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FREQUENCY OF HYPOCALCEMIA AMONG PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

Objective: The primary objective of this study was to determine the frequency of hypocalcemia among patients with chronic kidney disease and secondary objective was to determine the association between hypocalcemia and different variables

Study Design and Setting: The study was descriptive, cross-sectional, carried out in the Department of Internal Medicine, Central Park Teaching Hospital, Lahore during May 2025 to September 2025.

Methodology: Non-probability consecutive sampling was applied to include 109 patients aged 25-60 years with CKD of at least a year duration of treatment. Patients with known peripheral artery disease, lower limb amputation, patients with known hypertension or taking antihypertensive medications were not eligible to participate in the study. The operationally defined hypocalcemia was measured based on serum calcium levels. The analysis of data was done with SPSS version 27. Age, gender, duration of disease, stage of chronic kidney disease, body mass index, diabetes, and smoking status were stratified to consider the possible effect modifiers. Stratification was done and Chi-square test taken where p 0.05 was taken as significant.

Results: Among 109 patients, 59 (54.1%) were males and 50 (45.9%) females, with a mean age of 45.06±9.61 years. Hypocalcemia was observed in 21 (19.3%) patients. The mean serum calcium level was 8.36±1.06 mg/dl.

Conclusion: Hypocalcemia is typical among the CKD patients especially in the end stages of the condition. To enhance patient outcomes and reduce complications, it is crucial to detect and monitor calcium levels early.

Keywords: Calcium, Blood; Hypocalcemia; Kidney Failure, Chronic; Renal Insufficiency.

INTRODUCTION

Chronic kidney disease (CKD) is an irreversible loss of kidney function with structural or functional damage of the kidneys which has been present for more than three months. It is known to be one of the largest contributors to morbidity and mortality globally, is emerging as a public health concern and its prevalence has remained climbing, despite the long-term implications of the disease. CKD impacts negatively on many body systems and is linked to many complications like cardiovascular disease, anemia, electrolyte disorders, metabolic acidosis, mineral and bone disorders. The global prevalence of CKD is estimated to be 8-16% of the adult population, which is continually increasing due to the rising prevalence of diabetes mellitus, hypertension and obesity, as well as increased life expectancy and metabolic syndrome.[1-2]

The considerable economic burden of chronic kidney disease (CKD) is caused by the cost of treatment and care; this is more of a problem in LMICs, especially in Pakistan, where the problem is complicated by high delayed diagnosis, low screening rates, and scarce nephrology services. The burden of increasing rates of diabetes and hypertension drives up the incidence of CKD, and the lack of resources and delay in diagnoses raises the risk of complications and death. The biochemical disturbance of hypocalcemia is characterized by a decrease in the calcium level in the serum below the normal range. Calcium is essential for many physiological processes, such as maintaining neuromuscular transmission, muscle contraction and maintaining cardiac rhythm.[3-4]

As a result, alterations in calcium homeostasis can result in a large variety of biochemical, clinical, and/ or neurological symptoms including muscle cramps, paresthesia, tetany, seizures, cardiac arrhythmias, prolonged QT interval and skeletal deformities. Hypocalcemia can occur as a result of a variety of disorders such as deficiency of vitamin D, hypoparathyroidism, chronic kidney disease, pancreatitis, malabsorption syndromes, hypomagnesemia, and some drugs. The incidence of hypocalcemia depends widely on the different populations, nutrition, dietary calcium, vitamin D level, socioeconomic factors, and presence of chronic diseases.[5]

Hypocalcemia is commonly reported in Pakistan due to widespread nutrition deficiencies, insufficient calcium intake in diet, vitamin D deficiency, limited sunlight exposure especially in some communities, and increasing prevalence of chronic medical illnesses.[6] In addition, under diagnosis and delayed treatment is due to poverty, less awareness of seeking medical care for hypocalcemia, poor health education awareness and poor access to diagnostic facilities. Studies across the region have also indicated that prevalence of CKD is similar in Pakistan compared to rest of the world and there is an urgent need to recognize metabolic abnormalities associated with it at an early stage.[3-4]

