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Review Paper

The Critical Role and Therapeutic Necessity of Hypophosphatemic Formulations in Pediatric Chronic Kidney Disease

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ABSTRACT

Pediatric chronic kidney disease (CKD) represents a complex and evolving clinical entity with profound implications for long-term morbidity and quality of life. Unlike adult CKD, where the therapeutic focus often centers on dialysis adequacy and cardiovascular comorbidities, pediatric CKD care necessitates a developmentally sensitive and growth-oriented approach. One of the most critical, yet under-recognized, metabolic complications in this population is persistent hyperphosphatemia—a state of phosphate overload that exerts pathophysiological effects across skeletal, cardiovascular, endocrine, and neurological systems.

Phosphate is essential for multiple physiological processes, including skeletal mineralization, energy metabolism via ATP synthesis, cellular signaling pathways, and the regulation of acid-base balance. However, in the context of declining renal function, especially in the pediatric setting where high anabolic demands coexist with impaired renal excretory capacity, phosphate homeostasis is rapidly disrupted. This imbalance gives rise to secondary hyperparathyroidism, renal osteodystrophy, vascular calcification, and in severe cases, growth retardation and pubertal delay. The pediatric population, particularly in the early stages of growth, is uniquely susceptible to the consequences of hyperphosphatemia due to the dynamic interplay between growth plates, hormonal regulators, like PTH and FGF-23, and dietary intake. Traditional management strategies for hyperphosphatemia have focused on dietary phosphate restriction and phosphate binders. However, these approaches pose significant challenges in pediatric patients, including the risk of malnutrition, poor compliance due to palatability issues, and variable efficacy depending on phosphate source and bioavailability. In this context, the advent and refinement of hypophosphatemic nutritional formulations represent a significant paradigm shift. These specialized formulas are designed to meet growing children's full caloric, protein, and micronutrient needs while minimizing the intake of inorganic and highly absorbable phosphate. This systematic review explored the biochemical basis and clinical relevance of phosphate dysregulation in pediatric CKD, delineated its systemic complications with an emphasis on growth and bone health, and critically appraised the emerging role of hypophosphatemic formulas as a cornerstone

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therapeutic intervention. It synthesized findings from the current international clinical guidelines—including KDIGO, KDOQI, and ESPEN—while identifying critical gaps in pediatric-specific evidence. Moreover, it discussed the practical aspects of implementing hypophosphatemic strategies, such as regional availability, cultural adaptability, formulation palatability, and caregiver education.

Keywords: Hyperphosphatemia, Chronic kidney disease (CKD), Formula, Renal osteodystrophy, FGF-23, Secondary hyperparathyroidism, Child

Introduction

Pediatric chronic kidney disease (CKD) poses a uniquely multifaceted clinical challenge, merging the complexity of progressive nephron loss with the biological imperatives of childhood growth, neurodevelopment, and hormonal maturation. Among the spectrum of CKD-associated metabolic abnormalities, phosphate dysregulation—particularly sustained hyperphosphatemia—stands out not only for its prevalence but for its deep-rooted impact on multiple physiological axes. While adult CKD management typically addresses hyperphosphatemia to avert vascular calcification and cardiovascular mortality, in pediatric populations, the stakes are higher and more intricate: Phosphate imbalance derails linear growth, induces skeletal deformities, precipitates pubertal delay, and compromises neurocognitive integrity [1, 2].

Phosphate plays a central role in numerous biochemical and structural processes. It is a critical substrate for ATP generation, a structural component of nucleic acids and cellular membranes and an essential factor in bone mineralization. The kidney is the principal organ responsible for phosphate excretion, and its functional decline—beginning as early as CKD stage 2—triggers maladaptive hormonal cascades involving parathyroid hormone (PTH), fibroblast growth factor-23 (FGF-23), and vitamin D metabolites [3, 4]. These derangements collectively define the clinical entity known as CKD-mineral and bone disorder (CKD-MBD), which is not merely a skeletal syndrome but a systemic, progressive, and often silent determinant of long-term outcomes [5].

