A Review on Management of Phosphorus in Hemodialysis Patients

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Abstract
Hyperphosphatemia is a common complication of end-stage renal disease due to decreased renal phosphate excretion. The ideal range for serum phosphate levels in CKD patients is between 3.5 and 5.5 mg/dl. CKD-MBD is linked to bone disease, cardiovascular calcification and higher morbidity and mortality rates. The management of hyperphosphatemia consists of 4 main strategies: (i) restricting dietary phosphorous intake (ii) reducing its intestinal absorption (iii) phosphate remapping and (iv) treatment and prevention of renal osteodystrophy. Phosphate binder drug therapy is the cornerstone of management. But in dialysis patient an average phosphorous intake is about 1500 mg/day or 10,500 mg/week and if it has 50% of absorption rate then more than 5000 mg of excess phosphorous has to be removed by dialysis. Hence a neutral phosphate balance can’t be maintained only with conventional hemodialysis or peritoneal dialysis. Hence the 3Ds of therapy for hyperphosphatemia therapy includes diet, dialysis and drugs.

Index terms – Hyperphosphatemia, CKD-MBD, diet, phosphate binders, hemodialysis.

INTRODUCTION
Hyperphosphatemia is a common complication of end-stage renal disease (ESRD) due to decreased renal phosphate excretion 1. Pruritus, bone disease and calciphylaxis are some of the signs of hyperphosphatemia 2. The ideal range for serum phosphate levels in CKD patients are still up for debate 3. In general, high serum phosphate levels are only seen in advanced stages of the disease. In the early stages of CKD there will be increased levels of parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF23) which increases phosphate excretion to maintain normal serum phosphate concentration 4. The management of hyperphosphatemia is based on 4 main strategies: (i) restricting dietary phosphate intake; (ii) reducing its intestinal absorption; and (iii) phosphate remapping (iv) treatment and prevention of renal osteodystrophy. The KDOQI guidelines of 2011 suggested that phosphate levels should be kept between 3.5 and 5.5 mg/dl, whereas the subsequent KDIGO guideline of 2009 and its recent update in 2017 opted for a less strict control, suggesting elevated phosphate levels 3. First of all, dietary limitation of phosphorus in the conventional sense is challenging and unreliable in the modern period because of the large levels of "hidden phosphates" from food additives that are present in our diet 5. Dietary phosphate restriction and three times a week dialysis are not sufficient or reliable ways to lower phosphate levels to 5.5 mg/dl 6. The cornerstone of therapeutic management for hyperphosphatemia is phosphate binder drug therapy 1.

PHOSPHORUS AND ITS ABSORPTION
In several foods especially in protein sources the widely found mineral is phosphorus. Organic phosphorus occur in natural form in animal and plant foods and whereas inorganic phosphorus is found in food additives such as processed foods 7. The bioavailability for plant-derived phosphates is very low, whereas the bioavailability for processed foods are much higher, as they consists of added phosphate salts. The bioavailability lies between these two extremes for the dairy products and animal-derived protein foods such as natural unprocessed meats, poultry and fish 8. The active phosphorus transport in the renal proximal tubules, leads to the absorption of phosphorus 9. Absorption of dietary phosphorus occurs in gastrointestinal tract through two different mechanisms, they are transcellular and paracellular pathways. Transcellular transport is considered to make up 20-35% of total intestinal phosphate absorption, whereas paracellular diffusion tries to make up 65-30% 5. The transcellular pathway is facilitated by type II sodium-dependent co-transporter NaPi2b for active uptake of phosphorus 10. When the luminal phosphate concentrations are high it is responsible for intestinal paracellular absorption through the tight junction complexes such as claudins and occludins across cell membrane 11.

