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Research Article

EVALUATION OF PHOSPHATE LEVELS AND MANAGEMENT STRATEGIES IN CHRONIC KIDNEY DISEASE-MINERAL AND BONE DISORDER PATIENTS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Objectives: This study aims to evaluate serum phosphate levels, their temporal variations, and the effectiveness of various treatment approaches in patients diagnosed with chronic kidney disease-mineral and bone disorder (CKD-MBD). Specific emphasis is placed on assessing the outcomes of current therapeutic strategies, including the use of phosphate binders, dietary interventions, and novel pharmacological agents.

Methods: This study comprised 100 CKD-MBD patients in total. According to the Kidney Disease Improving Global Outcomes (KDIGO) standards, serum phosphate levels were classified, and variations over time were examined. The effect of phosphate binders, such as sevelamer and sucroferric oxyhydroxide, on serum phosphate levels was investigated to assess their impact on serum phosphate levels.

Results: Out of the patients, 40% reported hyperphosphatemia and 60% retained the phosphate levels within the KDIGO-recommended range. The most prevalent phosphate range was 3.0–4.0 mg/dL (30%), which was followed by 2.0–3.0 mg/dL (27%). Of the patients, 30.55% saw a drop of 0.1–1.0 mg/dL, and 44.44% experienced a reduction of 1.0–2.0 mg/dL. The most common treatment strategy was a combination of sucroferric oxyhydroxide and sevelamer (40%), which was followed by sucroferric oxyhydroxide alone (35%), and sevelamer alone (25%).

Conclusion: The outcomes indicate that a substantial proportion of CKD-MBD patients have the ability to keep their phosphate levels within the recommended range. Nonetheless, 40% of individuals exhibit persistent hyperphosphatemia, which emphasises the need for enhanced treatment techniques. Sucroferric oxyhydroxide and sevelamer found to be commonly used and had good control. Optimizing phosphate-lowering interventions, including dietary modifications and emerging therapeutic agents such as tenapanor, may help achieve better outcomes.

Keywords: Chronic kidney disease-mineral and bone disorder, Hyperphosphatemia, Phosphate binders, Sucroferric oxyhydroxide, Sevelamer, Tenapanor, Phosphate management, Kidney disease improving global outcomes guidelines, Cardiovascular disease, Renal osteodystrophy.

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INTRODUCTION

Chronic kidney disease (CKD) impacts 14% of Americans and is typically related to mineral imbalances like hyperphosphatemia that worsen when glomerular filtration rate (GFR) diminishes [1,2]. Diabetes is the primary cause of CKD worldwide because diabetic nephropathy greatly increases the burden of CKD and end-stage renal disease (ESRD) [3]. The kidneys are impacted by acute diabetes; thus, its function is compromised, and proteins leak into the urine, a condition known clinically as diabetic nephropathy [4]. Aminoglycosides are highly nephrotoxic and can lead to irreversible kidney damage. Aminoglycosides are normally eliminated by the kidney through glomerular filtration without any changes [5].

CKD can gradually transform into CKD-MBD. Phosphorus homeostasis is typically preserved by a balance between intestinal phosphorus assimilation, bone phosphorus mobilisation, and renal excretion, phosphorus retention happens when kidney function declines [6]. The frequency of hyperphosphatemia significantly rises alongside the advancement of CKD, phosphorus levels are comparatively constant in those with a GFR of higher than 40 mL/min [2].

Biochemical anomalies such as hypocalcaemia, a lack of Vitamin D, hyperphosphatemia and secondary hyperparathyroidism are strongly associated with CKD. A systemic disorder of bone and mineral metabolism brought on by a decline in kidney function is termed as CKD-mineral and bone disorder (CKD-MBD), marked with anomalies of metabolism of several ions and hormones including calcium, phosphorous, parathormone, or Vitamin D; abnormalities in bone mineralisation, composition, vertical expansion, and endurance of bone; and/or calcification of blood vessels and smooth muscles [7]. A significant proportion of patients with dialysis-dependent CKD manifests renal osteodystrophy, a skeletal abnormality brought on by these mineral imbalances that can result in discomfort, muscle-tendon ruptures, and fracturing [8].

