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A study of serum electrolytes and calcium in chronic kidney disease in rural Maharashtra

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Abstract
Background: Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for >3 months. With progressive loss of kidney function, derangements in electrolytes and acid-base inevitably occur and contribute to poor patient outcomes. The present study was undertaken to study the serum levels of calcium and electrolytes in various stages of CKD.
Method: This study was conducted in 150 newly diagnosed cases of CKD admitted in Medicine ward and those visiting OPD of Tertiary Care Hospital, Shri Vasantarao Naik Government Medical College, Yavatmal during a period from 1 February 2018 to 31 October 2019. These patients fulfilled the criteria set by National Kidney Foundations' Kidney Disease Outcome Quality Initiative for diagnosing CKD. They were studied and evaluated clinically, and laboratory investigated.
Results: Most of the patients were presented in stage III (34.7%) followed by in stage V (32.7%) and stage IV (30%). As CKD deteriorates, there was worsening in renal echogenicity in ultrasonography. The serum albumin was found to be decreased and urine albumin increased as CKD progresses. In different stages of CKD, the variation in level of serum sodium was insignificant (p>0.05), while that of increase in potassium and decrease in calcium as CKD deteriorates was significant (p<0.05).
Conclusion: Because of negligence and lack of awareness, most of the patients are detected in advanced stages of CKD and is associated with wide electrolyte and calcium abnormalities. Therefore, it is necessary to identify these patients in their early stages of CKD along with prompt and early recognition of derangements in electrolytes and calcium.

Keywords: CKD, electrolytes, calcium, ultrasonography, albumin, abnormalities

1. Introduction
Chronic kidney disease (CKD) has become a global epidemic with an estimated prevalence of 14% in the United States and 5–15% throughout the world [1, 2] and the expected incidence is approximately 5-8% every year [3]. CKD is associated with an increased risk of adverse cardiovascular outcomes, progression to end-stage renal disease (ESRD), and decreased survival. As the kidneys play a central role in the regulation of body fluids, electrolytes, and acid–base balance, CKD and ESRD predictably result in multiple derangements including hyperkalemia, metabolic acidosis, and hyperphosphatemia which, in turn, lead to serious complications including muscle wasting, bone-mineral disorder, vascular calcification and mortality [4].
Moreover, CKD is classified based on cause, glomerular filtration rate (GFR) category, and albuminuria category (CGA). Because of the central role of GFR in the pathophysiology of complications, the disease is classified into five stages on the basis of GFR [5]. CKD, also known as chronic renal disease, is a progressive loss in renal function over a period of months or years. It is a long-term condition caused by damage to both kidneys. The decrease in renal function interferes with the kidney's ability to maintain fluid and electrolyte homeostasis. In patients with CKD, including those undergoing maintenance hemodialysis therapy and those with pre-dialysis CKD stages various abnormalities related to electrolytes, mineral and bone disorders have been implicated as novel risk factors of morbidity and mortality [6, 7].
Importantly, the long-term effects of these derangements on soft tissue calcification have become an area of growing concern in the care of CKD patients. Early recognition of and intervention for fluid electrolyte and mineral disturbances may help prevent morbidity and mortality in CKD patients. The prevention of these imbalances requires proactive education of the patients, doctors, and caregiver to foster adequate fluid and nutritional intake and

adherence to periodic laboratory and clinical screening for early detection and correction the electrolyte and mineral imbalances [4, 8]. In our society, patients with CKD are on an increasing trend. Among them there is high prevalence of various dyselectrolemias which lead to increased morbidity and mortality. This study was conducted to know about the relevance of dyselectrolemias in these patients.