In children, the challenge of managing hyperphosphatemia is amplified by their ongoing growth and disproportionately high phosphate requirements. Paradoxically, the high amount of mineral needed for skeletal development becomes a pathological agent in the context of renal impairment. This duality necessitates a refined, developmentally attuned approach to phosphate control—one that limits serum phosphate without compromising nutritional adequacy [6]. Traditional dietary phosphate restriction, while conceptually sound, frequently collides with the high protein and caloric needs of pediatric patients, especially in infancy and early childhood. In such scenarios, hypophosphatemic nutritional formulations have emerged as a transformative intervention [7].

These specialized formulas are engineered to reduce bioavailable phosphate—particularly the inorganic additives most culpable for phosphate burden—while maintaining caloric density, protein quality, and micronutrient sufficiency [8]. Their use is especially relevant in pre-dialysis patients or those with early-stage CKD, where pharmacologic interventions may be deferred or minimized. Importantly, the role of these formulations transcends mere biochemical correction; they offer a platform for growth preservation and hormonal stabilization [9].

Despite their therapeutic promise, hypophosphatemic formulations remain underutilized and poorly standardized in pediatric nephrology. There exists a critical gap in guideline specificity, accessibility of age-appropriate products, and real-world implementation frameworks. Compounding these challenges is the paucity of pediatric-specific clinical trials, with most current recommendations extrapolated from adult data or based on expert consensus rather than high-grade evidence [10, 11].

This review sought to dissect phosphate metabolism in pediatric CKD, evaluate the short- and long-term consequences of sustained hyperphosphatemia, and critically appraise the therapeutic role of hypophosphatemic nutritional formulations. By integrating evidence from international guidelines, emerging clinical studies, and practical considerations in dietetics and patient adherence, we aimed to highlight hypophosphatemic formulas not as ancillary tools, but as foundational instruments in a growth-conscious, outcome-driven model of pediatric CKD care.

Pathophysiology of phosphate dysregulation in pediatric CKD

Phosphate homeostasis in healthy individuals is maintained by a delicate interplay between intestinal absorption, renal excretion, bone storage, and hormonal regulation involving FGF-23, PTH, and the active form of vitamin D, 1,25-dihydroxyvitamin D (calcitriol) [12, 13]. In pediatric patients with CKD, this regulatory network becomes progressively impaired due to declining nephron function, resulting in phosphate retention that initiates a cascade of pathophysiological events unique to the growing child.

The earliest detectable alteration occurs at CKD stages 2 or 3, where subtle phosphate accumulation is associated with a compensatory increase in FGF-23 secretion from osteocytes [14]. This hormone acts to suppress renal tubular reabsorption of phosphate and inhibit the synthesis of vitamin D. Initially protective, chronic FGF-23 elevation leads to a state of functional vitamin D deficiency, impairing intestinal calcium absorption and further destabilizing calcium-phosphate balance [15]. This biochemical milieu prompts secondary hyperparathyroidism (SHPT), wherein elevated PTH exacerbates bone resorption and further reduces skeletal phosphate buffering capacity, particularly detrimental in children with active growth plates [16].

Unlike in adults, where phosphate toxicity primarily contributes to cardiovascular calcification, in children, the consequences are compounded by the demands of ongoing somatic and skeletal development. Elevated phosphate levels interfere with chondrocyte differentiation and hypertrophic zone maturation within the epiphyseal growth plate, leading to delayed endochondral ossification and linear growth impairment [17, 18]. Concurrently, phosphate toxicity promotes vascular smooth muscle cell differentiation into osteoblast-like phenotypes, initiating medial calcification that may be undetected until adolescence or adulthood [19].

