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Original Article

Correlation of Hypocalcemia with eGFR in Chronic Kidney Disease: A Cross Sectional Study in Marine City Medical College and Hospital

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Abstract

Background: *Chronic Kidney Disease (CKD) poses a significant global health challenge. Its ramifications include advancing to End-Stage Renal Disease (ESRD) developing various complications stemming from compromised kidney function, and heightened vulnerability to Cardiovascular Disease (CVD). Interestingly, even within the bounds of normalcy, lower serum Calcium (Ca) levels emerge as a risk factor for precipitating a swift decline in estimated Glomerular Filtration Rate (eGFR) in CKD. Through extensive multivariable correlation analyses, it's been unveiled that serum calcium levels exhibit a correlation with eGFR. The current study aims at elucidating a link between serum calcium levels and eGFR among CKD patients.*

Materials and methods: *A cross-sectional study was conducted from January 2023 to December 2023, by the Department of Biochemistry in conjunction with the Department of Nephrology at Marine City Medical College & Hospital (MCMCH). Purposive sampling was employed to recruit a total of 224 subjects of 18 years and above, after following the inclusion criteria and obtaining permission from ethical/institutional review board (IRB). The study population was grouped as CKD: stage III (eGFR 30-59 ml/min/1.73m²) stage IV (eGFR 15-29 ml/min/1.73m²) and stage V (eGFR<15ml/min/1.73m²). A comprehensive clinical profile was documented for each participant, encompassing key variables such as serum creatinine, serum calcium and eGFR.*

Results: *The study revealed Male predominance (54%) with mean age 56.22±12.78. Among the study population 173 (77.2%) subjects had low serum calcium level (<8.5 mg/dl) of which 127 subjects were in CKD stage V. ANOVA test was significant for serum creatinine, serum calcium and eGFR in different stages of CKD. Pearson's correlation showed positive correlation between the eGFR and low serum calcium with a significant association of CKD stages (stage III, IV, V) with decreased serum calcium level in the study cases [χ^2 = 14.90; p= 0.0005].*

Conclusion: The study revealed a significant association between Hypocalcemia and decreased eGFR in CKD.

Key word: Chronic Kidney Disease (CKD); estimated Glomerular Filtration Rate (eGFR); Hypocalcemia.

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INTRODUCTION

Chronic Kidney Disease (CKD) poses a significant global health challenge due to its association with CVD and kidney failure progression.[1] In 2012, the WHO reported that 1.5% of worldwide deaths were linked to CKD.[2] Consequently, preventing the advancement of kidney dysfunction in CKD patients is paramount.[3] Numerous studies have investigated factors predictive of kidney dysfunction progression to identify individuals who require intervention.[4-7]

Metabolic conditions like hypertension, dyslipidemia, hyperuricemia, and diabetes contribute to CKD. However, CKD arises from various factors, leading to irreversible changes in kidney function and structure.[8,9] These factors may vary depending on underlying conditions and CKD severity. While most studies have focused on CKD patients with an eGFR < 60 ml/min/1.73 m², exploring factors associated with declining eGFR in individuals without CKD stages 3 and above is also crucial[10,11].

Although metabolic conditions are linked to kidney dysfunction, the correlation between serum Ca levels and CKD, remains unclear, especially in individuals without advanced CKD. Abnormal serum Ca levels affect neurological, gastrointestinal, and kidney functions. Severe hypercalcemia can reduce eGFR.[12] Both hypercalcemia from primary hyperparathyroidism and hypocalcemia from hypoparathyroidism treatment can induce kidney dysfunction.[13] However, the impact of serum Ca levels within a physiological range on kidney function decline requires further investigation.[14] Identifying modifiable risk factors for CKD progression is crucial for developing preventive strategies.[15,16] Disturbances in mineral metabolism are common in advanced CKD stages and may contribute to accelerated kidney function decline.[17,18] While hyperphosphatemia is consistently linked to CKD progression, evidence regarding calcium disturbances is less conclusive.[19-23] Recent studies have reported conflicting associations between serum calcium levels and CKD progression.[15,24] Understanding these associations is essential for designing effective preventive strategies. In this study, we investigated the association between serum Ca levels in a CKD general population. We considered multiple factors associated with kidney function, as well as those involved in calcium metabolism. The findings suggest that serum Ca levels serve as a valuable marker for predicting kidney dysfunction progression in individuals without CKD. The current study aims at elucidating a link between serum calcium levels and eGFR among CKD patients.

