NEW PHOSPHATE BINDER IN MANAGEMENT OF CKD-MBD

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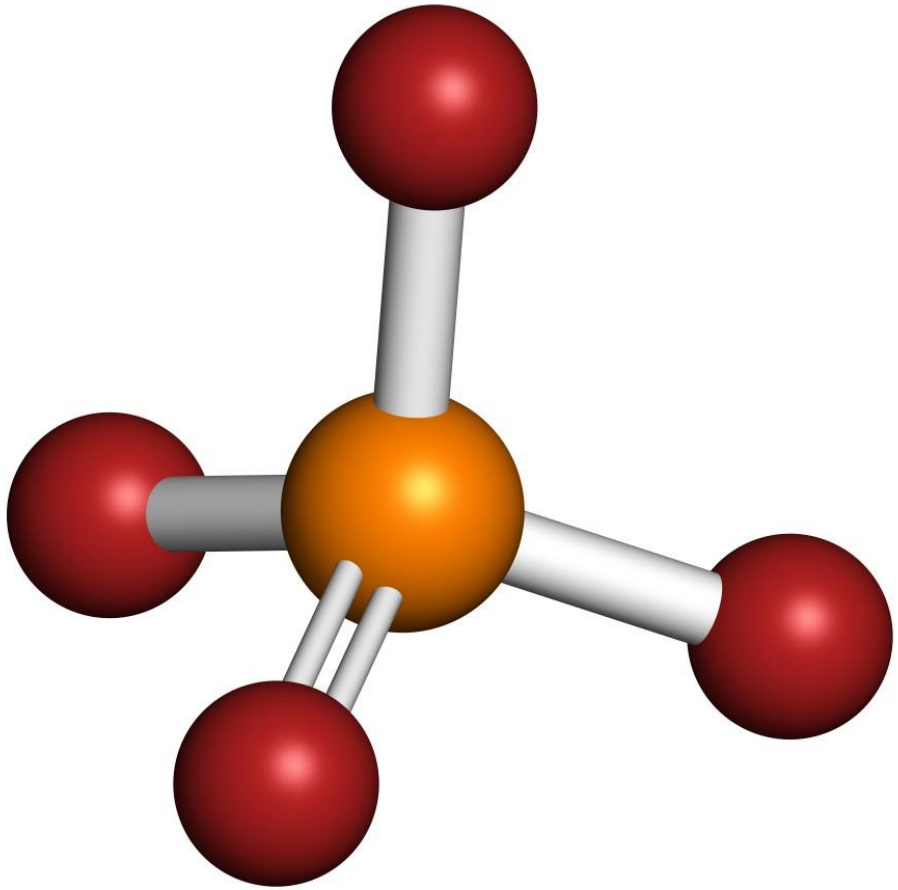
Professor of Nephrology Of HUMS



Kidney disease is an important public health problem with growing global burden.

The 2023 edition of the ISN-Global Kidney Health Atlas shows that 850 million people are affected worldwide by chronic kidney disease(CKD)

Stephenson Gehman GKHA. Global kidney health atlas 2023[Internet]; 2023. Available from: www.theisn.org/initiatives/global-kidney-health-atlas

CKD Stage	Prevalence of CKD-MBD
Stage 3 (eGFR 30–59 mL/min/1.73m²)	~40–50%
Stage 4 (eGFR 15–29 mL/min/1.73m²)	~60–80%
Stage 5 (eGFR <15 mL/min/1.73m² or on dialysis)	>90%

- **Phosphorus abnormalities are detected in ~40–50% of CKD stage 3–4 patients and in >80% of dialysis patients.**
- Secondary hyperparathyroidism (SHPT) is common, occurring in ~50–70% of stage 4 CKD and >90% of stage 5D (dialysis) patients.
- Vascular calcifications and bone disorders (osteodystrophy) are found in a majority of late-stage CKD patients.
- Hypocalcemia becomes more frequent as CKD progresses due to impaired vitamin D metabolism

DOI: 10.7860/JCDR/2020/44759.13902

CKD-MBD is systemic disease

CKD-MBD is known to be associated with increased CV

mortality, a significant cause of death in patients on dialysis.