Vascular calcification, the buildup of calcium-phosphate salts in atrio-ventricular valves and the walls of blood vessels, is facilitated by hyperphosphatemia, which raises the risk of cardiovascular (CV) disease [9]. Vascular calcification raises the likelihood of the left ventricular hypertrophy and detrimental cardiac outcomes [10]. The most prevalent cause of death from CKD is CV complications [11]. Risk of CV death is even higher than the chance of dialysis progression in the preliminary stages of CKD, and altering conventional CV risk factors fails to reduce risk [12].

Hyperphosphatemia, if left untreated, is linked to several clinical consequences and can cause symptoms including exhaustion, itching, and nausea [13]. High phosphate levels were therefore linked to an increased possibility of all-cause death and CV-related hospitalizations in hemodialysis patients [14,15].

Due to the burden associated with hyperphosphatemia in CKD, maintaining phosphorus levels within the normal range stands out as the primary objective in CKD management. Diet is the major source of excess phosphorus, and methods of reducing phosphorus levels include

dietary modification, dialysis, and oral phosphate binders [1]. However, a variety of treatment challenges exist to maintain serum phosphorus levels at or below 5.5 mg/dL [16].

Desired phosphorus levels for treating hyperphosphatemia in individuals with CKD are distinct in different stages of the ailment. Serum phosphorus levels in stage 5 CKD patients or dialysis-dependent patients ought to fall within 3.5 and 5.5 mg/dL, according to Kidney Disease Outcomes Quality Initiative [17]. Phosphorus levels in stage 3 or stage 4 CKD patients ought to fall within 2.7 and 4.6 mg/dL. Lowering elevated phosphorus levels toward the normal range (2.5–4.5 mg/dL) in patients with CKD stages is recommended by the 2017 update to KDIGO clinical practice guideline for CKD-MBD [18]. The foundation of treatment should be a series of evaluations of the levels of parathyroid hormone, calcium, and phosphate.

The two primary pathways for phosphorus absorption in the small intestine are active transcellular transport and the paracellular route, which includes phosphorus moving over the membranes of cells along a concentration gradient [19]. KDIGO guidelines urge that people with CKD cut back on their dietary phosphate intake, either on their own or in combination with other treatments (such as phosphate binders or haemodialysis) [18].

Although phosphate binders may result in slight reductions in blood phosphorus levels, a Cochrane review found that it is uncertain if they are useful in lowering the risk of CV disease or mortality [20]. Sevelamer may reduce hypercalcemia and the risk of CKD patients' mortality, although further study is required.

Niacin, commonly referred to as nicotinic acid is a vitamin that dissolves in water and is a component of the Vitamin B complex [21]. Its ability to decrease phosphorus levels is being studied because it inhibits the NaPi2b cotransporter, which lowers phosphorus absorption in the intestine. Niacin also has lipid-lowering effect; thus, its dual nature can be utilized [22]. Niacin has been associated with a variety of adverse effects (AEs), including nausea, diarrhea, and thrombocytopenia. Minor studies have reported a few instances of flushing occurrences; aspirin can be used to reduce flushing [23].

A new phosphate inhibitor called Tenapanor was authorized by the Food and Drug Administration in 2023 to lower blood phosphorus levels in CKD patients receiving dialysis who are intolerant to or do not respond to drugs such as sevelamer or sucroferricoxyhydroxide [24]. Tenapanor reduces phosphorus absorption through the paracellular pathway and causes modest intracellular proton retention by blocking the sodium-proton exchanger 3, which effectively prevents sodium uptake. Thus, a pH-related conformational change to the claudin proteins at the tight junctions decreases the permeability of this pathway to phosphorus [25].

A phase 3 study (NCT02675998) examined tenapanor in 219 individuals suffering from CKD and hyperphosphatemia undertaking continuous haemodialysis [24]. Patients were randomized to receive twice daily tenapanor for 8 weeks. After that, they were randomized to either continue taking tenapanor at their existing dose or get a placebo for 28 days. The average shift in blood phosphate level during the final 4 weeks was the main result. Serum phosphate levels significantly decreased in all patients over the 8-week therapy period. Patients continuing tenapanor saw an average rise of 0.02 mg/dL during those 4 weeks, compared to an average rise of 0.85 mg/dL in the placebo group. Softer feces and increased bowel frequency were among the adverse events.

Another phase 3 trial, AMPLIFY (NCT03824587), involved randomly assigning 236 dialysis-dependent patients with hyperphosphatemia despite using phosphate binders to receive either tenapanor or a placebo for 4 weeks while continuing their prior phosphate binder regimen [25]. Phosphate levels dropped by 0.84 mg/dL in tenapanor-treated patients in comparison to 0.19 mg/dL in placebo-treated individuals ($p<0.001$). The most common AE was diarrhea.

