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DISORDERS OF PHOSPHATE HOMEOSTASIS AND EXTRAOSSEOUS CALCIFICATION: THE ROLE OF PHOSPHATE BINDERS IN MAINTENANCE HEMODIALYSIS

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Aim

End-stage chronic kidney disease (CKD) has been one of the most pressing medical problems of the last decade. The relevance of the topic reflects the high cost of socio-medical problems, the fact that not all patients participate in program hemodialysis, as well as the fact that the number of patients requiring hemodialysis is increasing four times a year. In developed countries, end-stage CKD is steadily increasing, and elderly patients over 55 years of age have a share of the risk of death.

Keywords: chronic kidney disease, vascular calcification, hemodializ

Abstract

End-stage chronic kidney disease (CKD) has been one of the most pressing medical problems of the last decade. The relevance of this issue is determined by the high socio-economic burden, limited access of patients to maintenance hemodialysis, and the steadily increasing number of individuals requiring renal replacement therapy, which is reported to grow up to fourfold annually. In developed countries, the prevalence of end-stage CKD continues to rise, while patients over 55 years of age represent a group with particularly high mortality risk.

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Disorders of mineral and bone metabolism in CKD are closely associated with vascular and soft tissue calcification, which significantly contributes to cardiovascular morbidity and mortality in patients undergoing maintenance hemodialysis. Hyperphosphatemia plays a key pathogenetic role in the development of extraosseous calcification and is an independent predictor of adverse cardiovascular outcomes and all-cause mortality.

Phosphate binders constitute the cornerstone of hyperphosphatemia management in dialysis patients. However, different classes of phosphate binders have distinct effects on calcium–phosphorus balance, vascular calcification, and clinical outcomes. Calcium-containing binders may aggravate extraosseous calcification, whereas non-calcium-based binders demonstrate potential benefits in reducing vascular calcification and systemic inflammation.

This review analyzes current evidence regarding the role of phosphate binders in the formation and progression of extraosseous calcification in patients on maintenance hemodialysis, focusing on their mechanisms of action, efficacy, safety profile, and impact on cardiovascular risk.

Keywords: chronic kidney disease, vascular calcification, mineral and bone disorder, phosphate binders, hemodialysis.

Introduction

Maintenance hemodialysis profoundly disrupts all regulatory mechanisms of calcium–phosphorus metabolism. Clinical manifestations of mineral imbalance in dialysis patients are comparable in severity to anemia, arterial hypertension, and lipid metabolism disorders. Hypocalcemia is frequently accompanied by hyperphosphatemia, which in turn represents a strong predictor of mortality in patients receiving chronic hemodialysis. Elevated serum phosphate levels independently worsen prognosis, accelerate the progression of ischemic heart disease, exacerbate systolic hypertension and left ventricular hypertrophy,

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increase the risk of arrhythmias, and promote the development of acute and chronic heart failure.

Even adequate maintenance hemodialysis, despite correcting many metabolic abnormalities, generally fails to normalize phosphorus–calcium metabolism. Therefore, pharmacological correction remains essential.

Renal Osteodystrophy and Mineral Bone Disorders in CKD

Treatment of renal osteodystrophy begins with correction of mineral and hormonal disturbances, including the use of vitamin D analogues, reduction of serum phosphate levels, administration of calcimimetics, and, when indicated, surgical correction of hyperparathyroidism. Pharmacological management of uremic osteodystrophy includes antiresorptive agents such as bisphosphonates and denosumab, widely used in senile osteoporosis. However, these drugs are contraindicated in adynamic bone disease, and there is insufficient evidence that high-dose bisphosphonates improve outcomes or reduce CKD-associated mineral and bone disorders. According to KDIGO recommendations, their use may be acceptable in selected patients whose characteristics correspond to those included in clinical trials, despite the limited evidence base.