Approximately 70% of patients on dialysis have left ventricular hypertrophy, a known risk factor for CVD and mortality that is strongly associated with higher phosphate concentrations.

Hypocalcemia and low Vitamin D (both 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D) concentrations have been associated with increased risk of CVD.

- U.S. Renal Data System. 2019 Annual Data Report: Epidemiology of kidney disease in the United States. National Institute of Diabetes and Digestive and Kidney Diseases; 2019.
- Kidney Int. 1995;47:186-192.

Mortality Risk Associated with Elevated Serum Phosphate

Study Findings (Block et al.):

- Serum phosphate levels >6.5 mg/dL are associated with increased risk of death (RR 1.27).
- This risk persists even after accounting for potential confounding factors like age, comorbidities, and other biomarkers.

Implications:

- Elevated phosphate levels are not just markers of disease severity; they are independent risk factors for mortality.

Am J Kidney Dis. 1998;31:607-617.
Transplant. 2007;22:2909-2916.

Role in Atherogenesis

Mechanism:

- Hyperphosphatemia contributes to vascular calcification by increasing calcium-phosphate product deposition in vascular smooth muscle cells.
- This promotes osteogenic transformation of vascular cells, a hallmark of vascular calcification.

Calcification stiffens arterial walls, contributing to atherosclerosis and cardiovascular events.

U.S. Renal Data System. 2019 Annual Data Report: Epidemiology of kidney disease in the United States. National Institute of Diabetes and Digestive and Kidney Diseases; 2019.

Hyperphosphatemia and CKD Progression

Mechanism:

Phosphate retention leads to increased secretion of fibroblast growth factor-23 (FGF-23) and parathyroid hormone (PTH).

Elevated FGF-23 has been linked to:

- **Renal tubulointerstitial fibrosis.**
- **Direct nephrotoxic effects.**

Persistent hyperphosphatemia drives a vicious cycle of secondary hyperparathyroidism and further nephron damage

Association between CKD-MBD and mortality in older patients with advanced CKD – results from the EQUAL study

Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD) is a common complication of CKD, associated with higher mortality in dialysis patients. Its impact in non-dialysis patients remains uncertain.

Population:
EQUAL cohort
1294 CKD non-dialysis

Exposure:
Baseline and time-dependent PTH, phosphate, and calcium, and their combined effect