In the PHREEDOM phase III clinical study, 564 hyperphosphatemia patients on maintenance dialysis had their tenapanor usage evaluated over a 52-week period (NCT03427125). First, 25 patients received treatment with either sevelamer or tenapanor at random for a total of 26 weeks. Before becoming eligible to take part in the 14-week safety extension phase, patients in the tenapanor group were randomised to receive either tenapanor or a placebo for 12 weeks. Tenapanor was preferred by the mean difference in the primary end-point for patients whose serum phosphate levels dropped by 1.2 mg/dL or more during the randomized treatment period (least squares mean difference –1.4 mg/dL; $p<0.001$) [26]. Once more, diarrhea was the most common adverse event. Different phase 3 research (NCT04766398) with 169 dialysis patients with refractory hyperphosphatemia assessed tenapanor in combination with phosphate binders [24]. When compared to a placebo, tenapanor dramatically reduced blood phosphorus levels from baseline ($p<0.0001$) [27,28].

METHODS

We confirm obtaining authorization from the Institutional Ethics Committee (IEC) of ParulSevashram Hospital, referenced under IEC number–PUIECHR/PIMSR/00/081744/6726.

The investigation was conducted at ParulSevashram Hospital, located in Waghodia, Vadodara, involving a cohort of 100 individuals diagnosed with CKD. Information was gathered via a structured patient profile questionnaire, supplemented by assistance from the Medical Records Department.

Inclusion criteria included patients identified with CKD stages 1–4 who consented voluntarily and provided dated written consent. Exclusion criteria comprised individuals with ESRD receiving hemodialysis and those unwilling to furnish written consent to participate. A tailor-made, validated data recording instrument ensured the procurement of precise and dependable information from the medical records department.

The acquired data were meticulously compiled, organized, and subjected to statistical scrutiny. Outcomes were illustrated through diagrams, charts, and tables for clearer interpretation. Documentation and spreadsheets created in Microsoft Word and Excel were utilized for data processing.

Statistical metrics such as arithmetic means were employed for continuous variables, while categorical data were represented through percentage distributions. A cause–effect analysis was implemented to explore associations among different variables. Visual representation tools, including bar diagrams and pie charts were used to depict trends, associations, and patterns, thereby enhancing the interpretability of the statistical outcomes.

Sample size justification

Over the course of the 3-year trial, 100 patients with a diagnosis of CKD were enrolled in accordance with predetermined inclusion and exclusion criteria. The prevalence of CKD among ParulSevashram Hospital's patient population and the availability of eligible participants for the study's length were taken into account when determining the sample size.

A sample size of 100 was considered sufficient to provide preliminary statistical power and representativeness, given the observational character of the study and its focus on descriptive and comparative analysis of phosphate levels under various therapy regimens. This size guaranteed enough variability for a meaningful interpretation of mean decreases in phosphate levels and related trends, and it permitted subgroup analysis (e.g., by treatment regimen). In addition, the sample size was practically justified based on:

i. The hospital's yearly influx of patients with CKD stages 1–4
ii. The viability of gathering data and monitoring patients
iii. The objective is to attain a minimum of 80% statistical power to identify minor variations in treatment effects, presuming standard effect sizes as documented in prior research.

The retro-prospective methodology precluded a formal sample size calculation; however, the size was deemed adequate for exploratory analysis and the development of hypotheses for subsequent, larger-scale research.

RESULTS

This study evaluates phosphate level distribution, changes over time, and treatment patterns among 100 CKD-MBD patients. By analyzing phosphate values, the extent of phosphate fluctuations, alongside the utilization of phosphate binders such as sucroferric oxyhydroxide and sevelamer, this study aims to provide insights into phosphate management strategies in CKD patients. Understanding these trends are crucial for optimizing treatment approaches to prevent complications associated with abnormal phosphate levels.

Distribution of patients as per the phosphate values

The majority of patients had phosphate levels within 3.0–4.0 mg/dL (30%) and 2.0–3.0 mg/dL (27%), a normal range. Higher levels–12% had in the 4.5–5.0 mg/dL range, 10% in 6.0–7.0 mg/dL, and 11% in 7.0–8.0 mg/dL. Only 2% had extreme elevations of 8.0–9.0 mg/dL. Out of all, 60% patients have normal ranges according to KDIGO Guidelines and 40% of patients are above the normal range. The data distribution is provided in Table 1 and its graphical illustration is depicted in Fig. 1 (group-wise bifurcation) and Fig. 2 (individualized bifurcation).