PHOSPHATE HOMEOSTASIS
1% of the body's weight is made up of phosphorus. The majority of the body's organic phosphorus stores or hydroxyapatite crystals, are found in bone (85%). Less than 1% of the total phosphorus is contained in extracellular fluid, and the majority of other phosphates (14%) are intracellular. Adults typically have serum phosphorus levels between 0.81 and 1.45 mmol/L (0.81 to 2.5 mg/dl ). Extracellular phosphate is necessary for the mineralization of the bone matrix, but intracellular phosphate is engaged in intermediate metabolism and other vital cell processes. The amount of dietary phosphate consumed, the level of blood phosphate, and the activity of the hormones PTH, FGF23, various phosphatonin, and vitamin D are all important determinants of renal phosphate reabsorption 12. PTH, a phosphaturic hormone, lowers the reabsorption of phosphorus by the kidneys. The third primary and most recently identified phosphorus-regulating hormone, FGF23, is stimulated by both PTH and 1,25D. In bone, osteocytes create FGF23. A phosphaturic hormone called PTH, FGF23, controls the level of serum phosphorus. This hormone's primary job is to encourage phosphaturia 9.
PHOSPHATE AND CKD-MBD
A common co-morbidity in CKD patients is Chronic Kidney Disease - Mineral Bone Disorder (CKD-MBD) 13. In Chronic kidney disease, CKD-MBD is linked to bone disease, cardiovascular calcification, and higher rates of morbidity and mortality. It is diagnosed in the presence of bone abnormalities, cardiovascular or other soft-tissue calcification 14. During the early course of progressive renal insufficiency SHPT (Secondary Hyperparathyroidism) develops as a common consequence of chronic kidney disease-mineral bone disorder. It acts as an adaptive response to maintain phosphorous and calcium homeostasis 15. In the development of CKD-MBD, there are only few data available to explore the role of abnormal phosphate homeostasis and increased phosphate levels 16. In stage 3b of CKD patients the most important parameters such as the biochemical parameters of Chronic kidney disease-Bone mineral density alteration starts so routine examination should be done in CKD patients in stages 2-3a 17. The discovery of Klotho, was first thought to be a progeria-causing protein, and bone-derived phosphaturic fibroblast growth factor 23 (FGF23) as related factors has clarified the pathophysiology of CKD-MBD 18. Phosphate retention is the primary initiator and driver of the mineral and endocrine abnormalities that make up CKD-MBD 6. The primary preventive measures to manage risk factors are crucial in CKD-MBD 17. Dietary and lifestyle changes, dialysis, and medication treatment with phosphate binders, active/analog vitamin D and/or calcimimetics are the three cornerstone strategies that collectively work to regulate the three major laboratory values in CKD-MBD. The 3Ds of hyperphosphatemia therapy include diet, dialysis, and medications19.

HYPERPHOSPHATEMIA IN HEMODIALYSIS
Serum phosphorus levels over 4.5 mg/dl (1.45 mmol/L) in adults and over 7 mg/dl (2.26 mmol/l) in children are considered hyperphosphatemia. Clinical signs of severe acute hyperphosphatemia include tetany, increased neuromuscular excitability, and musculoskeletal weakness 12. There is evidence that higher serum phosphorus levels are linked to higher cardiovascular morbidity and mortality. According to a significant nationwide investigation, the risk of mortality for hemodialysis patients with chronic renal disease increased by 6% for every 1 mg/dl. To reduce excessive phosphorus levels, oral phosphate binders (PBs) can be used in conjunction with dialysis and dietary restrictions. Dietary restrictions should be designed to reduce phosphorous intake while maintaining adequate protein and other nutrient intake 20.

Phosphorus intake should be limited to 900 mg/day in CKD patients receiving dialysis, with or without the use of phosphate binders. It has not been demonstrated that restricting phosphorus intake improves these patients’ survival rates. After a maximum of three years of follow-up, the use of binders (chelating agents) has been linked to a 25-29% reduction in overall mortality and a 22% reduction in cardiovascular mortality 12.