Materials and Method

This observational descriptive cross-sectional study was conducted in 150 newly diagnosed cases of CKD admitted in Medicine ward and those visiting OPD of Tertiary Care Hospital in Maharashtra during a period from 1 February 2018 to 31 October 2019. All patients had been informed about the purpose and procedures of this study, for which they had given a written consent in accordance with the guidelines set by the Declaration of Helsinki. The study was initiated only after approval by Regional Institutional Ethics Committee. Patients with CKD- on renal replacement therapy, on diuretics, ACEIs and ARBs, on mineral and electrolye supplements and binders, patients with CKD whose ultrasonography showing size of more than 8 cm, pregnant women, patients with disorders of thyroid, adrenal, parathyroid glands, acute kidney injury (AKI) and those suspecting of having AKI were excluded from the study.

Socio-demographic profile of the patients and clinical symptoms among the CKD patients were recorded. Detailed clinical examination of candidates was done, and major findings were noted. Body Mass index along with general and systemic examination findings were tabulated. For laboratory investigations blood was collected on admission and serum sodium, potassium and calcium were estimated from non hemolysed sample. Investigations such as CBC-HB, RBSL, RFT - blood urea and serum creatinine, LFT-serum albumin, serum electrolytes - serum sodium and serum potassium, serum calcium (total), urine routine examination- urine albumin, ultrasonography of abdomen with pelvis and GFR eMDRD were done.

Serum Electrolytes and Calcium Sampling

3ml of blood sample was collected in a plain container by antecubital venupuncture under strict aseptic precautions from study participants. Blood was allowed to stand for 45 min at room temperature to allow complete clotting and clot retraction. Serum was then analyzed in autoanalyzer. Serum electrolytes and calcium was determined using NANOLAB240, Trivitron Healthcare analyser which uses enzymatic colorimetry. After the calibration and standardization of analyser, the normal reference range of various parameters used in this study is given below.

Parameters	Normal reference range
Serum Creatinine	0.8-1.3 mg/dL
Blood Urea	15-40 mg/dL
Serum Sodium	135-145 mmol/L
Serum Potassium	3.5-5 mmol/L
Serum Calcium (Total)	8.5-10.2 mg/dL
Serum Albumin	3.5-5 mg/dL

Those having deranged renal function test were advised to have ultrasonography of abdomen and pelvis. Ultrasound of the kidneys and liver was performed using the standard B Mode grey scale ultrasound with sector curved array transducer of 3.5-5 MHz. The parenchymal echogenicity of both the liver and kidney was assessed by applying low tissue harmonic and speckle reduction imaging to reduce the interobserver bias. The gain and time gain compensation were adjusted manually. The longitudinal length was measured in a section visually estimated to represent the largest longitudinal section. The width and thickness were measured in a section perpendicular to the longitudinal axis of the kidney as assessed from the longitudinal image. Classification of parenchymal echogenicity of kidney according to Hricak *et al*. was done [9]. Glomerular filtration rate was calculated using equation MDRD:

eGFR (mL/min per 1.73 m2) = 186.3 × PCr (e−1.154) × age (e−0.203) × (0.742 if female) × (1.21 if black)

Subjects were divided into various stages depending upon GFR using KDIGO 2012 guidelines. Urine albumin was detected using Urine Dipstick Method- measures albumin concentration via a colorimetric reaction between albumin and tetrabromophenol blue producing different shades of green according to the concentration of albumin in the sample.

Statistical Analysis

Descriptive statistics was used to summarize patients' demographics and survey responses. Data were presented as means ± standard deviation for continuous variables and as proportions for categorical variables. $p<0.05$ was considered as statistically significant. The software package IBM SPSS statistics (version. 20, IBM SPSS Statistics, Chicago, IL) was used for all calculations. Chi-square/Fischer exact test was used for categorical data to test for association.

Observation and Results

A total of 150 cases were studied in present study, out of which majority belonged to age group of 41 to 60 years (42%), followed by 61 to 80 years (38%). Mean age was found to be 55.58±14.17 years, ranged from 23-88 years with male preponderance (64.67%). Most of the cases (46%) were farmers from rural areas (64.67%) as shown in table 1.