At the cellular level, hyperphosphatemia triggers pro-inflammatory and pro-oxidative signaling cascades that disrupt endothelial function and may affect neurogenesis and synaptic pruning during critical windows of cognitive development [20]. These systemic effects underscore phosphate's role as more than a metabolic ion—it is a pleiotropic effector capable of altering structural, hormonal, and neurological trajectories during childhood.

Moreover, the pediatric kidney has a diminished adaptive capacity compared to adults, with age-related variability in glomerular filtration rate (GFR), tubular transporter expression, and phosphate handling kinetics [21]. This makes the threshold for phosphate toxicity lower and the onset of its systemic sequelae earlier and more severe in the pediatric context. The net result is a phenotype of CKD-MBD that includes not only classical signs, such as elevated serum phosphate and PTH, but also subtle manifestations, such as growth velocity deceleration, increased fracture risk, and early cardiac remodeling [22].

Thus, phosphate dysregulation in pediatric CKD is not merely a late-stage marker of renal insufficiency; it is an early, central, and modifiable driver of multisystem pathology. Understanding these mechanisms is vital for guiding early intervention strategies—particularly nutritional and pharmacologic measures that address phosphate overload before irreversible developmental losses occur.

Clinical consequences and complications of hyperphosphatemia in pediatric CKD

Hyperphosphatemia in the context of pediatric CKD represents a potent, multisystem disruptor with far-reaching implications across the skeletal, cardiovascular, endocrine, neurological, and psychosocial domains. Unlike adult CKD patients—where hyperphosphatemia primarily correlates with vascular pathology—children endure a dual burden: The disruption of critical growth trajectories and the early initiation of irreversible metabolic and structural damage [23].

Mineral bone disorder and skeletal dysplasia

The hallmark complication of phosphate dysregulation in children is CKD-MBD. Chronically elevated phosphate levels suppress vitamin D production and induce SHPT, which in turn accelerates bone turnover and compromises mineralization. In growing children, this cascade disrupts endochondral ossification and leads to rickets-like features: Widening of growth plates, metaphyseal flaring, and lower-limb deformities [24, 25]. Prolonged phosphate imbalance contributes to low peak bone mass, increasing fracture susceptibility and the likelihood of early-onset osteoporosis in adulthood [26].

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Growth retardation

Growth impairment in pediatric CKD is multifactorial, yet hyperphosphatemia exacerbates it significantly. Elevated serum phosphate inhibits chondrocyte hypertrophy and disrupts the signaling axis of insulin-like growth factor-1 (IGF-1) and growth hormone (GH), both vital for linear height progression [27]. Additionally, skeletal resistance to GH in the uremic milieu is compounded by PTH excess and phosphate toxicity. Children with sustained hyperphosphatemia often exhibit decreased growth velocity, height-for-age z-score reduction, and delayed skeletal maturation [28].

Cardiovascular calcification and early vascular disease

Vascular calcification—once considered a late-stage adult complication—has currently been documented in pediatric CKD, particularly in those with prolonged hyperphosphatemia and elevated calcium-phosphate product. Phosphate-induced phenotypic transformation of vascular smooth muscle cells into osteoblast-like cells initiates medial arterial calcification, contributing to increased arterial stiffness, elevated pulse wave velocity, and left ventricular hypertrophy (LVH) [29, 30]. These subclinical changes foreshadow a trajectory of premature cardiovascular morbidity and mortality, with dialysis-dependent adolescents already exhibiting coronary artery calcification rates comparable to middle-aged adults [31].

Neurocognitive and developmental impact

The neurological ramifications of hyperphosphatemia remain underrecognized but increasingly substantiated. Elevated phosphate levels are associated with systemic inflammation and endothelial dysfunction, both of which impair cerebral perfusion. Animal models suggest that phosphate toxicity can influence hippocampal plasticity and synaptic maturation, while human data link CKD to lower cognitive performance, especially in attention, executive function, and processing speed domains [32, 33]. These effects are amplified in children, where brain development is in a critical window of plasticity.