Patients with a long-term kidney disease are more likely to develop hypocalcemia as the advance of kidney failure significantly disturbs calcium and phosphate balance. All these abnormalities are known together as CKD-mineral and bone disorder (CKD-MBD) and happen early in the course of CKD and get even worse as the kidneys deteriorate. The kidneys also are important in converting vitamin D to the biologically active form, and helping to excrete phosphate. As progress to renal dysfunction, vitamin D is poorly activated, intestinal calcium absorption is diminished and there will be hyperphosphatemia with a secondary hyperparathyroidism, which ultimately contributes to decreasing levels of calcium in serum.[7-8]

Hypocalcemia (low calcium levels) also exacerbates secondary hyperparathyroidism and is responsible for renal osteodystrophy, vascular and soft tissue calcification, skeletal deformities, pathological fractures, muscular weakness, cardiovascular disease, and death in CKD patients. Awareness of hypocalcemia prevalence is frequently high in patients with CKD, with a prevalence score repeatedly reported in several international and local studies from 30% to more than 50% of patients at various stages of the disease, in different patient groups, and even in health care settings. Hospital-based studies have found hypocalcemia in as many as 44.2% of the patients with CKD in Pakistan, indicating the significant burden of this metabolic abnormality in the Pakistani population.[9-10]

Mineral metabolism disturbances in advanced CKD necessitate regular monitoring to prevent complications and enhance patient well-being. While the link between CKD and hypocalcemia is established, local prevalence data in Pakistan is scarce, primarily due to previous studies being limited in scope. Therefore, this study aimed to assess hypocalcemia prevalence in CKD patients at a tertiary care hospital to inform local clinical practices.

METHODOLOGY

The study was carried out in the Department of Internal Medicine of Central Park Teaching Hospital Lahore from May 2025 to September 2025 after the approval and ethical clearance of the study synopsis from the Institutional Ethical Review Committee (CPMC/IRB-No/1524A dated (1st May, 2025). The study was conducted as a descriptive, cross-sectional one with the aim of finding the proportion of patients with hypocalcemia in chronic kidney disease (CKD). The sampling method used for patient recruitment was non-probability type of consecutive sampling technique. All the patients who met the eligibility criteria and came in the study period were consecutively taken up until the desired sample size was reached. Since a complete sampling frame does not exist, this sampling technique was selected for: practicality, feasibility, and frequent use in hospital based cross sectional studies.

The sample size was determined using WHO sample size calculator using hypothesis: desired confidence of 95%, margin of error of 8% and frequency of deficiency of calcium in chronic kidney disease patients of 23.8%.[11] With these assumptions, the minimum sample size required was 109 patients. The calculated sample size was deemed to be sufficient to estimate the frequency of hypocalcemia to an acceptable level of accuracy, and feasible regarding study time and resources within the institution.

Patients of all ages, ranging from 25 to 60 years old, both males and females, who had a diagnosis of chronic kidney disease at least 1 year ago by operational definition who visited (both in and out) the Department of Internal Medicine were eligible to be included in the study. Standard clinical and laboratory evidence of the diagnosis of CKD was already present in patients' clinical records and had already been made by the treating physician. Limiting the study to patients with at least 1 year of diagnosis ensured that only patients with proven CKD were included, and reduced the chance that patients with a transient and/or reversible renal dysfunction were included.

Those people who refused to take the study were not included. Furthermore, patients who had previous peripheral artery disease (PAD) based on medical records and clinical assessment were excluded. Patients with both lower limb amputated (physically verified) and confirmed as such were also excluded. Those who had a history of hypertension or were on an antihypertensive drug (history also confirmed by medical records) were excluded. Also, patients with familial dyslipidemia (FDD) described in their health records were excluded, as the disease nature may be influenced and considerations of results from the study may be confounded by this genetic lipid disorder. Strict application of inclusion/exclusion criteria resulted in a relatively homogeneous study group with a relatively small number of major confounding effects.

Eligible patients were approached while visiting their own physician or when admitted to a hospital; these were subject to approval by the Institutional Ethical Review Committee (IERC). Each subject was fully informed about the aims, advantages and ways in which the study was to be carried out in a language easily understood. It was explained to the subjects that participation in the study was completely voluntary and that no procedure would be performed in the event that they did not wish to participate. All participants signed informed consent forms prior to enrolling in the study. To ensure anonymity and confidentiality during the research process, every participant had a unique identification number.