TREATMENT
Dietary Restrictions: In diet the major challenge is to reduce phosphate intake 21. A patient quality of life may get affected negatively due to dietary restrictions which further causes some difficulties while interacting socially and leads to negative clinical outcomes. To avoid severe negative consequences associated with electrolyte overload, dieticians along with nephrologists advise the dialysis patient to consume low amount of fluid, K, Na and phosphate 22. Phosphorous is ingested as a food additive and natural component, as it is spread widely in nature and foods that we consume 21. Control of adequate phosphate provides resources for change in diet, adapting binder prescriptions which reflects the habit of non-linear eating, and clinical staff provides validation that suggests, important aspect of long term treatment of hemodialysis is management of hyperphosphatemia 24. Malnutrition occurs due to the restriction of protein in diet 25. Also a major risk factor for mortality in CKD patients 25. Increased content of Phosphorus to protein rich foods are milk, eggs mainly egg whites which contain low phosphatate and oily fish. Eggs are easy to cook, and contains leucine, while omega 3 fatty acid and vitamin D are rich in oily fish. Eggs and milk contain proteins which are slowly digested and allows for the synthesis of muscle protein 26. So awareness should be made regarding diet to dialysis patient for the better improvement in QOL 27.

Pharmacological Treatment:
Tenapanor
Tenapanor is a sodium/hydrogen exchanger isoform 3 (NHE3) non-binder inhibitor. A unique method of treating hyperphosphatemia is offered by tenapanor, an experimental first-in-class non binder phosphate absorption inhibitor that targets the main absorption pathway 6. Tenapanor directly reduces the amount of sodium that is absorbed, which results in a minor amount of intracellular proton retention and is thought to cause alterations in the conformation of tight junction protein 4. By locally inhibiting the sodium/hydrogen exchanger isoform, the drug tenapanor prevents paracellular absorption of phosphate in the GI tract 11.

Sevelamer
The first anion exchange binder which was introduced without metals that is also non-absorbable is sevelamer hydrochloride 3. It converts chloride ions into phosphate ions 4. Sevelamer may be superior to other phosphate binders because it causes fewer episodes of hypercalcemia, has an anti-inflammatory impact, lowers total cholesterol and low-density lipoprotein (LDL) cholesterol, and lowers uric acid levels 28. Cost, gastrointestinal side effects, and a relatively high pill burden are clinical problems with sevelamer therapy 3.

Lanthanum Carbonate
Lanthanum carbonate was introduced as the first palatable phosphate binder in 2004 3. It contains the rare earth element lanthanum, a trivalent cation that binds phosphate most effectively between the pH ranges of 3-5 29. The non-absorbable molecule lanthanum phosphate is formed in the digestive tract when lanthanum carbonate binds to phosphate 3. The pills must be thoroughly chewed in order to dissolve lanthanum carbonate due to their low solubility 30. Only 0.001% of an oral dose of lanthanum is absorbed
systemically, after which it is primarily eliminated through the bile and faeces. In contrast to sevelamer, lanthanum has a low pill burden. The key side effects of lanthanum were nausea, vomiting, diarrhoea, intradialytic hypotension, cramps, myalgia, and abdominal pain.

Calcium Based Compounds
In many regions of the world, calcium-based binders are still the most frequently recommended phosphate binders today. Calcium-containing binders are inexpensive and widely available, but for the past 20 years, they have not appreciably improved phosphorus management in dialysis patients. Both calcium carbonate and calcium acetate are widely accessible, reasonably priced, and useful for lowering serum phosphate levels. Although intravenous injections of activated vitamin D were used clinically to treat hyperphosphatemia, complications such as hypercalcemia, excessive parathyroid suppression, a dynamic bone disease, and calcification of soft tissues and blood vessels emerged.

Nicotinamide
The intestinal sodium-dependent phosphate transporter NaPi2b (also known as Ntp2b) is inhibited by nicotinamide and nicotinic acid (commonly known as niacin, which is converted to nicotinamide in the body). Numerous controlled and uncontrolled investigations conducted on chronic hemodialysis patients and non-dialysis CKD patients, respectively, demonstrated that niacin or nicotinamide therapy decreased serum phosphate. Flushing, nausea, diarrhoea, thrombocytopenia, and buildup of potentially hazardous metabolites were some of the negative consequences.