Delayed puberty and hormonal dysregulation

The endocrine axis in children with CKD is vulnerable to phosphate-induced disruption. Chronic hyperphosphatemia interferes with hypothalamic-pituitary-gonadal signaling, resulting in delayed onset of puberty, impaired gonadotropin release, and altered sex steroid synthesis. These effects, combined with growth hormone resistance, contribute to delayed skeletal maturation and psychosocial distress [34].

Psychosocial and quality of life deterioration

Children subjected to long-term phosphate restriction and chronic illness often experience reduced health-related quality of life. Diet monotony, medication burden, physical limitations, and social isolation lead to anxiety, depression, and academic underperformance. Moreover, visible skeletal deformities and short stature may compound body image concerns and peer rejection [35].

Collectively, these complications are neither isolated nor sequential—they interact in a vicious cycle where one pathology exacerbates another. Hyperphosphatemia must thus be viewed not as a mere lab value to be corrected, but as a biologically aggressive condition that shapes the developmental, cardiovascular, and psychosocial destinies of children with CKD.

Management and therapeutic strategies for hyperphosphatemia in pediatric CKD

Managing hyperphosphatemia in children with CKD is a multifaceted and evolving challenge that requires an integrated, patient-specific, and developmentally appropriate approach. Unlike adults, pediatric patients experience ongoing linear growth, fluctuating metabolic demands, and dynamic renal handling of electrolytes—all of which complicate standard phosphate-lowering strategies. The overarching goal is not only to normalize serum phosphate levels, but to support optimal skeletal development, hormonal homeostasis, cardiovascular integrity, and psychosocial well-being [36].

Dietary phosphate restriction and hypophosphatemic nutritional formulas

Nutritional management is the cornerstone of first-line intervention. Given the centrality of nutrition to growth and neurodevelopment, indiscriminate phosphate restriction in children carries the risk of calorie and protein malnutrition. Hypophosphatemic formulas are designed to circumvent this risk by offering balanced macronutrient profiles with reduced phosphate content—particularly through the elimination of inorganic phosphate additives and modulation of protein sources [37].

These formulations are especially valuable in infants and toddlers reliant on formula-based diets and in children with early-stage CKD where pharmacologic therapies may not yet be indicated. Studies have dem-

onstrated improved serum phosphate control, delayed onset of secondary hyperparathyroidism, and enhanced adherence with hypophosphatemic formulas compared to standard phosphate-lowering diets [38].

Nevertheless, barriers to implementation remain: Limited availability in resource-poor settings, lack of standardized prescription protocols, high cost, and poor palatability. These factors necessitate innovation in formula design and expansion of accessibility through healthcare policy interventions [39].

Phosphate binders

When dietary measures are insufficient, phosphate binders serve as the primary pharmacological adjunct. These agents function by binding dietary phosphate in the gastrointestinal tract, thereby reducing its systemic absorption. Pediatric options include:

1) Calcium-based binders (e.g. calcium acetate, calcium carbonate): Effective and inexpensive, but pose a risk of positive calcium balance and vascular calcification, especially when combined with vitamin D analogs [40].

2) Non-calcium-based binders (e.g. sevelamer, lanthanum carbonate): Avoid calcium overload and may offer additional lipid-lowering benefits, but require higher pill burdens and may reduce absorption of fat-soluble vitamins [41].

3) Iron-based binders (e.g. ferric citrate, sucroferric oxyhydroxide): Provide the dual benefit of managing phosphate and improving iron status, though long-term safety data in pediatric cohorts are still limited [42].

Binder selection should be individualized based on phosphate levels, calcium status, iron indices, and tolerability. Frequent monitoring and dose titration are essential, particularly during growth spurts and changes in dietary patterns.

