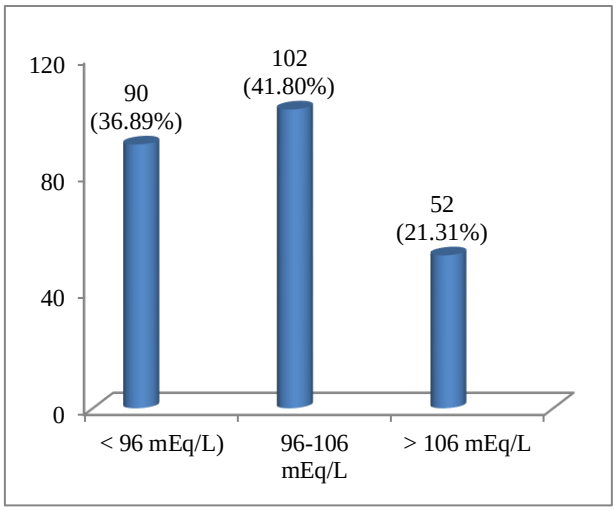

Figure 8: Serum chloride levels (mEq/L) in CKD patients.

Table 3: Association of hematologic indices with severity of CKD patients.

Indices	Mild (A) (mean± SD) (n=109)	Moderate (B) (mean±SD) (n=85)	Severe (C) (mean± SD) (n=50)	p-value (A vs. B)	p-value (A vs. C)	p-value (B vs. C)
Age (years)	57.26±11.11	57.59±12.91	50.12±13.12	0.8486	0.0005	0.0016
Systolic BP (mm Hg)	131.76±27.96	135.84±31.50	145.08±28.20	0.3414	0.0061	0.0897
Diastolic BP (mm Hg)	80.29±14.50	82.19±16.48	85.80±13.14	0.3949	0.0234	0.1888
Blood urea (mg/ dL)	63.4220.30	112.50±34.27	196.87±64.40	0.0001	0.0001	0.0001
Serum creatinine (mg/ dL)	2.21±0.40	3.98±0.75	9.00±2.42	0.0001	0.0001	0.0001
Hemoglobin (gm %)	8.55±2.50	7.81±2.43	6.13±2.03	0.0397	0.0001	0.0001
Serum sodium (mEq/L)	137.43±10.39	137.88±10.53	136.10±8.43	0.7664	0.4290	0.3104
Serum potassium (mEq/L)	3.74±1.35	4.14±1.37	4.90±1.66	0.0433	0.0001	0.0047
Serum calcium (mmol/L)	1.08±0.14	1.13±0.24	1.10±0.21	0.0710	0.4791	0.4644
Serum chloride (mEq/L)	95.41±10.17	99.72±10.76	100.79±9.15	0.0048	0.0017	0.5570

Table 4: Correlation coefficient of eGFR with different variables.

Variables	Pearson Correlation coefficient (r)	p-value
Age	0.011	0.8643
Systolic BP	-0.150	0.0190
Diastolic BP	-0.116	0.0704
Blood urea	-0.736	< 0.00001
Serum creatinine	-0.778	< 0.00001
Hemoglobin	0.312	<0.00001
Serum sodium	-0.042	0.5137
Serum potassium	-0.281	< 0.00001
Serum calcium	-0.108	0.0923
Serum chloride	-0.736	< 0.00001

Table 4 depicted the correlation coefficient of eGFR with different variables including the electrolytes. Negative Pearson's correlation coefficient value indicate the level of systolic BP, diastolic BP, urea, creatinine, sodium, potassium, calcium, chloride increase with the decline of GFR and positive Pearson's correlation coefficient value indicate the level of hemoglobin decrease with the decline of GFR. On correlating eGFR with various parameters, statistical significance was observed with systolic blood pressure (r= -0.150, p= 0.0190), B. Urea (r= -0.736, p= 0.00001), S. Creatinine (r= -0.778, p= 0.00001), hemoglobin (r= 0.312, p= 0.00001), serum potassium (r= -0.281, p= 0.00001), serum chloride (r= -0.736, p= 0.00001).

Table 5: Comparison of Atypical vs. Typical electrolyte abnormalities in CKD patients.

Electrolytes		Risk factor association				Chi-square test value with Yate's correction	p-value
Serum sodium	Typical hypernatremia (N=42)	known	(%)	unknown	(%)	0.597	0.4398
		17	6.97%	25	10.25%		
	Atypical hyponatremia (N=85)	known	(%)	unknown	(%)		
		27	11.07%	58	23.77%		
Serum potassium	Typical hyperkalemia (N=44)	known	(%)	unknown	(%)	13.664	0.0002
		24	9.84%	20	8.20%		
	Atypical hypokalemia (N=90)	known	(%)	unknown	(%)		
		19	7.79%	71	29.10%		
Serum calcium	Typical hypercalcemia (N=18)	known	(%)	unknown	(%)	3.658	0.0558
		11	4.51%	7	2.87%		
	Atypical hypocalcaemia (N=171)	known	(%)	unknown	(%)		
		60	24.59%	111	45.49%		
Serum chloride	Atypical hyperchloremia (N=52)	known	(%)	unknown	(%)	2.335	0.1265
		23	9.42%	29	11.89%		
	Typical hypochloremia (N=90)	known	(%)	unknown	(%)		
		27	11.07%	63	25.82%		

Table 6: Comparison of atypical vs. typical electrolyte abnormalities in CKD patients with age.

