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Serum Phosphate as an Additional Marker for Initiating Hemodialysis in Patients with Advanced Chronic Kidney Disease

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ABSTRACT

Chronic kidney disease (CKD) is characterized by a gradual and irreversible decline in the kidney function. When an adult's glomerular filtration rate (GFR) falls to 60 ml/min/1.73 m² or below, it indicates a loss of at least half of the normal kidney function. Phosphorus, an essential intracellular anion, is the predominantly stored in bones and soft tissues, with serum phosphorus representing less than 1% of the total body phosphorus content. However, serum phosphorus serves as an indicator of the total body phosphate levels. A significant decline in GFR hampers renal phosphate excretion and disrupts hormonal regulation, often the resulting in phosphate retention and hyperphosphatemia in advanced CKD patients. Prior studies have shown that the CKD patients with severe hyperphosphatemia, especially those delaying renal replacement therapy (RRT), experienced higher phosphate retention. This study aimed to assess the role of serum phosphate in advanced CKD and explore hyperphosphatemia's potential as a marker for guiding the initiation of RRT. Conducted over 18 months on 60 advanced CKD patients at Kempegowda Institute of Medical Sciences, serum phosphate levels were measured, and patients were monitored for dialysis needs over six months. Data analysis was performed using SPSS (Version 26.0) with a significance level of 5% ($\alpha = 0.05$). Among the patients (mean age: 58.4), 66.7% were male, and 81.7% required hemodialysis. The mean serum phosphate level was higher in patients needing dialysis (7.64 vs. 5.05, $P < 0.001$), with a serum phosphate threshold of 6.10 predictive of dialysis (sensitivity: 98%). These findings suggest hyperphosphatemia may help determine the timing of dialysis initiation in advanced CKD patients.

INTRODUCTION

Chronic kidney disease (CKD) remains a significant global health issue, characterized by a progressive and often irreversible loss of kidney function, leading to end-stage renal disease (ESRD) if untreated. CKD impacts millions worldwide, resulting in high morbidity, mortality, and substantial healthcare costs. The condition is defined by a decrease in glomerular filtration rate (GFR), where a GFR of less than 60 ml/min/1.73 m² signifies a substantial loss of kidney function. This progressive decline in renal function impairs the body's ability to effectively filter waste products, regulate electrolytes, and maintain fluid balance, which can culminate in severe systemic complications. One of the primary metabolic disturbances in CKD is mineral imbalance, notably involving calcium, phosphorus, and parathyroid hormone levels, leading to conditions such as mineral and bone disorder (MBD). Among these, phosphorus dysregulation and its impact on CKD patients, especially those at advanced stages of the disease, have become areas of focused research [1,2].

Phosphorus is an essential mineral predominantly found in bones and, to a lesser extent, in soft tissues. In healthy individuals, less than 1% of the body's total phosphorus is found in the bloodstream, where it plays critical roles in cellular metabolism, ATP synthesis, and intracellular signaling. Serum phosphate, there-

-fore, is a surrogate marker of total body phosphate, providing insight into phosphate balance and kidney function. The kidneys are primarily responsible for regulating serum phosphate levels, reabsorbing most of it and excreting the rest to maintain an optimal balance. However, in patients with CKD, the decline in GFR compromises this regulatory process, leading to phosphate retention and, ultimately, hyperphosphatemia. This excess phosphate in the bloodstream, a condition known as hyperphosphatemia, is associated with increased cardiovascular morbidity, vascular calcification, bone disorders, and poor outcomes in CKD patients [3].

The management of hyperphosphatemia is crucial in patients with CKD, especially those approaching ESRD. Dietary phosphate restriction, phosphate binders, and close monitoring of serum phosphate levels are typically recommended to control serum phosphate. However, as kidney function continues to deteriorate in advanced CKD stages, these interventions may become insufficient to manage rising serum phosphate levels effectively. Advanced CKD patients frequently require renal replacement therapy (RRT), including hemodialysis or peritoneal dialysis, to support kidney function by removing waste products and maintaining electrolyte balance. Hemodialysis is commonly employed in advanced CKD and ESRD, traditionally initiated based on clinical symptoms and kidney function tests, particularly GFR levels. Yet, despite these markers, there is increasing recognition that additional biochemical indicators, such as serum phosphate, could provide valuable insights for the timely initiation of dialysis [4,5].