Vitamin D therapy and calcimimetics

Vitamin D analogs (e.g. calcitriol, paricalcitol) remain central to the management of secondary hyperparathyroidism but must be used judiciously to avoid exacerbating hyperphosphatemia. These agents increase intestinal calcium and phosphate absorption while suppressing PTH secretion [43].

Calcimimetics (e.g. cinacalcet), though not yet approved in all regions for pediatric use, have shown promising off-label efficacy in children undergoing dialysis. They activate the calcium-sensing receptor on parathyroid cells, thereby reducing PTH secretion without increasing phosphate or calcium levels [44].

Dialysis optimization

In children receiving dialysis, phosphate removal is determined by frequency, modality, and duration of treatment. While conventional hemodialysis removes moderate amounts of phosphate, intensified strategies, such as nocturnal hemodialysis or frequent peritoneal dialysis may enhance clearance [45]. Adjustments in dialysate calcium concentration and the use of individualized dialysis prescriptions can optimize outcomes.

Emerging therapies

Novel agents under investigation for pediatric use include:

1) Tenapanor: An inhibitor of sodium/hydrogen exchanger 3 (NHE3) that reduces phosphate absorption via the paracellular pathway [46].

2) Nicotinamide: Suppresses the NaPi2b transporter in the intestine; early studies show efficacy but concerns remain regarding hepatotoxicity and thrombocytopenia [47].

Biotherapeutics targeting FGF-23, microbiome modulation, and precision nutrition platforms represent future directions in pediatric phosphate management.

Monitoring and multidisciplinary care

KDIGO and KDOQI guidelines recommend age-adjusted phosphate targets and emphasize regular monitoring of serum calcium, phosphate, PTH, 25(OH)D, and growth parameters. The integration of nephrologists, pediatric endocrinologists, renal dietitians, pharmacists, and caregivers is essential for sustained adherence and outcome optimization [48].

Education and behavioral support are equally critical, particularly in adolescence, where treatment fatigue and social pressures may reduce compliance. Mobile health tools, adherence-tracking apps, and patient engagement programs are emerging adjuncts to traditional care.

Discussion

The evidence synthesized in this review strongly underscores the multifactorial complexity and high clinical relevance of hyperphosphatemia in pediatric CKD. Far beyond a simple biochemical abnormality, elevated

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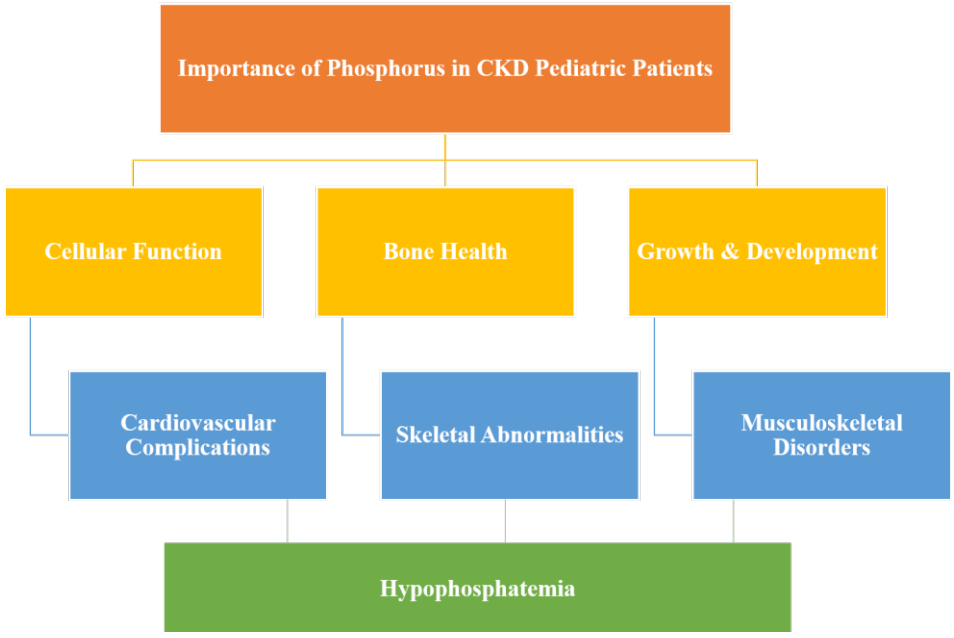