Bisphosphonates selectively accumulate in osteoclasts, where they inhibit phosphatase activity and isoprenoid synthesis, suppressing osteoclast function and bone resorption. Oral bisphosphonates exhibit very low bioavailability (<1%), and approximately 50% of the absorbed drug is not taken up by bone and is excreted by the kidneys. Consequently, their efficacy depends on renal function and bone metabolic activity. These agents are contraindicated in patients with a glomerular filtration rate below 30 ml/min and low bone turnover markers indicative of adynamic osteodystrophy.

Several clinical trials and meta-analyses have evaluated bisphosphonates (risedronate and alendronate) in CKD patients, primarily with GFR >30 ml/min. These studies demonstrated increased bone mineral density of the lumbar spine but not the femoral neck, with only modest reductions in fracture risk. Data on

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their use in advanced CKD and long-term therapy beyond five years remain lacking.

Denosumab and Osteoanabolic Therapy. Denosumab is a monoclonal antibody against RANKL that inhibits osteoclast differentiation and activity, reducing bone resorption. Unlike bisphosphonates, denosumab is not renally excreted but metabolized by the reticuloendothelial system, allowing its use in severe renal impairment. The FREEDOM trial demonstrated its efficacy in reducing vertebral and hip fracture risk, including in patients with CKD. However, denosumab may induce hypocalcemia, secondary hyperparathyroidism, and vitamin D deficiency, which require appropriate supplementation. Evidence regarding its long-term safety and efficacy in CKD stages III–V remains limited.

Another therapeutic approach involves osteoanabolic agents such as recombinant parathyroid hormone (teriparatide, abaloparatide), indicated in patients with low or normal parathyroid hormone levels and confirmed adynamic bone disease. These agents increase bone turnover and mineral density without exacerbating extraosseous calcification, although hypercalcemia remains a potential adverse effect.

Phosphate Binders and Extraosseous Calcification. Correction of hyperphosphatemia is primarily achieved through phosphate binders, which reduce intestinal phosphate absorption by forming insoluble complexes excreted via the gastrointestinal tract. A major limitation of phosphate binder therapy is poor patient adherence due to high pill burden, large tablet size, and gastrointestinal adverse effects. Phosphate binders are classified as: Aluminum-based binders, associated with aluminum toxicity, anemia, and encephalopathy; Calcium-based binders (calcium carbonate and acetate), which may aggravate vascular and soft tissue calcification;

Magnesium-containing binders, which may reduce vascular calcification but increase serum magnesium levels;

Non-calcium, non-magnesium binders, including:

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Sevelamer hydrochloride, the first non-metal, non-absorbed anion-exchange binder;
Bixalomer, another non-absorbed polymer binder;
Lanthanum carbonate, a chewable binder requiring fewer tablets but associated with gastrointestinal adverse effects;
Iron-based binders (ferric citrate, sucroferric oxyhydroxide), which form insoluble complexes in the intestine with minimal gastrointestinal toxicity and mild increases in serum iron levels.
Sevelamer hydrochloride effectively corrects hyperphosphatemia and demonstrates additional benefits, including improved endothelial function, reduced systemic inflammation (lower C-reactive protein and interleukin-6 levels), hypolipidemic and hypoglycemic effects through bile acid binding. Its efficacy has been confirmed in multiple clinical trials.
Cardiovascular Implications of Mineral Disorders in CKD Cardiovascular disease accounts for 30–50% of mortality in hemodialysis patients. Vascular and valvular calcification, arterial stiffness, left ventricular hypertrophy, and myocardial dysfunction are highly prevalent in CKD and are closely linked to disturbances in calcium–phosphorus metabolism. Emerging biomarkers such as fibroblast growth factor-23 (FGF-23) and Klotho have been implicated in the pathogenesis of vascular calcification, endothelial dysfunction, and cardiac hypertrophy.

Conclusion

Disturbances of calcium–phosphorus metabolism in patients on maintenance hemodialysis play a central role in the development of extraosseous calcification and cardiovascular complications. Phosphate binders remain a key component of CKD-MBD management. Non-calcium-based phosphate binders appear to offer advantages in reducing vascular calcification and improving cardiovascular risk

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profiles. Further large-scale, long-term studies are required to establish optimal therapeutic strategies and improve outcomes in this high-risk population.

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