Compounds Containing Magnesium
It has been suggested that magnesium carbonate, which has a generally favourable gastrointestinal tolerance profile, is a suitable substitute for calcium acetate as a phosphate binder, enabling hemodialysis patients to lower their calcium load. Although a recent observational study has shown that mortality in dialysis patients is highest among those with the lowest serum magnesium, it is generally true that magnesium-based phosphate binders are less potent than most calcium salts and can have significant systemic absorption resulting in increased serum magnesium levels.

Ferric Citrate
The active component of ferric citrate hydrate is ferric citrate which is a novel phosphate binder. It works well to raise serum iron levels and lower serum phosphate levels. Ferric citrate binds with phosphate in the digestive system in exchange for citrate for the formation of ferric phosphate which is insoluble and expelled in the faeces. Iron can also be supplied as ferric citrate, however if the amount of ferric citrate is merely changed in relation to the phosphorus level, the amount of iron may decrease or become excessive. Citrate has been demonstrated to improve metal absorption, raising the danger of aluminium poisoning. As a result, all citrate-containing items are often avoided by CKD or dialysis patients.

Sucro Ferric Oxyhydroxide
A polynuclear, palatable phosphate binder with an iron base is called sucroferric oxyhydroxide. Patients undergoing dialysis are advised to utilise sucroferric oxyhydroxide. Since iron(III)-oxyhydroxide is essentially insoluble, the duodenal iron transporters are somewhat prevented from absorbing iron. In preclinical tests, sucroferric oxyhydroxide showed a high capacity for phosphate binding across the normal gastrointestinal pH range and little iron release.

Bixalomer
Similar to sevelamer in terms of phosphate reducing capability, bixalomer is a resin-based phosphate binder. Compared to sevelamer, it seems to be more gastrointestinal tolerable because the molecule absorbs less water, which results in less edoema and more fluidity.

Dialytic Control of Phosphorus
The management of hyperphosphatemia also includes the removal of phosphate using dialysis. Dialysis membrane surface area, blood and dialysate flow rates and ultrafiltration volume significantly influence clearance of phosphorus by hemodialysis. Although patients with ESRD have access to a variety of dialysis techniques, approximately 90% of patients receiving maintenance dialysis use intercenter conventional hemodialysis. Alternative to conventional hemodialysis include peritoneal dialysis and home dialysis. A rapid decline in serum phosphate levels occurs within first 60-90 minutes of introduction of hemodialysis, followed by a diminished phosphate gradient between plasma and dialysate which results in less effective transfer of phosphorus. About 1,800 – 3,600 mg of phosphorus per week can be removed by conventional hemodialysis. Around 300 mg /d of phosphate is removed by peritoneal dialysis. But in dialysis patient an average phosphorus intake is about 1,500mg/day or 10,500mg/week and if it has 50% of absorption rate then more than 5,000 mg of excess phosphorus has to be removed by dialysis. Hence a neutral phosphate balance can’t be maintained only with conventional hemodialysis or peritoneal dialysis. Hemodiafiltration may be another desirable approach, providing the benefits of diffusive hemodialysis and large convective volumes together but no extra benefits compared to high flux hemodialysis have been definitely confirmed.

CONCLUSION
All possible efforts should be made in the management of patient with ESRD to preserve the residual renal function because it is responsible for the clearance of uremic solutes including phosphate. Unfortunately dialysis such as hemodialysis and peritoneal dialysis have reduced phosphate excretion capacity and moreover phosphate intake is increasing due to wide use of phosphate containing food additives. Based on recent KDIGO guidelines it was estimated that 1 in 3 patients is not getting below 5.5mg/dl phosphorus and 2 in 3 are not getting towards the normal phosphorus level. Hence the entire healthcare team must have a complete understanding of why and how phosphorus must be regulated in order to ensure the well being of CKD patients.

REFERENCES