MATERIALS AND METHODS

A cross-sectional study was conducted in the Department of Biochemistry, in collaboration with the Department of Nephrology in MCMCH, from January 2023 to December 2023 after obtaining clearance from the ethical review board (IRB). The study encompassed 224 participants aged 18 years and above. These subjects were stratified into three groups as CKD: stage 3, stage 4 and stage 5. Key variables examined included serum calcium, serum creatinine and eGFR. eGFR was determined using the Cockcroft and Gault equation: eGFR = (140 – Age in years) × Weight (kg) × [0.85 if female] / 72 × [Serum Creatinine (mg/dL)].

Inclusion Criteria

- Adult subjects of any gender and Subjects diagnosed with CKD stage III, stage IV and stage V.

Exclusion Criteria

- Subjects with CKD stage 5 undergoing dialysis, Renal Replacement Therapy, Calcium supplementation and Subjects exhibiting psychological instability were excluded.

Bedridden patients, Pregnant individuals, Subjects diagnosed with malignancy, HIV positive and Individuals positive for HbsAg were also excluded.Data collection and sampling procedure

Data collection utilized a pre-tested structured questionnaire with all variables interest. Subjects were recruited from the Department of Nephrology (MCMCH). Following a brief history-taking, the purpose of the study was explained to each subject. Verbal and written consent was obtained and the subjects were asked to present to the Department of Biochemistry Laboratory at MCMCH between 8:00-9:00 am. Then 5ml of blood was drawn from median cubital vein with strict aseptic precautions without applying tourniquet to prevent venous stasis, which could falsely elevate calcium levels. The blood was collected in a Red-top tube without anticoagulants for ionized calcium measurement and is promptly sent to the Biochemistry Department without delay.

Analysis is conducted to determine the levels of serum calcium and serum creatinine.

Data analysis was done by Microsoft Excel on Windows 10 and IBM-SPSS (Statistical Package for Social Science) version 23. For Qualitative data, mean and standard deviation was calculated. Statistical significance across different stages of CKD was assessed by Student's t-test, Chi-square tests and ANOVA tests. Data was presented in tables.

RESULTS

A total of 224 subjects aged over 18 years were included in this study using purposive sampling method after permission from IRB. The study group was categorized as stage III, stage IV and stage V. Male was predominant (54% vs 46%) and the mean age was 56.22 ± 12.78 years. There was a significant differences in eGFR between male and female cases, but no significant differences were noted in serum creatinine and serum calcium between genders. ANOVA tests for serum creatinine, serum calcium and eGFR across different stages of CKD revealed significant differences in serum creatinine distribution among the three stages of CKD, with means in stage III at 1.87 ± 0.34 mg/dl, stage IV at 2.92 ± 0.61 mg/dl, and stage V at 8.64 ± 4.13 mg/dl (Table-I).

$F = 77.64$, $p < 0.00001$]. Significant differences were observed in eGFR across the three stages of CKD, with means in stage III at 35.83 ± 5.23 ml/min/1.73m^2, stage IV at 21.2 ± 4.63 ml/min/1.73m^2 and stage V at 7.04 ± 3.21 ml/min/1.73m^2 [Table-II, $F = 775.05$, $p < 0.00001$]. Serum calcium distribution also displayed significant differences among the three stages of CKD, with means in stage III at 8.44 ± 0.76 mg/dl, stage IV at 8.12 ± 0.69 mg/dl, and stage V at 7.71 ± 1.01 mg/dl (Table-III, $F = 8.89$, $p = 0.0002$). A significant positive correlation between eGFR and serum calcium was observed (Fig: I).