The conventional approach for initiating hemodialysis has largely relied on the presence of uremic symptoms, such as nausea, fatigue, and mental confusion, or based on GFR reaching critically low levels. However, GFR alone may not fully reflect the metabolic burden experienced by advanced CKD patients. Hyperphosphatemia represents a metabolic marker that could indicate an increased need for hemodialysis beyond the traditional reliance on symptomatic presentations and GFR decline. Elevated serum phosphate levels in advanced CKD patients can signify impaired phosphate excretion and progressive phosphate accumulation, which dialysis can help alleviate by removing excess phosphate from the bloodstream. This insight is crucial since delaying dialysis in hyperphosphatemic patients can increase the risk of complications, such as vascular calcification, cardiovascular disease, and bone abnormalities. Therefore, investigating serum phosphate as an additional marker for dialysis initiation could be a critical advancement in managing advanced CKD patients [6].

In clinical practice, several studies have explored the association between elevated serum phosphate levels and adverse outcomes in CKD, particularly related to cardiovascular health. Elevated serum phosphate has been independently linked to increased all-cause mortality, cardiovascular mortality, and rapid progression to ESRD. Furthermore, it has been observed that phosphate retention and hyperphosphatemia develop before other overt symptoms of kidney failure appear, suggesting that serum phosphate could serve as an early indicator of the need for RRT. Patients with advanced CKD who present with significant hyperphosphatemia are at higher risk of experiencing phosphate-related complications that may not be immediately addressed by conservative management strategies alone. This observation supports the hypothesis that serum phosphate levels might guide the timing of hemodialysis initiation, potentially improving outcomes for patients with advanced CKD [7,8].

Previous research has examined various biochemical parameters in CKD patients to assess dialysis timing, yet serum phosphate's role as a dialysis marker remains less established. Phosphorus metabolism in CKD is regulated by complex hormonal mechanisms involving parathyroid hormone (PTH), fibroblast growth factor-23 (FGF-23), and vitamin D, all of which are altered as kidney function declines. In advanced CKD, the feedback mechanisms that normally control phosphate excretion and absorption become disrupted, leading to elevated PTH and FGF-23 levels as the body attempts to compensate for rising phosphate levels. While PTH and FGF-23 can also serve as indicators of mineral dysregulation, serum phosphate is a more direct measure of phosphate retention and the renal system's inability to maintain homeostasis. Thus, incorporating serum phosphate into the decision-making process for hemodialysis initiation could provide a more comprehensive assessment of metabolic status in CKD patients [9,10].

One potential advantage of using serum phosphate as an additional marker is its ease of measurement and the ability to track it longitudinally. Regular monitoring of serum phosphate levels in CKD patients could enable clinicians to observe trends indicating phosphate retention progression. For instance, patients showing a steady rise in serum phosphate despite conservative management may benefit from early initiation of hemodialysis. Studies have shown that high serum phosphate levels are predictive of adverse outcomes, including increased risk of hospitalization and mortality, which further supports the utility of serum phosphate monitoring. Additionally, a specified serum phosphate threshold for initiating hemodialysis could improve clinical decision-making, providing a more objective measure to balance the risks and benefits of dialysis in advanced CKD patients [11].

To assess serum phosphate's role in dialysis timing, this study aims to evaluate serum phosphate levels in patients with advanced CKD and their potential predictive value in determining dialysis initiation. By examining the relationship between serum phosphate levels and the need for hemodialysis, this research could contribute to a more refined approach for managing CKD progression and identifying patients who might benefit from early intervention. Through this study, we seek to determine if

hyperphosphatemia can be a reliable marker for dialysis initiation, improving outcomes and quality of life for CKD patients. In summary, as the burden of CKD continues to grow, understanding and utilizing serum phosphate as a marker could significantly impact clinical practices, helping healthcare providers make more informed decisions on the timing of hemodialysis and thereby enhance patient care in advanced CKD [12].

MATERIAL AND METHODS

This prospective observational study was conducted at the Department of General Medicine, Kempegowda Institute of Medical Science, Bangalore. Ethical approval has been obtained from the Ethical Approval Committee of Kempegowda Institute of Medical Science, Bangalore.

Study Population:

The study population consisted of 60 advanced chronic kidney disease (CKD) patients who were treated at the Kempegowda Institute of Medical Sciences, Bangalore, over an 18-month period. These patients had a mean age of 58.4 years, with 66.7% being male. Within this cohort, 81.7% required hemodialysis, highlighting the severity of their kid-ney function decline and need for renal replacement therapy.