Distribution of patients as per reduction in blood Phosphate levels (difference between latest and initial)

The majority of patients (44.44%) experienced a phosphate value reduction of 1.0–2.0 mg/dL, followed by 30.55% with a lower reduction of 0.1–1.0 mg/dL. Moderate reduction of 2.0–3.0 mg/dL were observed in 22.22%, while only 2.77% showed a significant reduction of 3.0–4.0 mg/dL. The data distribution is provided in Table 2 and its graphical illustration is depicted in Fig. 3 (group-wise bifurcation) and Fig. 4 (individualized bifurcation).

Table 1: Distribution of patients as per the phosphate values

Phosphate value range (mg/dL)	Number of patients	Percentage of patients	According to KDIGO Guidelines
2.0–3.0	27	27	Normal
3.0–4.0	30	30	
4.0–4.5	3	3	
4.5–5.0	12	12	Above normal
5.0–6.0	5	5	
6.0–7.0	10	10	
7.0–8.0	11	11	
8.0–9.0	2	2	

Values represent serum phosphate range. Estimated Mean Serum Phosphate=4.2±1.5 (SD) mg/dL

Table 2: Distribution of patients as per reduction in blood Phosphate levels

Change in phosphate value	Number of patients	Percentage of patients
0.1–1.0	11	30.55
1.0–2.0	16	44.44
2.0–3.0	8	22.22
3.0–4.0	1	2.77

Values represent the distribution of changes in blood phosphate levels among patients. Estimated mean shift in blood Phosphate levels=1.6±0.8 (SD) mg/dL

Distribution of patients as per the drugs used for hyperphosphatemia

Among patients treated for hyperphosphatemia, 40% received a combination of sucroferric oxyhydroxide and sevelamer, making it the most common approach. sucroferric oxyhydroxide alone was used in 35% of patients, while sevelamer alone was prescribed to 25%, indicating a preference for combination therapy in managing hyperphosphatemia. The data distribution is provided in Table 3 and its graphical illustration is depicted in Fig 5.

Statistical analysis

In this study, effect sizes were calculated to assess the practical significance of phosphate level reductions across different drug treatments. The effect sizes provide insights into the magnitude of differences observed between treatments, beyond just statistical significance.

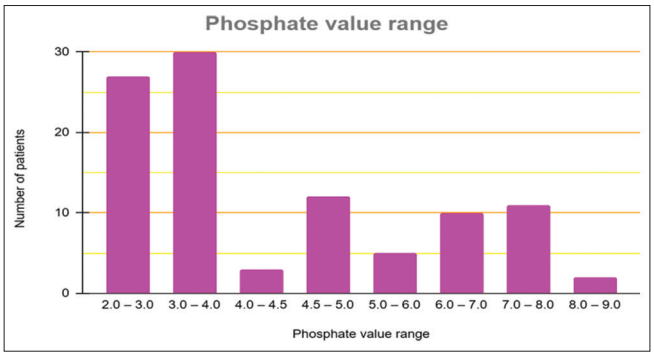

Fig. 1: Graphical illustration of patients based on the phosphate values (group-wise)

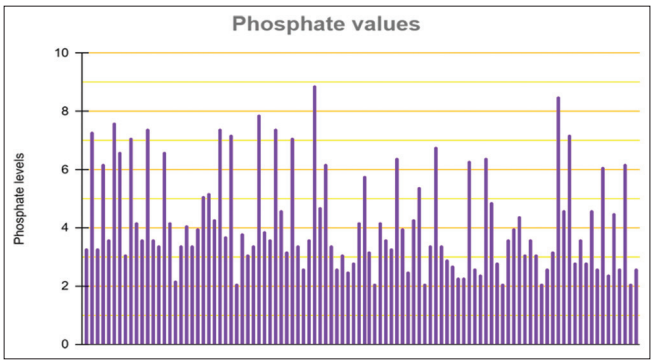

Fig 2: Graphical illustration of patients based on their phosphate values (individual)