Among the study population, 173 (77.2%) subjects exhibited low serum calcium levels (<8.5 mg/dl), with 127 subjects in CKD stage V (Table-IV). Association tests revealed a significant association between CKD stages (III, IV, V) and decreased serum calcium levels (Table-V, χ^2value = 14.90, p = 0.0005).

Table I Serum creatinine level according to CKD stages (n = 224)

Variable	CKD Stage	Number (n)	Mean± SD	Range	Significance
S. Creatinine (mg/dl)	Stage III	28	1.87 ± 0.34	1.42-3.17	F = 77.64
	Stage IV	43	2.92 ± 0.61	1.8-4.2	p<0.00001 Highly
	Stage V	153	8.64 ± 4.13	3.2-21.5	Significant
	Total	224	6.69 ± 4.46	1.42-21.5	

Table II Distribution of eGFR according to CKD stages (n = 224)

Variable	CKD Stage	Number (n)	Mean± SD	Range	Significance
eGFR (ml/min/1.73m^2)	Stage III	28	35.83 ± 5.23	29.9-50.2	F = 775.05
	Stage IV	43	21.2 ± 4.63	15.0-29.2	p<0.00001 Highly
	Stage V	153	7.04 ± 3.21	2.0-14.3	Significant
	Total	224	13.35 ± 10.81	2.0-50.9	

Table III Distribution of S. calcium according to CKD (n = 224)

Variable	CKD Stage	Number (n)	Mean± SD	Range	Significance
S. Calcium (mg/dl)	Stage III	28	8.44 ± 0.76	6.7-10.3	F = 8.89
	Stage IV	43	8.12 ± 0.69	6.0-10.3	p=0.0002
	Stage V	153	7.71 ± 1.01	4.7-11.1	Highly
	Total	224	7.88 ± 0.96	4.7-11.0	Significant

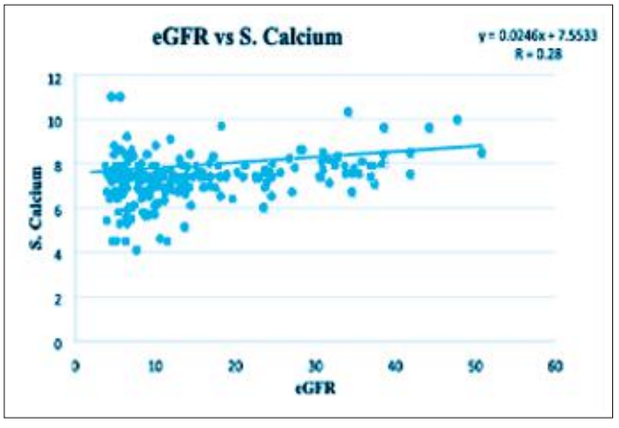

Figure I Scatter diagram shows positive significant correlation between eGFR and S. Calcium in the study cases

Table IV Distribution of low S. calcium level in the study cases (n=224)

S. Calcium (mg/dl)	Stage III	Stage IV	Stage V	Number (n)	Percentage (%)
Low (<8.5 mg/dl)	14	32	127	173	77.2%
Normal (8.5 to 10.5 mg/dl)	14	11	24	49	21.9%
High (>10.5 mg/dl)	00	00	02	02	0.9%
Total	28	43	153	224	100%
	(12.5%)	(19.2%)	(68.3%)		

Table V CKD stages with low S. calcium level in the study cases (n=224)

CKD Stages	Decreased Calcium	Normal/increased Calcium	Number (n)
Stage III	14	14	28
Stage IV	32	11	43
Stage V	127	26	153
Total	173	51	224

χ^2value = 14.90, p= 0.0005 (Significant)