Table 1: Socio-demographic profile of the patients

Socio-demographic details		Frequency	Percentage
Age groups (In years)	20-40	25	16.67
	41-60	63	42
	61-80	57	38
	>80	05	3.33
Gender	Male	97	64.67
	Female	53	35.33
Occupation	Daily wager	29	19.33
	Farmer	69	46
	Housewife	52	34.67
Residence	Rural	97	64.67
	Urban	53	35.33

The most common presenting complained was easy fatigueness (67.33%) followed by breathlessness (38%). Co-morbidities included hypertension (30%), diabetes mellitus (DM) (4.67%), hypertension and DM (5.33%) and other co-morbidities (14.67%) like coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), etc. 11 (7.33%) patients suffering from CKD gave positive family history. Out of 150 patients of CKD, 79 (52.67%) had

addictions, 83(55.33%) used well water and rest of 67 (44.67%) used tap water for drinking.

Majority of patients (51.33%) had normal physique with healthy BMI range from18.5-24.9. 36% of cases were overweight with BMI range 25-29.9. Rest 19 cases (12.67%) cases were underweighted. The mean BMI was 23.75±3.2415, ranged from 14.4-29.74. Most of the patients had pallor (68.67%) and 79 patients had high blood pressure (BP >140/90 mmHg). Rest of clinical findings were pedal edema (48%), flaps (13.33%), basal crepitations (22.67%) and raised JVP (21.33%).

Figure 1 show the stages of CKD based on MDRD formula of eGFR. Most of the patients was presented in stage III followed by in stage V and stage IV.

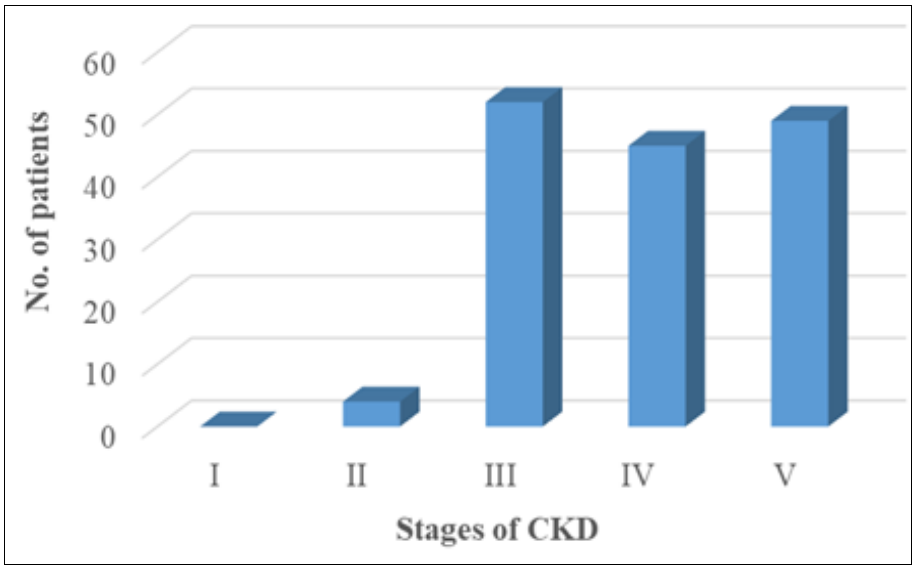

Fig 1: Stages of CKD based on MDRD formula of eGFR

Blood urea levels were found to be higher in 141 (94%) patients and normal in 9 (6%) patients whereas serum creatinine was raised in 138 (92%) of patients and normal in 9 (6%) patients. Among 150 patients of CKD, 68 (45.3%) had hypoalbuminemia (serum albumin <3.5 mg/dL) and 82 (54.7%) patients had albumin in normal range. All the patients had positive urine albumin value as trace 1, 2 and 3. Majority of patients (49 cases, 32.7%) had urine albumin value 2; followed by urine albumin level 1 (30%) and 31 (20.7%) had urine albumin level 3. In 25 patients (16.7%) traces of albumin were seen in urine. The mean values of all the elements are shown in table 2.