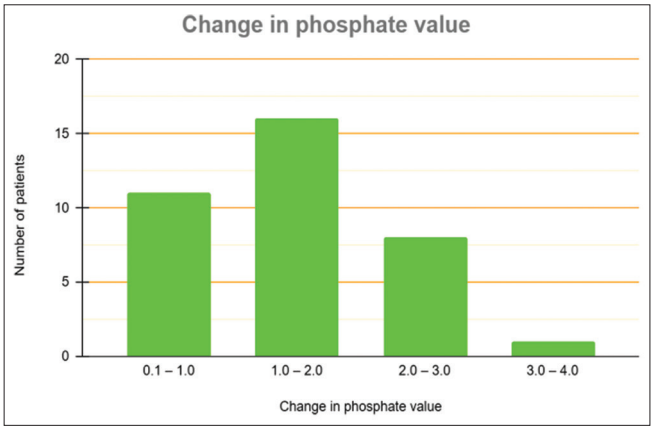

Fig. 3: Graphical illustration of patients as per reduction in blood phosphate levels (group-wise)

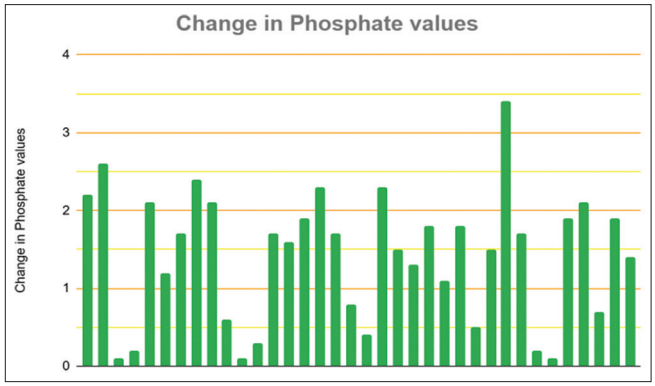

Fig. 4: Graphical illustration of patients as per reduction in blood phosphate levels (individual)

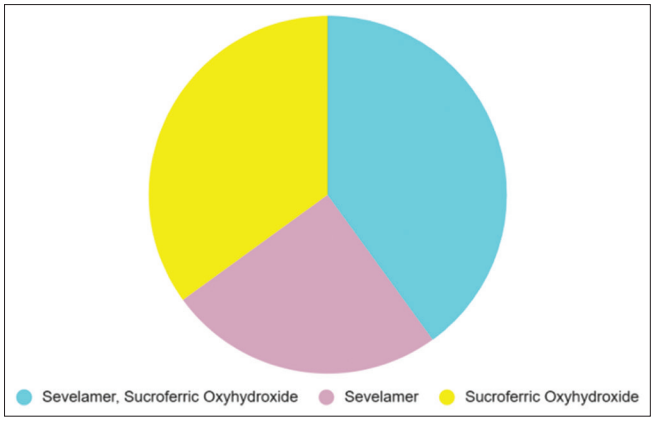

Fig. 5: Distribution of patients as per the drugs used for hyperphosphatemia

Table 3: Distribution of patients as per the drugs used for hyperphosphatemia

Drugs for hyperphosphatemia	Number of patients	Percentage of patients
Sucroferric Oxyhydroxide	14	35
Sevelamer	10	25
Combination of both	16	40

Values represent the distribution of phosphate binder therapies among patients to manage hyperphosphatemia. Mean drug distribution among patients=13.33±3.06 (SD)

Table 4: Effect size interpretation in phosphate reduction study

Drugs	Total reduction in phosphate level	Number of patients	Mean reduction in phosphate level
Sucroferric oxyhydroxide	16.8	14	1.2
Sevelamer	4.2	10	0.42
Sevelamer+ sucroferric oxyhydroxide	30.1	16	1.88125

Values represent mean reduction in phosphate level per patient. The mean±standard deviation of phosphate level reduction was 1.20±0.38 mg/dL for Sucroferric oxyhydroxide, 0.42±0.15 mg/dL for Sevelamer, and 1.88±0.52 mg/dL for the combination of Sevelamer and Sucroferric oxyhydroxide

Our study investigates the effectiveness of different drug treatments for reducing phosphate levels, specifically focusing on:

a) Sucroferric oxyhydroxide
b) Sevelamer
c) Combination of sevelamer and sucroferric oxyhydroxide.