Electrolytes		Age (< 45 years = 59 cases and > 45 years = 185 cases)				p-value (two tailed fisher's test)
Serum sodium	Typical hypernatremia (n=42)	< 45 years	(%)	> 45 years	(%)	0.0044
		4	1.64%	38	15.57%	
	Atypical hyponatremia (n=85)	< 45 years	(%)	> 45 years	(%)	
		28	11.48%	57	23.36%	
Serum potassium	Typical hyperkalemia (n=44)	< 45 years	(%)	> 45 years	(%)	0.0454
		8	3.28%	36	14.75%	
	Atypical hypokalemia (n=90)	< 45 years	(%)	> 45 years	(%)	
		32	13.11%	58	23.77%	
Serum calcium	Typical hypercalcemia (n=18)	< 45 years	(%)	> 45 years	(%)	0.2863
		3	1.23%	15	6.15%	
	Atypical hypercalcemia (n=171)	< 45 years	(%)	> 45 years	(%)	
		51	20.90%	120	49.18%	
Serum chloride	Atypical hyperchloremia (n=52)	< 45 years	(%)	> 45 years	(%)	0.0003
		3	1.23%	49	20.08%	
	Typical hypochloremia (n=90)	< 45 years	(%)	> 45 years	(%)	
		28	11.48%	62	25.41%	

Comparison of atypical vs. typical electrolyte abnormalities in CKD patients in this study group. When association of hyponatremia with risk factor (known and unknown) is compared, chi-square value found to be 0.597 (p=0.4398) which is not statistically significant. When association of hypokalemia with risk factor (known and unknown) is compared, chi-square value found to be 13.664 (p=0.0002) which is statistically extremely significant. When association of hypocalcaemia with risk factor (known and unknown) is compared, chi-square value found to be 3.658 (p=0.0558) which is not statistically significant. When association of hypochloremia with risk factor (known and unknown) is compared, chi-square value found to be 2.335 (p=0.1265) which is not statistically significant (Table 5).

When association of hyponatremia with age (<45 years and >45 years) is compared, p value by two tailed Fisher's test was found to be 0.0044 which is statistically extremely significant. When association of hypokalemia with age (<45 years and >45 years) is compared, p value by two tailed Fisher's test was found to be 0.0454 which is statistically significant. When association of hypocalcaemia with age (<45 years and >45 years) is compared, p value by two tailed Fisher's test was found to be 0.2863 which is statistically not significant. When association of hypochloremia with age (<45 years and >45 years) is compared, p value by two tailed Fisher's test was found to be 0.0003 which is statistically extremely significant (Table 6).

DISCUSSION

The current study was cross sectional study done at PRM MCH, Baripada, between May 2018 and January 2019 to find out the different electrolytes disturbances found in different stages of CKD, to find out its relation with the severity of the disease and to find out its aetiologies.

In this study group, 64.34%(157) of patients were male and 35.66%(87) of patients were female with M: F of 1.8:1. Maximum number of cases (190 cases) (77.87%) are in stage 4 and 5 with eGFR < 30 ml/ min. 112(71.34%) male patients had stage 4 and stage 5 chronic kidney disease. As per the patients enrolled in the database of "The Indian CKD Registry", a voluntary reporting body of CKD patients data, initiated in June 2005, 70% of them are males and 73.6% of them have CKD stage 4 and 5.[8]

The average age of the patients in this study was 55.91±12.49 years. Most of the patients (185 cases, 75.82%) are above 45 years of age, but still 24.18%(59 cases) of the CKD patients were below 45 years of age, which was significant in number. According to Suhnggwon Kim et al, average age of the CKD patient was with mean 50.5 years and standard deviation 11.1 years.[11] Advanced age is a well-known risk factor for chronic kidney disease; Imai E et al.[12]