Figure 1. Pathophysiologic changes in phosphorus alteration

phosphate levels serve as a nodal point in the pathogenesis of a wide array of developmental, cardiovascular, skeletal, and neurocognitive derangements in this vulnerable population [49, 50]. Yet, despite decades of recognition, phosphate remains under-monitored, under-targeted, and often inadequately managed in pediatric nephrology [51].

Pediatric CKD patients face a distinct set of challenges: They are growing, hormonally evolving, neurologically plastic, and often dependent on caregivers for nutrition and medication adherence [52]. Hyperphosphatemia in this context is not merely a late-stage dialysis-related phenomenon—it begins early, accelerates systemic derangements, and imprints on future health trajectories [53]. Figure 1 shows pathophysiologic changes in phosphorus alteration.

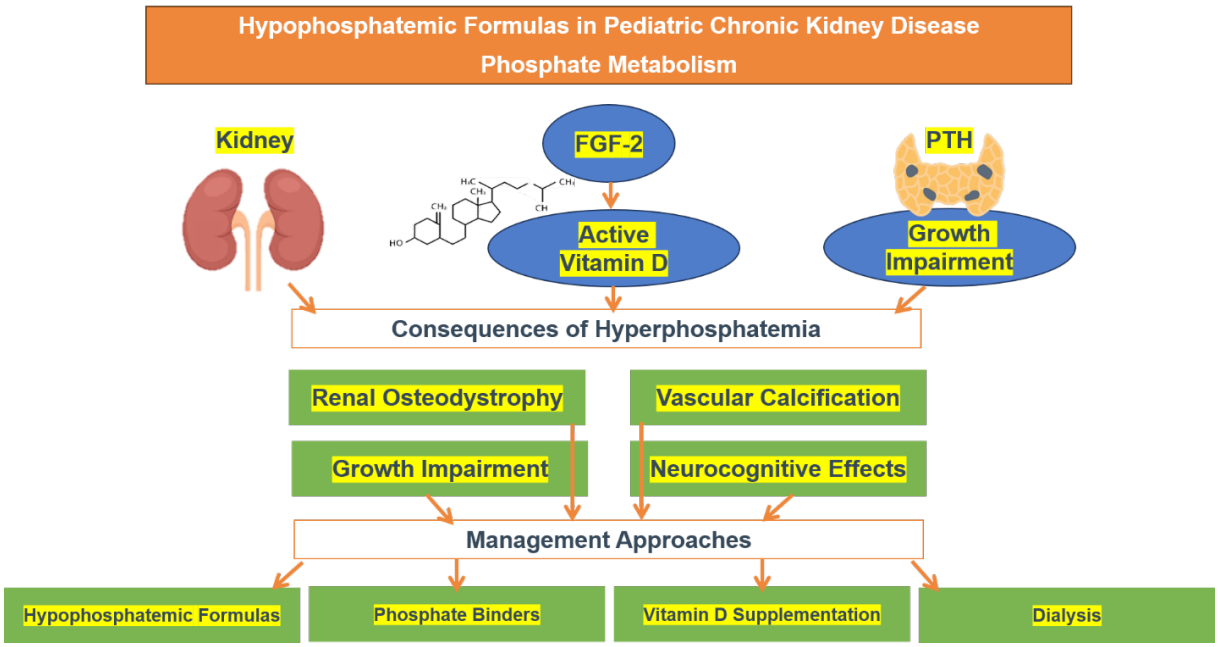

Figure 2. Indications of hypophosphatemic formula in pediatric diseases

Hypophosphatemic formulas represent an underutilized yet highly promising therapeutic tool that directly addresses the dual need for phosphate control and nutritional sufficiency. Their effectiveness is supported not only by improved biochemical parameters but also by ancillary outcomes, such as delayed onset of secondary hyperparathyroidism, preserved growth velocity, and reduced reliance on phosphate binders [54, 55]. Moreover, the palatability, composition, and accessibility of these formulas play a nontrivial role in treatment adherence—an aspect frequently overlooked in guideline recommendations [56]. Figure 2 shows the indications of hypophosphatemic formula in pediatric diseases. Nonetheless, significant gaps persist. Most clinical trials evaluating phosphate-lowering strategies have been conducted in adult populations or have not stratify the results by age. There is a striking lack of randomized controlled trials assessing long-term outcomes of hypophosphatemic formula use in children. Furthermore, regional disparities in product availability, insurance coverage, and healthcare provider training continue to limit real-world implementation [57].

An additional consideration is the psychosocial burden borne by pediatric CKD patients. The long-term imposition of restrictive diets, polypharmacy, and invasive treatments has measurable effects on the quality of life and psychosocial development. Interventions, like hypophosphatemic formulas—which can simultaneously alleviate biochemical risk and reduce treatment burden—may confer dual clinical and psychosocial benefits [58]. As such, they deserve greater emphasis in both clinical guidelines and policy planning.

From a translational standpoint, future directions must include the development of age-adjusted phosphate targets, expanded access to pediatric-specific formulations, and digital health tools to monitor dietary intake and adherence. Collaborative care models integrating nephrology, endocrinology, nutrition, psychology, and patient education will be vital in achieving sustainable, patient-centered phosphate control [59, 60].