Data Analysis:

Data analysis for this study was conducted using SPSS software, version 26.0, with a significance level set at 5% ($\alpha = 0.05$). The primary objective was to investigate the association between serum phosphate levels and the need for hemodialysis in patients with advanced chronic kidney disease (CKD). Descriptive statistics were used to summarize patient demographics, comorbidities, and laboratory values, such as serum urea, creatinine, estimated glomerular filtration rate (eGFR), and phosphate levels. Comparative analyses were performed to assess differences between patients who required hemodialysis and those who did not. The study specifically evaluated the predictive power of serum phosphate for dialysis initiation through a receiver operating characteristic (ROC) curve analysis. This analysis identified a serum phosphate threshold of 6.10 as a sensitive predictor (sensitivity of 98%) for hemodialysis, thus establishing hyperphosphatemia as a potential marker for determining dialysis timing in advanced CKD patients.

RESULT

Table 1:Patient Characteristics

Patient Characteristics		
Age, Mean±SD		58.38±12.77
Gender, N (%)	Male	40 (66.7)
	Female	20 (33.3)
Comorbidities, N (%)	Diabetes	41 (68.3)
	Hypertension	39 (65.0)
0personal History, N (%)	Smoker	21 (35.0)
	Alcoholic	18 (30.0)
Hemodialysis, N (%)	Yes	49 (81.7)
	No	11 (18.3)
Diagnosis, N (%)	DKD	37 (61.7)
	Glomerulonephritis	6 (10.0)
	HKD	13 (21.7)
	Iga Nephropathy	4 (6.7)

The study included 60 patients with a mean age of 58.38 ± 12.77 years. Of these, 40 (66.7%) were male and 20 (33.3%) were female. A majority had comorbidities, with 41 patients (68.3%) diagnosed with diabetes and 39 (65%) with hypertension. Regarding personal habits, 21 patients (35%) were smokers, and 18 (30%) were alcoholics. Hemodialysis was required by 49 patients (81.7%), while 11 patients (18.3%) did not undergo dialysis. The diagnoses included diabetic kidney disease (DKD) in 37 patients (61.7%), glomerulonephritis in 6 patients (10%), hypertensive kidney disease (HKD) in 13 patients (21.7%), and IgA nephropathy in 4 patients (6.7%).

Table 2: Laboratory Parameters

Laboratory Parameters	Mean	Std. Deviation
Urea	152.40	40.882
Creatine	8.058	2.1716
Egfr	7.22	2.532
Phosphate	7.170	1.1563

The laboratory parameters for the 60 patients showed elevated urea (152.40), creatinine (8.058), and phosphate (7.170) levels, along with a low eGFR (7.22), indicating significant renal impairment. These findings suggest compromised kidney function across the studied population. The elevated markers highlight the severity of kidney dysfunction in these patients.

Table 3: Association of Study Variables with Hemodialysis

Variables	Hemodialysis		P Value
	Yes	No	
Age	57.20±12.23	63.64±14.41	0.133
Urea	165.92±31.99	92.18±7.985	**<0.001**
Creatine	8.75±1.75	4.96±0.34	**<0.001**
Egfr	6.31±1.623	11.27±1.737	**<0.001**
Phosphate	7.645±0.6127	5.055±0.2423	**<0.001**

The association of study variables with hemodialysis showed that patients on hemodialysis had significantly higher levels of urea (165.92 vs. 92.18), creatinine (8.75 vs. 4.96), and phosphate (7.645 vs. 5.055), and lower eGFR (6.31 vs. 11.27) compared to those not on hemodialysis, with all differences being statistically significant ($p < 0.001$). Age did not show a significant difference between the two groups ($p = 0.133$).

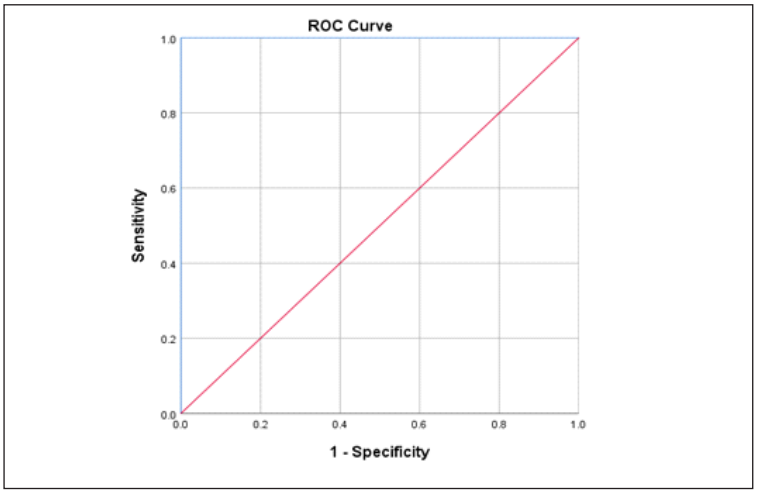

Figure 1: ROC Curve

Table 4: ROC Curve of Phosphate in Predicting Hemodialysis

Area Under the Curve: Phosphate in Predicting Hemodialysis				
			Asymptotic 95% Confidence Interval	
Area	**Std. Error**	**P Value**	**Lower Bound**	**Upper Bound**
1.000	**0.000**	**0.000**	1.000	1.000
Cut-Off Value			6.1	
Sensitivity			98%	
Specificity			0%	