All the relevant information was recorded on a predesigned and structured data collection proforma. Demographic data such as gender and age was recorded. The participants' body weight and height were measured using light weight clothing and no footwear under the clothes. Body mass index (BMI) was determined as weight(kg)/ht²(m). Patient interviews and hospital records were used to collect clinical data such as the duration of the chronic kidney disease, clinical stage of chronic kidney disease, diabetic status and smoking status. The stage of the CKD was documented as per the operational definition used in the study. The smoking status was divided into current smokers and non-smokers, and the diabetic status was divided as diabetic and non-diabetic according to the diabetic history or information in the medical records.

The venous blood samples were drawn from each individual on admission to the hospitals with proper aseptic precautions and were used for biochemical assessment, which was approximately 3 cc blood. Blood samples were sent straight to the hospital lab to be analysed. Serum calcium was analysed by standard laboratory methods routinely used by the hospital laboratory and appropriate quality control was undertaken. The laboratory personnel/man conducting the analysis operated as per the standard working procedure and maintained accuracy and reliability of the test result. Participants were divided into two groups (hypocalcemia or normal serum calcium) using the predetermined operational definition. Serum calcium level and the calcium classification were recorded in the study proforma. Confidentiality of patient information was ensured during the process of data collection by ensuring access to records is limited to the principal investigator and research supervisors only. All completed proformas have been kept in a secure way and have been utilized just for research.

At the end of data collection period, all the collected data was thoroughly inspected for completeness, consistency and accuracy for data entry. Data was then entered into the Statistical Package for the Social Sciences (SPSS) version 27.0 for statistical analysis. There were quantitative variables like age, body weight, height, body mass index, duration of chronic kidney disease, which were summarized by mean and standard deviation since they are measured on a continuous scale. Qualitative variables such as gender, stage of CP, hypocalcemia (present/absent), diabetic status and smoking status were expressed as frequencies and percentiles. The main end-point of the study was the occurrence of hypocalcemia in a chronic kidney failure population. Data was subdivided by ages, gender, body mass index, duration of CKD, stage of CKD, diabetic status and smoking status to assess the impact of potential confounding factors. After stratification, Chi-square test was used to assess for associations between hypocalcemia with categorical study variables. A p-value of ≤0.05 was considered statistically significant.

RESULTS

One hundred and nine patients who were diagnosed with chronic kidney disease were included in the present study and analyzed. There was a slight predominance of males, with 59 (54.1%) of the study population considered males and 50 (45.9%) as females. The ages of the participants varied from 25 to 60 years. According to age distribution 37 (33.9%) patients were 25-40 age group and 72 (66.1%) were 41-60 age group. The present study had a population with a mean age of 45.06±9.61 years which show that majority of the patients with chronic kidney disease in the present study were middle aged adults. Results indicated that within the age range studied, the level of CKD was higher in older people.

In terms of anthropometric characteristics of the cases, those of 78 patients (71.6%) were 24.9 kg/m² or below and 31 patients (28.4%) had a BMI of >24.9 kg/m². The mean weight of the subjects was 73.59±9.66 kg while the mean height was 1.69±0.08 m. The calculated mean BMI was 25.63±4.13 kg/m². These results suggest that majority of the participants were identified as having a BMI of ≤24.9 kg/m² but the overall mean BMI of the study population were slightly above the normal range.

Regarding the duration of chronic kidney disease, 29 (26.6%) patients had a duration of ≤18 months, while the rest of the patients had the chronic kidney disease for more than 18 months. The mean duration of chronic kidney disease was 22.48±6.50 months which depicts that majority of population had chronic kidney disease of longer duration before they presented to the tertiary care hospital.

The distribution of patients according to CKD stage showed that 41 (37.6%) patients were in Stage 1, 29 (26.6%) were in Stage 2, 25 (22.9%) were in Stage 3, 8 (7.3%) were in Stage 4, and only 6 (5.5%) patients were in Stage 5. As such, the majority of the participants (nearly two thirds) had early stage chronic kidney disease (Stage 1 and 2) as opposed to fewer patients with advanced stage chronic kidney disease (Stage 3 and 4).

In terms of smoking status, 22 (20.2%) participants identified themselves as being a current smoker and 87 (79.8%) identified as a non-smoker. Also, the assessment of diabetic status revealed that 32 (29.4%) of the patients were known diabetics while majority of the patients (77 [70.6%]) had previously unknown diabetic status. The results of this study show that majority of the patients, enrolled in the study were non smokers and non diabetic, even though they had chronic kidney disease.