In this study group, 36.07% had determined causes of chronic kidney disease and hypertension was the most common (32.38%) etiology associated with chronic kidney disease. Surprisingly, only 2.87% patients of chronic kidney disease had diabetes; and rest of the 63.93% cases had undetermined etiology, which is an important finding. Patients in this category presented more frequently with few symptoms until late in the disease. These patients have unexpected electrolytes disturbances like hyponatremia, hypokalemia,

hypocalcaemia, hypochloremia. Dietary habits, use of indigenous medicines, herbal products, environmental factors and possibility of industrial contamination must be considered as distinctive risk factors; in this population of this part of Odisha; though it remains unknown whether any of these have an adverse effect on renal function or not. Jha V et al, Lai MN et al, have already established an association of chronic kidney disease with herbal medicines.[13,14] CKD of undetermined etiology has also been reported from other parts of South Asia and amongst South Asians living in UK.[15] In Srilanka, Bandara et al, studied male paddy farmers of poor socioeconomic status who present with progressive non-proteinuric renal failure; concluded fluoride, aluminum, cadmium, environmental toxins such as residual pesticides, and cyanobacteria in drinking water as probable etiologies.[16] Maternal malnutrition and resultant low birth weight in the offspring might predispose to CKD, possibly due to low nephron numbers. Some types of hereditary or acquired tubulointerstitial disease may cause serum electrolyte abnormalities in CKD which is required to be evaluated. But since most of the cases of undetermined etiology in this area are in low socioeconomic status and mostly present in late stages, it is very difficult or a challenge in this counterpart to evaluate the exact etiology. 36.89% of cases were found to be hyponatremic and 17.21% were found to be hypernatremic in this study group. In earlier stages of CKD, the serum sodium level was not depleted below the clinical reference range; however with progression of CKD from mild to severe form, hyponatremia occurred. Yee J et al, showed that hyponatremia usually occurs with severe CKD; usually with GFR below 10 ml/min.[17]

S. Korgaonkar et al, a cohort study in US suggests that patients who have CKD and low or even low-normal serum potassium are at a higher risk for dying than those with mild to moderate hyperkalemia.[18] A significant proportion, 36.89% of cases, in this study group, was found to be hypokalemia. Association of hypokalemia with unknown risk factor is statistically extremely significant, as chi-square value was found to be 13.664 with p=0.0002. Though, hypokalemia is not common in CKD, in this study, more than one third of the cases are hypokalemia. Hypokalemia in CKD usually might be due to reduce dietary potassium intake, especially in association with excessive diuretic therapy or concurrent GI losses. Inappropriate prescription of diuretics might be responsible for it. Verification of the prescription and the drug should always be done to correlate this. Excessive carbohydrate rich meal in a malnourished patient can provoke hypokalemia due to stimulus of endogenous insulin. Especially in starvation, hypokalemia can occur. Intestinal loss of potassium due to diarrhea is a globally important cause of hypokalemia in light of the world wide prevalence diarrheal disease, especially in this part of country. Hypokalemia can also occur as a result of primary renal potassium wasting in association with other solute transport abnormalities. However after, whatever the evaluation were done which is possible by us, authors did not get any such cause. In this study, the serum potassium level is increasing with the severity of the chronic kidney disease, which is statistically significant.

Hypocalcemia was found in 70.08% of cases and hypercalcemia in 7.38% cases. GFR hypercalcemia develops when the input of calcium to the circulation exceeds its removal by the kidneys filtration rate independent of the tubular calcium reabsorption rate. This readily occurs in patients with CKD.[19] Association of atypical hypocalcaemia with undetermined etiology is statistically insignificant. So may be the hormone involving the calcium and phosphorous metabolism is not involved in this atypical presentation. The defect in the rennin-angiotensin system may be involved in the atypical presentation. In this study, authors observed that, atypical hyponatremia, atypical hypokalemia and atypical hypochloremia are more common in younger age group i.e. below 45 years of age; which is statistically significant.

CONCLUSION

Authors commonly come across CKD patients with precipitating factors like hypertension, diabetes, h/o renal disease, recurrent UTI, family history and all others. However, cases with atypical manifestations found to have no specific etiology. In atypical patients some interesting observation is made in relation to cause, with three possible sites of defect; first one is rennin-angiotensin system defect, second one is genetic and third one is environmental (particularly water intake in work place). In this part of the land, authors observed in this study, the younger patients with chronic kidney disease present more commonly with atypical hyponatremia, atypical hypokalemia, atypical hypocalcaemia and atypical hypochloremia. Future studies should be done on this aspect to know the etiology.

ACKNOWLEDGEMENTS

Authors would like to thank Dr. Arunima Pattanaik, Dr. Sambit Parida, Dr. Soumyasmruti Parida, Nibedita Mantry, Swarnalata Samal, Saraswati Sahoo, Rubina Soren, Mamata Nayak, Suchismita Patra, staffs of Department of Medicine, PRM Medical College, Baripada, Odisha, India for their cooperation in collection of data.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Behera BP. Comparative study of serum electrolytes Na^+, K^+, Ca^{++} in patients of chronic kidney disease in relation to its severity. Int J Res Med Sci 2020;8:1766-73.