The ROC curve for phosphate in predicting the need for hemodialysis showed an area under the curve of 1.000 (with a standard error of 0.000), indicating perfect discrimination. The cutoff value for phosphate was 6.1, with a sensitivity of 98% and a specificity of 0%. This suggests that phosphate levels above 6.1 are highly sensitive for predicting the need for hemodialysis, but the test lacks specif-icity, as it does not accurately distinguish between patients who do and do not require hemodialysis.

DISCUSSION

The role of serum phosphate as a marker for initiating hemodialysis in patients with advanced chronic kidney disease (CKD) has garnered increasing attention in nephrology. Chronic kidney disease is characterized by a

progressive and often irreversible decline in renal function, with patients ultimately requiring renal replacement therapy (RRT) such as hemodialysis or peritoneal dialysis to sustain life. The current standard for initiating hemodialysis is based on clinical indicators like uremic symptoms and a critically low glomerular filtration rate (GFR). However, recent research suggests that serum phosphate levels could provide additional insights, particularly in patients whose renal function is deteriorating to end-stage renal disease (ESRD) and who may benefit from more timely dialysis intervention [13,14].

Phosphate metabolism plays a critical role in CKD management due to the kidneys' central function in phosphate regulation. In healthy individuals, phosphate is predominantly stored in bones, with a small proportion circulating in serum. The kidneys maintain serum phosphate levels by reabsorbing or excreting phosphate based on the body's needs. However, in CKD, declining GFR impairs this regulatory mechanism, leading to phosphate retention and hyperphosphatemia, especially as patients progress to ESRD. This retention results from both reduced renal excretion and disrupted hormonal regulation, notably involving fibroblast growth factor-23 (FGF-23) and parathyroid hormone (PTH). Hyperphosphatemia is associated with adverse clinical outcomes, such as vascular calcification, cardiovascular disease, and bone abnormalities. Therefore, addressing phosphate retention is essential to improve the quality of life and prognosis for advanced CKD patients [15].

The study outlined here investigated the potential of serum phosphate as a predictive marker for hemodialysis initiation in patients with advanced CKD. Conducted over 18 months, the study included 60 patients with advanced CKD at the Kempegowda Institute of Medical Sciences in Bangalore. The primary outcome measure was the requirement for hemodialysis over a six-month follow-up period, with data collected on serum phosphate levels, demographic factors, and relevant clinical and laboratory parameters. Statistical analysis revealed a significant association between elevated serum phosphate and dialysis need, with a threshold serum phosphate level of 6.10 showing high sensitivity (98%) for predicting dialysis initiation. This threshold suggests that serum phosphate could serve as an early warning sign for CKD patients approaching a point where traditional markers alone may not capture the full scope of metabolic derangements [16].

The implications of these findings are substantial, as they suggest that serum phosphate monitoring could enhance the decision-making process for dialysis initiation. While GFR remains a reliable measure of renal function, it may not fully encapsulate the metabolic disruptions occurring in CKD, particularly with regard to mineral imbalance. For instance, GFR measurement does not account for the complex interactions between phosphate, PTH, and FGF-23, which are critical in managing phosphate metabolism. Thus, integrating serum phosphate as a complementary marker could provide a more holistic view of a patient's metabolic status. Elevated serum phosphate could reflect the progressive accumulation of phosphate that traditional GFR thresholds or uremic symptoms might not yet indicate, particularly in asymptomatic patients. By identifying hyperphosphatemia early, clinicians can anticipate the need for hemodialysis and potentially reduce the risk of complications from delayed treatment, such as cardiovascular issues and bone disease [17].

Hyperphosphatemia's link with adverse cardiovascular outcomes highlights the importance of timely intervention. High serum phosphate levels are associated with increased vascular calcification, which can lead to cardiovascular morbidity and mortality-two prominent causes of death in CKD patients. This association underscores the utility of serum phosphate as a predictor of clinical risk, beyond the renal context, supporting its role as an additional marker in the initiation of hemodialysis. As kidney function declines and hyperphosphatemia worsens, the patient's cardiovascular burden increases, underscoring the need to manage serum phosphate proactively. Early dialysis could help mitigate this burden by providing an external means to control phosphate levels that the kidneys can no longer manage [18].