The biochemical parameters were analyzed and the mean serum calcium level of the study population was found to be 8.36±1.06 mg/dl. From the operationally defined hypocalcemia, 21 (19.3%) patients were diagnosed with hypocalcemia, while 88 (80.7%) patients had normal serum calcium levels. Thus, it was found that about 20% of the patients with chronic kidney disease were hypocalcemic. It further illustrates the hypocalcemia as an important metabolic disturbance in CKD patients, suggesting that routine clinical management of this patient population needs frequent calcium monitoring.

Stratification analysis was performed to determine the association between hypocalcemia and different demographic and clinical characteristics of the study participants. Results showed that the gender and hypocalcemia was not correlated significantly with each other (p=0.858) (18.6% male and 20.0% female were hypocalcemic). Likewise, there was no significant difference by age group (p=0.655) with hypocalcemia seen in 21.6% of the 25-40 year age group, and 18.1% of the 41-60 year age group. There was also no statistically significant association between BMI and hypocalcemia (p=0.103) however patients with BMI>24.9 kg/m² were relatively more likely to be hypocalcemic than those with BMI ≤24.9 kg/m².

Similarly, there was no significant difference between duration of chronic kidney diseases and hypocalcemia (p=0.821). Hypocalcemia occurred in 20.7 % of the patients with disease duration of ≤18 months and 18.8 % with the disease duration >18 months. There was no statistically significant association between smoking status and hypocalcemia, with 13.6% of current smokers and 20.7% of non-smokers having reduced serum calcium levels (p=0.558). Likewise, diabetic status was not significantly associated with hypocalcemia (p=0.930) which was found in 18.8% of diabetic patients and 19.5% of non-diabetic patients.

Hypocalcemia however, showed a statistically significant association with the stage of chronic kidney disease (p=0.001). Hypocalcemia frequencies showed a lot of variation among the different stages of CKD; 14.6% at stage 1, 6.9% at stage 2 and 8.0% at stage 3. Hypocalcemia was found at a significantly higher percentage in the more advanced stages of the disease with 100% (10/10) of patients in Stage 4, and 50% (4/8) of patients in Stage 5, being affected with hypocalcemia.

Table-1: Frequency distribution of different variables (n=109)

Variables		Frequency	Percent
Gender	Male	59	54.1
	Female	50	45.9
Age groups	25-40 years	37	33.9
	41-60 years	72	66.1
	Mean age (years)	45.06±9.61	
BMI	≤24.9 kg/m^2	78	71.6
	>24.9 kg/m^2	31	28.4
	Mean weight (kg)	73.59±9.66	
	Mean height (m)	1.69±0.08	
	Mean BMI (kg/m^2)	25.63±4.13	
Duration of CKD	≤18 months	29	26.6
	>18 months	80	73.4
	Mean duration of CKD (months)	22.48±6.50	
Stage of CKD	Stage-1	41	37.6

	Stage-2	29	26.6
	Stage-3	25	22.9
	Stage-4	8	7.3
	Stage-5	6	5.5
Current smoker	Yes	22	20.2
	No	87	79.8
Known diabetic	Yes	32	29.4
	No	77	70.6
Hypocalcemia	**Mean serum calcium level (mg/dl)**	8.36±1.06	
	Yes	21	19.3
	No	88	80.7

Table-2: Stratification of hypocalcemia with respect to different variables

Variables		**Hypocalcemia**		**p-value**
		Yes	No	
Gender	Male	11(18.6%)	48(81.4%)	0.858
	Female	10(20.0%)	40(80.0%)	
Age groups	25-40 years	8(21.6%)	29(78.4%)	0.655
	41-60 years	13(18.1%)	59(81.9%)	
BMI	≤24.9 kg/m^2	12(15.4%)	66(84.6%)	0.103
	>24.9 kg/m^2	9(29.0%)	22(71.0%)	
Duration of CKD	≤18 months	6(20.7%)	23(79.3%)	0.821
	>18 months	15(18.8%)	65(81.3%)	
Stage of CKD	Stage-1	6(14.6%)	35(85.4%)	0.001
	Stage-2	2(6.9%)	27(93.1%)	
	Stage-3	2(8.0%)	23(92.0%)	
	Stage-4	8(100.0%)	0(0.0%)	
	Stage-5	3(50.0%)	3(50.0%)	
Current smoker	Yes	3(13.6%)	19(86.4%)	0.558
	No	18(20.7%)	69(79.3%)	
Known diabetic	Yes	6(18.8%)	26(81.3%)	0.930
	No	15(19.5%)	62(80.5%)	