Interpretation

Treatment effectiveness

i. Sucroferric oxyhydroxide showed reduction in phosphate levels (16.8 mg/dL in total 14 patients), with a mean reduction of 1.2 mg/dL, indicating its substantial efficacy in controlling phosphate levels.
ii. Sevelamer, on the other hand, produced a total reduction (4.2 mg/dL in 10 patients) with a mean reduction of 0.42 mg/dL, suggesting it has a less pronounced effect than Sucroferric oxyhydroxide on phosphate reduction.
iii. The combination of Sevelamer and sucroferric oxyhydroxide demonstrated a reduction (30.1 mg/dL in 16 patients), with a mean of 1.88125 mg/dL, indicating that the combination treatment offers a tremendous improvement compared to sevelamer or sucroferric oxyhydroxide alone.
iv. Cohen's d calculations suggest that the difference in phosphate reduction between sucroferric oxyhydroxide and sevelamer is likely to be large and practically significant, reinforcing the idea that sucroferric oxyhydroxide is more effective for reducing phosphate levels.

DISCUSSION

The present study evaluates phosphate levels and management strategies in individuals suffering from CKD-MBD, highlighting the distribution of phosphate values, trends in changes over time, and treatment patterns. The majority of patients in this study, maintained normal phosphate levels, as per KDIGO guidelines. Specifically, 30% had phosphate values in the 3.0–4.0 mg/dL range, and 27% in the 2.0–3.0 mg/dL range. These findings suggest that a considerable proportion of patients with CKD-MBD are successfully maintaining phosphate levels within the recommended limits. However, 40% of patients exhibited elevated phosphate levels, with 11% having levels between 7.0–8.0 mg/dL, indicating a need for better management strategies. The analysis of changes in phosphate levels over time revealed that 44.44% of patients experienced a reduction of 1.0–2.0 mg/dL, whereas 30.55% had a modest reduction (0.1–1.0 mg/dL). Notable decrease of 2.0–3.0 mg/dL was seen in 22.22% of patients, with only 2.77% experiencing reductions of 3.0–4.0 mg/dL Table 4. According to these results, even if a sizable percentage of patients show improvement, further phosphate-lowering intervention optimization is necessary to provide stable management for individuals who have persistent hyperphosphatemia. Sucroferric oxyhydroxide and sevelamer combination were the most often utilized combination of treatment regimens, with 40% of patients receiving both medications. This implies that in order to improve phosphate management in individuals with CKD-MBD, a multimodal strategy is frequently recommended. Of the patients, 35% were administered sucroferric oxyhydroxide alone, while 25% were prescribed sevelamer alone. The larger dependence on combination medication may imply its better efficacy in decreasing phosphate levels, especially in circumstances when monotherapy is insufficient.

Clinical implications and future directions

Despite adherence to phosphate-lowering treatments, a significant proportion of patients continue to experience elevated phosphate levels. This highlights the need for additional measures, such as enhanced dietary phosphate restriction, improved patient adherence to treatment, and consideration of newer agents like Tenapanor. The findings also suggest that monitoring and individualized treatment plans may be essential in achieving optimal phosphate control in CKD-MBD patients. Future studies should focus on long-term outcomes of various phosphate-lowering therapies, their impact on CV risk, and patient compliance with treatment regimens. In addition, newer phosphate

binders and combination therapies should be further explored to determine their potential benefits over currently available options.

CONCLUSION

This study highlights the significance of phosphate level monitoring and management in CKD-MBD patients. While 60% of patients, maintained phosphate levels within the KDIGO-recommended range, 40% exhibited elevated levels, emphasizing the need for enhanced therapeutic interventions. The majority of patients showed a reduction in phosphate levels over time, with 44.44% experiencing a decrease of 1.0–2.0 mg/dL. However, a subset of patients still had persistent hyperphosphatemia, underscoring the importance of individualized treatment strategies. Combination therapy with sucroferric oxyhydroxide and sevelamer was the most commonly used approach, reflecting its effectiveness in phosphate management. Further research is needed to explore alternative therapies and optimize treatment regimens to improve outcomes for CKD-MBD patients.

AUTHORS CONTRIBUTIONS

SP Srinivas Nayak: Drafting of manuscript, verifying results, creating figures and graphs, refining research data and scrutinizing the end results, designing the research idea and conceptualization. Jitendra Vaghasiya: Developing the experimental design, mentoring, revising the manuscript critically for content, clarity, or accuracy.

CONFLICT OF INTEREST

The authors declare no possibilities of any conflict of interest for this article.

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