Ultrasonography grading based on renal parenchymal echogenicity were classified as 0, I, II, and III. No cases were having Grade 0. Majority of cases had Grade I on USG with 38.67%, followed by 33.33% had Grade III and remaining 28% had Grade II.

Table 2: Mean of blood urea, serum creatinine, serum and urine albumin, serum electrolytes and calcium

Variables	Mean ± SD	Min - Max
Blood Urea	96.570±63.62	23 - 338
Creatinine	4.403±3.807	1.2 – 18.1
Serum albumin	3.500±0.602	2 – 4.8
Urine albumin	1.725±0.796	0 (Trace) - 3
Sodium	132.727±10.11	106 - 165
Potassium	4.009±1.283	1.2 - 9
Calcium	8.518±0.964	6 – 10.6

There was no statistically significant correlation was found between socio-demographic profile of the patients and stages of CKD.

However, the correlation between blood urea, serum creatinine and serum albumin levels with stages of CKD was found to be very significant with p value <0.0001. All the patients were reported to have albuminuria. Higher levels of urine albumin were found to be associated with higher stages of CKD with a p value of <0.0001, (Table 3).

Table 3: Chi-squared association between levels of blood urea, serum creatinine, serum, and urine albumin with stages of CKD

Parameters		Stages of CKD				Total
		II	III	IV	V	
Blood urea level	Normal	02	09	01	00	12 (8%)
	Hyper	02	43	44	49	138 (92%)
Serum creatinine level	Normal	03	06	00	00	9 (6%)
	Hyper	01	46	45	49	141 (94%)
Serum albumin level	Hypoalbuminemia	00	14	17	37	68 (45.3%)
	Normal	04	38	28	12	82 (54.7%)

Urine albumin	TRACE	02	14	06	03	25
	1+	02	23	14	06	45
	2+	00	11	20	18	49
	3+	00	04	05	22	31

It was found that as stage of CKD progresses, grading on ultrasonography of medico-renal disease also increased. We found significant correlation between stages of CKD and USG grading with p-value <0.0001 as shown in table 4.

Table 4: Chi-squared association between USG grades and stages of CKD

USG grades	Stages of CKD				Total
	II	III	IV	V	
I	03	36	15	04	58 (38.7%)
II	01	12	19	10	42 (28%)
III	00	04	11	35	50 (33.3%)
Total	04 (2.7%)	52 (34.7%)	45 (30%)	49 (32.7%)	150 (100%)

Serum sodium, potassium, and calcium levels as hypo, normal and hyper were studied with reference to CKD stages as shown in table 5. There was no correlation was found between serum sodium level and stages of CKD (p=0.2527). A statistically significant p value was found out upon comparing various potassium levels (0.0232) and blood calcium levels (0.0270) with the stages of CKD.

Table 5: Chi-squared association between levels of electrolytes and calcium level with stages of CKD

Electrolytes		Stages of CKD				Total
		II	III	IV	V	
Sodium level (mmol/L)	Hypo (<135)	02	24	21	26	73 (48.7%)
	Normal (135-145)	02	28	22	18	70 (46.7%)
	Hyper (>145)	00	00	02	05	07 (4.7%)
Potassium level(mmol/L)	Hypo (<3.5)	03	19	15	09	46 (30.7%)
	Normal (3.5=5)	01	29	20	25	75 (50%)
	Hyper (>5)	00	04	10	15	29 (19.3%)
Calcium level (mg/dL)	Hypo (<8.5)	02	13	21	30	66 (44%)
	Normal (8.5-10.2)	02	36	23	18	79 (52.7%)
	Hyper (>10.2)	00	03	01	01	05 (3.3%)

The comparison of means of parameters such as sodium, potassium, calcium, urea, creatinine, serum and urine albumin and stages of CKD was studied by means of ANOVA as shown in table 6.