DISCUSSION

CKD is characterized by reduced kidney function, typically indicated by eGFR < 60 mL/min per1.73 m^2, or evidence of kidney damage persisting for at least 3 months, regardless of the underlying cause. DM and hypertension are primary culprits of CKD across various economic settings, with disparities in its incidence, prevalence, and progression influenced by factors such as ethnicity and social determinants of health, potentially including epigenetic factors. Many individuals with CKD may be asymptomatic or present with vague symptoms. Diagnosis often occurs through screening tests like urinary dipstick or blood tests, or when symptoms become pronounced. GFR serves as a key indicator of overall kidney function. Two hundred and twenty four (224) subjects aging more than 18 years were included in this study by purposive sampling method. The study group was divided into stage III, stage IV and stage V. The study revealed a male predominance in gender distribution, with a mean age of 56.22 ± 12.78. There was significant differences in eGFR between male and female cases. Among the study population, 173 (77.2%) subjects had low serum calcium levels, of which 127 were in CKD stage V. ANOVA test revealed statistically significant differences in serum creatinine, serum calcium and eGFR across different stages of CKD. Pearson's correlation analysis indicated a positive correlation between eGFR and serum calcium levels. Scatter diagrams further illustrated a significant positive correlation between eGFR and serum calcium levels among the study cases.

The findings of our study align with those of previous research conducted by Satoru Mizushiri et al. Cynthia J Janmaat et al. Lim et al. A. Sinha et al. and other relevant studies.[1,15,25,26] However Schwarz et al.[23]reported a conflicting associations in their research where there was no association between low serum calcium and CKD progression.[23] But Lim et al. reported that low serum calcium was linked to a faster decline in kidney function.

The study also revealed that increased serum creatinine and decreased eGFR are indicators of disease progression. Hypocalcaemia was the most relevant finding among the CKD stage V subjects which showed a strong association of CKD stages with decreased serum calcium level. Among the other findings a significant positive correlation was found between the eGFR and lower serum calcium. As per Satoru Mizushiri et al.

lower serum Ca levels, even when they were within a normal physiological range, were a significant risk factor for a rapid decrease in eGFR, independent of metabolic risk factors such as blood pressure, dyslipidemia and diabetes.[1]

These metabolic risk factors were not associated with eGFR and so these metabolic risk factors can be used to predict CKD only after the kidney function has declined to certain levels. Instead, lower serum Ca levels is the most relevant marker to predict those at risk for worsening kidney function while kidney function is normal or only mildly decreased. Serum Ca levels are regulated through feed-back mechanisms, where PTH, Vit D and serum ionized Ca it self coordinate to regulate Ca transport at the gut, kidney, and bone. Thus, any abnormality in the mechanisms will affect the results. Furthermore association does not indicate a cause and effect relationship. Therefore, the observed association between lower serum Ca levels and a rapid decrease in eGFR does not simply mean that lower serum Ca levels impair kidney function. Thus, lower serum Ca levels appears not to be simply as reflection of a steady or rapid decrease in eGFR. The following results appear to warrant further studies examining whether intervention to increase serum Ca levels is useful in preventing worsening kidney dysfunction. We used a CKD population with different progressive stages and thus examined the association between serum Ca levels and changes in eGFR in CKD population. We could find a significant association between decreased serum Ca levels and changes in eGFR. These results suggest that lower serum Ca levels can be a useful marker to predict those at-risk for worsening of kidney function in ordinary clinical settings and thus, further studies using cohort populations with longer follow-up periods are warranted.

LIMITATIONS

The study was a cross sectional study of short duration with small sample size. Further, we did not do follow up on changes in eGFR in order to evaluate time-dependent changes in eGFR precisely.

CONCLUSIONS

Despite the acknowledged limitations, the study was able to find a significant association between low serum calcium levels and changes in eGFR. Future research could address these limitations to further strengthen the evidence base. Consequently, additional investigations utilizing cohort studies with extended observation periods are justified to validate these findings.

RECOMMENDATION

Further multicenter studies in large scale is required to establish a validated result. The sample size could be increased substantially so that a generalized conclusion could be made among the Bangladeshi population. Study on different tertiary level hospital of different parts of Bangladesh involving a large population size will be more representative of entire country. Community based interventions should be aimed to convey awareness to follow a healthy lifestyle and promote healthy food alternatives.

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DISCLOSURE

Both the authors declared no competing interest.

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