The current paradigm for managing hyperphosphatemia in pediatric CKD requires recalibration. Phosphate must be re-framed as a developmental toxin, not just a dialysis-related solute. Hypophosphatemic formulas, when deployed early and strategically, have the potential to change the trajectory of pediatric CKD from progressive decline to growth preservation and improved quality of life. The time has come to elevate these tools from adjunctive options to essential components of pediatric renal care frameworks [61].

Conclusion

Hyperphosphatemia in pediatric CKD is not merely a laboratory abnormality—it is a biologically active and developmentally disruptive force that permeates virtually each axis of child health. From skeletal deformities and stunted linear growth to cardiovascular remodeling, neurocognitive impairment, delayed puberty, and diminished quality of life, its effects are pervasive and often irreversible if not promptly addressed. The compounded nature of these consequences mandates a proactive, integrative, and pediatric-specific management paradigm.

This review emphasizes the urgent need to transition from reactive to anticipatory care models in pediatric nephrology. Hypophosphatemic formulas stand out as a uniquely effective, yet underutilized, modality that simultaneously meets the metabolic demands of phosphate control and the nutritional imperatives of childhood growth. When introduced early and embedded within a multidisciplinary framework—including dietary counseling, pharmacologic precision, caregiver education, and psychosocial support—these formulations can redefine therapeutic trajectories for children with CKD.

The future of pediatric phosphate management lies in personalization. Precision nutrition, digital adherence tools, and age-stratified treatment algorithms must be developed to ensure that children with CKD receive care not borrowed from adult models but built for their unique biology. To achieve this, hypophosphatemic formulations should no longer be considered ancillary. They must be regarded as foundational elements in the early, sustained, and comprehensive management of phosphate burden.

In conclusion, the pediatric nephrology community must embrace a new standard: One in which phosphate is not simply lowered, but metabolically tamed; where nutrition is not restricted, but refined; and where growth is not sacrificed, but safeguarded. Accordingly, we can hope to disrupt the cascade of CKD-related complications and offer children with kidney disease not just survival, but thriving futures.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research. As patients were under 16 years old all the parents or guardians were informed and signed the informed consent form.

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interpretation of the results, and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

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