Table 6: ANOVA comparison of sodium, potassium, calcium, blood urea, creatinine, serum albumin and urine albumin with stages of CKD

Parameter	Stages of CKD				P value
	II	III	IV	V	
Serum Sodium	124.5±16.78	133.05±8.71	134.13±7.85	131.75±12.4	0.260
Serum Potassium	2.35±1.14	3.77±1.21	3.88±1.27	4.51±1.18	0.001
Serum Calcium	8.62±1.55	8.88±0.78	8.43±1.00	8.19±0.94	0.003
Blood Urea	48.75±23.71	57.43±30.82	84.6±39.67	153±69.58	<0.001
Serum creatinine	1.3±0.08	1.72±0.34	3.04±0.67	8.74±3.85	<0.001
Serum albumin	3.92±0.33	3.69±0.59	3.55±0.60	3.21±0.51	<0.001
Urine albumin	1.00±0	1.50±0.68	1.72±.071	2.36±0.74	<0.001

Discussion

In the present study, majority of patients belonged to the age group of 41-60 years with mean age of 55.58 years. The youngest patient was 23 years and the oldest 88 years of age. This shows the broad variation in age group highlighting the preponderance of CKD across a very large age group. We observed male preponderance with male to female ratio of 1.83:1. Majority of patients were farmers (46%) as this being a rural area. These results are similar to the study conducted by Pathak A *et al*. [10] and Sharma SK *et al*. [11]. Out of the 18 studies analysed by the National Kidney Foundations K/DOQI, 17 reported that the male sex was more at risk for CRF and 14 showed that the male sex was associated with a faster rate of progression to ESRD [12]. Hypertension was seen in 30% of patients while diabetes was observed in 4.67% and both diabetes and hypertension in 5.33% of cases. Remaining 14.67% cases showed other comorbidities like COPD, CVA, and IHD. This trend is similar to that reported by Pathak A *et al*. [10] and Agarwal SK *et al*. [13]. The cause of CKD was unknown in 90 cases in present study which is comparable with the other studies [14, 15]. Only 11 cases out of 150 gave positive family history of having CKD to other members. 52.67% of cases had a history of addiction. Most common presenting symptoms was fatigue (67.33%) followed by breathlessness (38%). Majority of patients on examination had pallor (68.67%) and high blood pressure (52.67%). These results are comparable with the study conducted by Pathak A *et al*. [10] and Sathyan P *et al*. [16]. We did not found any correlation between CKD stages and BMI, as similar to Zaman *et al*. study [17]. The lower BMI might not lead a diabetic patient

to develop CKD, but there are possibilities that CKD can lead the patient to experience reduced BMI.

In current study, blood urea was raised in all the cases. There was strong association of CKD stages with blood urea. Only 6% had normal serum creatinine values, rest had raised serum creatinine and association between serum creatinine rise and CKD stages was found to be statistically significant with p-value <0.001. Majority patients were in stage III of CKD with 34.7% of patients, followed by 32.7% of patients in Stage V. 30% of cases presented with stage IV CKD. These results are consistent with the observations made in the CKD registry of India report, where 48% presented in stage 5, while remaining stages in decreasing frequency. This reflects the lack of awareness about CKD among the public and the failure of medical practitioners to screen the at-risk population and to diagnose CKD at an early stage, which would enable appropriate treatment to be instituted so as to prevent or reduce the rate of progression of CKD. We found significant correlation between stages of CKD and USG grading with p-value <0.0001. The grading of renal echogenicity increases, as the CKD progresses. These findings are correlated with the study done by Liborio AB *et al*. [18] and Shivashankara VU *et al*. [19].