DISCUSSION

Chronic kidney disease (CKD) is a significant health problem worldwide, the epidemiological rates imply that the mentioned condition is present in over 10 percent of the adult population in the world, that is, over 800 million people, and the disease prevalence rate only increases in line with the rates of diabetes mellitus, hypertension, and obesity.[12]

Among the host of systemic complications that accompany CKD, mineral and bone metabolic dysregulation, also known as CKD-mineral and bone disorder (CKD-MBD), is one of the most clinically important conditions, and hypocalcemia is one of the most important biochemical manifestations of progressive renal failure.[13]

The current research was conducted to estimate the incidence of hypocalcemia in patients with CKD in a tertiary care hospital in Lahore, and the results obtained can be added to the growing literature on the derangements of mineral metabolism in this patient group. In the present study, 21 (19.3) out of 109 patients who were recruited and put under CKD were found to have hypocalcemia and the mean serum calcium of the sample was 8.36±1.06 mg/dl. This is comparatively lower than Yong et al. reported in a retrospective cohort study of Singapore with pre-dialysis CKD stage 4-5, 169 of 400 patients (42.2) showed evidence of hypocalcemia; there was a marked higher incidence of severe hypocalcemia in stage 5 as compared to stage 4 (40.5% vs. 25.9%; $p = 0.004$).[14]

In another study, 26% patients had hypocalcemia among CKD patients.[15] In another study, 8.4% patients had hypocalcemia among CKD patients.[16]

The difference between the two studies can probably be explained by the difference in the CKD stage distribution between the two study groups because the Singapore cohort would have had a more severely ill population (stages 4- 5) whereas the current study covered a wider range of CKD spectrum. Equally, a subsequent study (published in the Journal of Pharmacy and Therapeutics and Clinical Practice (JPTCP)) looking into the electrolytes imbalance in CKD patients found that 35% of the research population had hypocalcemia associated with bone pain and muscle spasms, just 30% of which in the study herein is reported.[17]

Hypocalcemia in chronic kidney disease (CKD) has been well described in the pathophysiology literature recently. The GFR slowly decreases and eventually the kidneys are unable to regulate levels of calcium and phosphate. The decreased number of nephrons results in impaired ability to excrete phosphate, which results in phosphate retention, and decreased activity of renal 1α-hydroxylase results in decreased conversion of 25(OH)D to the biologically active form, calcitriol. The net effect of this reduction is a decrease in calcium absorbed in the gut that directly leads to a decrease in serum calcium levels and can provoke secondary hyperparathyroidism, resulting in a further increase in the progression of chronic kidney disease–mineral and bone disorder (CKD-MBD).[13] Such changes are more severe as kidney function decreases, which explains the greater occurrence of hypocalcemia in patients with advanced CKD.

In a deeper dive of vitamin D metabolism and secondary hyperparathyroidism in CKD, published in Nutrients (2022), Brandenburg and Ketteler also detailed that supply of calcitriol within the parathyroids is also essential for calcium-sensing receptor (CaSR) function, and that it promotes expression of the intestinal calcium transport proteins. The authors suggested that adequate treatment of vitamin D deficiency and careful management of calcium homeostasis are important aspects of care of patients with CKD, because they will help both in reducing mineral metabolism disturbances and in improving patients' long-term outcomes.[18]

These mechanisms together form the basis for the formation of secondary hyperparathyroidism (SHPT) which at first may be a compensatory mechanism in response to continued hypocalcemia but eventually becomes maladaptive as SHPT progresses. Chronically stimulated parathyroid glands will produce an excessive amount of parathyroid hormone, which naturally leads to an increased bone turnover, skeletal demineralization, the deposition of calcium in the vascular system and cardiovascular complications. The systematic review and meta-analysis published in Frontiers in Endocrinology (2024) found that SHPT is quite common in patients with chronic kidney disease (CKD) throughout the world, thereby revealing the massive burden of mineral and bone disorders in patients with CKD as well as the strong link between renal function decline and calcium metabolism abnormalities.[19]