Another advantage of using serum phosphate as an additional marker is its ease of measurement and the feasibility of routine monitoring. Regular assessment of serum phosphate levels enables the tracking of trends in phosphate retention, potentially flagging patients who are not responding well to conservative management such as dietary phosphate restriction and phosphate binders. Such patients may benefit from early dialysis initiation to control their phosphate levels effectively. Notably, the study found that a mean serum phosphate level of 7.64 in patients who required dialysis compared to 5.05 in those who did not, with a P-value <0.001, suggesting a statistically significant difference that may guide clinical thresholds.

The findings also point to the potential for serum phosphate to serve as a more specific marker when paired with GFR and other traditional indicators. Elevated serum phosphate levels, even in the absence of overt uremic symptoms, may signal a need for dialysis, providing a metabolic benchmark that complements GFR's functional perspective. This combination could yield a more balanced approach to dialysis initiation, particularly for patients who might otherwise be delayed in receiving dialysis due to an absence of symptoms or a borderline GFR [19,20].

In advanced CKD, hormonal dysregulation of phosphate by PTH and FGF-23 also becomes relevant. As kidney function declines, these hormones attempt to compensate for reduced phosphate excretion, leading to secondary hyperparathyroidism and increased FGF-23 levels. While these hormones reflect an attempt by the body

to manage phosphate retention, they may not suffice to maintain homeostasis, as shown by rising serum phosphate levels. Thus, serum phosphate offers a more direct measure of phosphate retention and impending metabolic stress than PTH or FGF-23 levels alone. This direct relationship between serum phosphate and renal phosphate retention makes serum phosphate a potentially straightforward and reliable marker for clinicians considering RRT [21].

Furthermore, using serum phosphate as an indicator for dialysis initiation could improve clinical outcomes by enabling a more proactive approach to patient management. Rather than waiting for the onset of uremic symptoms or a critical GFR threshold, physicians could initiate dialysis based on a rising trend in serum phosphate levels, preempting complications that might arise from prolonged hyperphosphate mia. This strategy could ultimately reduce hospitalizations, slow disease progression, and possibly extend the patient's life expectancy by managing CKD more effectively before complications develop [22].

An important consideration in adopting serum phosphate as an additional marker is its standardization in clinical protocols. Establishing serum phosphate thresholds for dialysis initiation, as suggested by the study, could lead to more uniform practices across healthcare settings. The study's threshold of 6.10 for predicting dialysis initiation provides a foundation for these clinical guidelines, yet further research across diverse patient populations may be needed to validate this cut-off universally. Additionally, more extensive studies could explore the relationship between serum phosphate levels and other patient outcomes, such as quality of life, hospitalization rates, and long-term survival in advanced CKD patients, to further refine its use as a marker [23].

The limitations of relying solely on GFR and symptomatic presentation for dialysis initiation are underscored by this study's findings on serum phosphate's potential role. GFR-based criteria, while valuable, may not fully reflect the metabolic strain on patients in advanced CKD stages. Hyperphosphatemia's role in predicting dialysis needs speaks to a broader trend in nephrology that seeks to incorporate additional biochemical markers in decision-making. As CKD management evolves, markers like serum phosphate may help bridge the gap between functional impairment and metabolic burden, providing a more nuanced approach that could reduce the risk of both delayed and premature dialysis initiation [24].

Serum phosphate shows promise as an additional marker for hemodialysis initiation in patients with advanced CKD, particularly those exhibiting phosphate retention not adequately managed by conservative means. This research highlights that elevated serum phosphate levels are significantly associated with a need for dialysis, offering a predictive threshold that could enhance clinical decisions. By incorporating serum phosphate monitoring into routine CKD management, healthcare providers can anticipate dialysis needs earlier, potentially improving patient outcomes by mitigating the risks associated with delayed treatment. As the global burden of CKD rises, innovative approaches like this could have significant implications for healthcare systems and patient care, emphasizing the importance of further research to establish serum phosphate as a standardized marker in CKD management [25].

CONCLUSION

This study indicates that serum phosphate levels can be a useful marker for initiating hemodialysis in advanced chronic kidney disease (CKD). Elevated serum phosphate, reflecting phosphate retention, correlates with a higher dialysis need. A threshold value of 6.10 for serum phosphate, with a 98% sensitivity, offers clinicians a biochemical guide to dialysis timing, complementing traditional markers like GFR and uremic symptoms. Early dialysis based on serum phosphate could reduce complications such as cardiovascular and bone disorders, enhancing outcomes in CKD. Further research is needed to confirm these findings and standardize phosphate use in dialysis decisions.

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