It was found in current study that serum albumin values were decreased in 45.33% cases of those having hypoalbuminemia, 14 were in stage II, 17 in stage III and 37 in stage V. As there is progression in CKD, i.e., when GFR<60 ml/min, there was increase in number of patients those having decreased serum albumin. The correlation was statistically significant with p-value of <0.001. Low level of serum albumin indicates a decline in circulating protein levels or serum protein concentrations, protein losses or inflammation. These findings are comparable with the study conducted by Lang J *et al*. [20]. Almost all of the patients had positive urine albumin. Majority of patients (49 cases, 32.7%) had urine albumin value 2; followed by 45 patients (30%) who had urine albumin level 1. In 25 patients (16.7%) traces of albumin were seen in urine. As stage of CKD progresses, there was also rise in urine albumin level, that is patients with urine albumin 3+ were found to be more in stage V than other stages and was absent in stage I. Similar findings are reported by Glassock RJ *et al*. [21].

The level of serum sodium was of low in 48.67% and normal in 46.67% cases. Only 7 cases had raised serum sodium values i.e., hypernatremia. The mean value observed in stage II CKD patients was 124.5±16.78. It was 128.95±26.09 in stage III patients and 134.13±7.85 in stage IV patients. We saw that there was more incidence of hyponatremia than hypernatremia. These findings are correlated with the other studies [22, 23]. Hyponatremia is a common complication in CKD patients and proper management of it is necessary to prevent morbidity and mortality. On comparing the various levels of serum sodium with different stages of CKD, we did not find any correlation between serum sodium levels and CKD stages. This finding is similar to the study done by Poudel K *et al*. [3] and Cole NI *et al*. [24]. In current study hypokalemia was seen in 30.67% cases and hyperkalemia in 19.33%. Out of 46 patients those were having hypokalemia (potassium <3.5 mmol/L), 3 patients were in stage II, 19 patients in stage III, 15 in stage IV and 9 patients were in stage V. Potassium was in normal range (potassium 3.5-5 mmol/L) in 1, 29, 20 and 26 patients in stages II, III, IV and V respectively. Hyperkalemia (potassium >5 mmol/l) was present in 4, 10 and 14 patients in stages III, IV and V respectively. These findings are similar to that done by Gilligan S *et al*. [25]. Serum potassium was found to be gradually raised with mean serum potassium in stage II patients was 2.35±1.14 which showed linear rise and in stage V cases mean serum potassium was 4.51±1.18. There was significant correlation of serum potassium rise and severity of CKD with p-value 0.001. As the stages of CKD gets worse the serum potassium value is also found to be raised. These findings are correlated with the earlier studies [3, 26].

Hypocalcemia is a known entity in patients with CKD. In present study, hypocalcemia was observed in 44% cases and hypercalcemia was seen in just 3.3% cases. 66 patients who had hypocalcemia were 2 patients of stage II, 13 patients of stage III, 21 patients of stage IV and 30 patients of stage V of CKD. Hypercalcemia in one patient each of stages IV and V of CKD. Serum calcium levels were 8.62±1.55 in stage II CKD; stage III was having 8.88±0.78; stage IV had 8.43±1.00; stage V CKD patients had value of 8.19±0.94. The gradual fall in the serum calcium level was seen. It can be postulated that hypocalcemia becomes prevalent as the severity of CKD increases. As there is deterioration of CKD, the level of serum calcium tends to fall. Statistically significant association was seen with p-value of <0.001. These finding are similar to the previous studies [3, 27, 28].

Limitations of Study

Present study was a hospital-based study, so this could overestimate the prevalence of various stages of CKD. As it is a cross- sectional study, we did not follow up the patient further and hence we did not know the mortality of these patients. Instead of following up after 3 months, we included this patient under the guidance of radiological imaging whose kidney size was less than 8 cm. Because of lack of investigations like renal biopsy, we did not know the etiology of CKD of those patients who had no hypertension or diabetes mellitus.

Conclusion

In the present study, majority of patients were in advanced stages of CKD, because of the negligence and lack of awareness and decreased accessibility to medical services. This is associated with wide electrolyte and calcium abnormalities which increases morbidity and mortality in them. Therefore, it is necessary to identify these patients in their early stages of CKD along with prompt and early recognition of the derangements in electrolytes and calcium.

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Conflict of interest

The author declares no conflict of interest

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