This increase of hypocalcemia with the increase of the severity of the renal disease was observed and confirmed by the results of present study which showed a statistically significant association between hypocalcemia and the increasing of the renal disease stage. This finding is consistent with the known inverse association between estimated glomerular filtration rate (eGFR) and availability of calcitriol that has been described by others.[13]

Others showed a similar increase in the prevalence of severe hypocalcemia with the various stages of CKD, with 25.9% of stage 4 CKD patients having severe hypocalcemia as compared with 40.5% of stage 5 CKD patients ($p=0.004$). These findings further support that declines in renal function significantly raise the risk of hypocalcemia that can lead to clinically significant problems.[14]

The finding that parathyroid hormone was significantly higher in patients with eGFR < 60, irrespective of comparable vitamin D levels, further underscores this association, supporting the premise that declining renal function is an important risk factor for hypocalcaemia in patients with CKD.[20]

The CKD-MBD StatPearls review (2024) corroborates this staging-dependent trajectory, noting that serum calcium concentrations generally remain within normal limits until eGFR declines to approximately 20 mL/min/1.73 m², at which point progressive hypocalcemia becomes manifest, corresponding clinically to CKD stages 4 and 5.[13]

Special attention needs to be paid to the cardiovascular implications of hypocalcemia in patients with CKD. The authors of an incident hemodialysis retrospective cohort study of 332 patients published in Scientific Reports

(2020) found that three-quarters of the patients enrolled in the study developed true hypocalcemia (ionized calcium <1.15 mmol/L), and that a portion of them had a condition they called hidden hypocalcemia, where the ionized calcium is lower than <1.15 mmol/L. That study found significantly increased composite risk of all-cause mortality and cardiovascular events in patients with concealed hypocalcemia, which the total serum calcium measure, like that used in the current study, could conceal, thus revealing the potential to underestimate prevalence and clinical impact of hypocalcemia in CKD patients.[21] This consideration represents an important methodological dimension that future investigations in this setting should address.

Monitoring and management of CKD-MBD that comprises hypocalcemia has seen its importance restated in the current international recommendations. In coverage of the 2023 KDIGO Controversies Conference on CKD-MBD, Ketteler and colleagues (2025) pointed out that monitoring and correction of serum calcium, phosphate, and vitamin D levels are still some of the core elements involved in the comprehensive management approach to CKD-related complications such as cardiovascular calcification and renal osteodystrophy.[22]

In a parallel therapeutic review, Zaimi et al. (2024) highlighted that the management of hypocalcemia in CKD should incorporate vitamin D analogues, phosphate binders, and dietary modifications, and that correction of hypocalcemia is indispensable to mitigating secondary hyperparathyroidism-driven bone resorption and vascular injury.[23]

The fact that hypocalcemia was found in the present study with a relatively lower prevalence of 19.3 as opposed to various international reports is also possibly an indication of a level of ascertainment in the outpatient population with fairly intact residual renal function and ability to ingest vitamin D supplementation, although this is speculative without detailed stage-wise data.

LIMITATIONS

The current research has a number of methodological weaknesses that should be mentioned. First, the cross-sectional design will not allow determining temporal or causal associations between CKD stage and hypocalcemia; longitudinal data will be needed to describe the natural course of calcium dysregulation through disease course. Second, the research was done in one centre, Lahore, and thus reduces the extrapolation of the results to different geographic, demographic and clinical locations. Third, the small sample size (n = 109) might have limited statistical power to subgroup analyses, especially stage-stratified comparisons. It is suggested that future multi-centre, longitudinal research using larger and heterogeneous patient groups, detailed mapping of mineral metabolism (ionized calcium, parathyroid hormone, FGF23, 25-hydroxyvitamin D, etc.), be conducted to give a more complete definition of the epidemiology of hypocalcemia in CKD patients in Pakistan and the broader South Asian population.

CONCLUSION

Hypocalcemia is a common finding among CKD patients, particularly in advanced stages of the disease. Early detection and monitoring of calcium levels are essential to reduce complications and improve patient outcomes.

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