Follow up: 5 years

Results

CKD-MBD prevalence at baseline: 94%

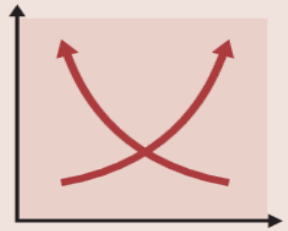
PTH

U-shaped association
All-cause and CV mortality

Phosphate

Linear association
All-cause, CV and non-CV mortality

Calcium



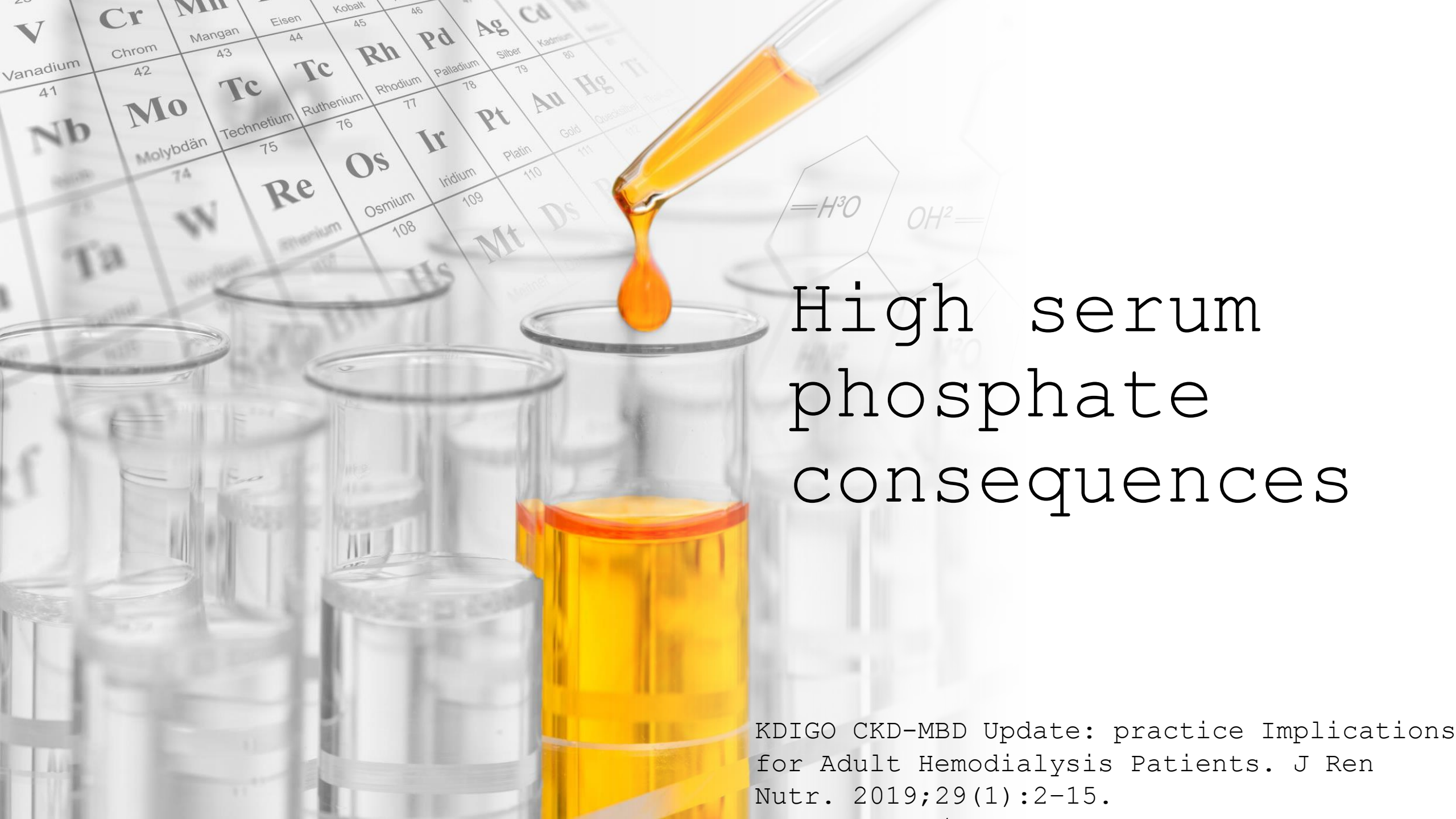
Not associated with mortality but effect modifier

Magagnoli, L. *et al.*
NDT (2023)
@NDTSocial

CKD-MBD is very common in older non-dialysis patients with advanced CKD. PTH and phosphate are independently associated with all-cause mortality in this population

Table 1. The degree of phosphate control is associated with reduced risk of cardiovascular (CV) morbidity and mortality

Author	Year of publication	No. of patients	Study type	Mortality	Morbidity
Block *et al.*[5]	2004	40,538	Observational	X	• All-cause hospitalization • CV hospitalization
Slinin *et al.*[98]	2005	14,829	Observational	X	CV events
Block *et al.*[75]	1998	6407	Observational	X	
Danese *et al.*[100]	2008	22,937	Observational	X	
Lopes *et al.*[41]	2020	17,414	Prospective cohort	X	



High serum phosphate consequences

KDIGO CKD-MBD Update: practice Implications for Adult Hemodialysis Patients. J Ren Nutr. 2019;29(1):2-15.

Hyperphosphatasemia is defined by a serum level higher than 4.5 mg/dL or 1.78 mmol/L.

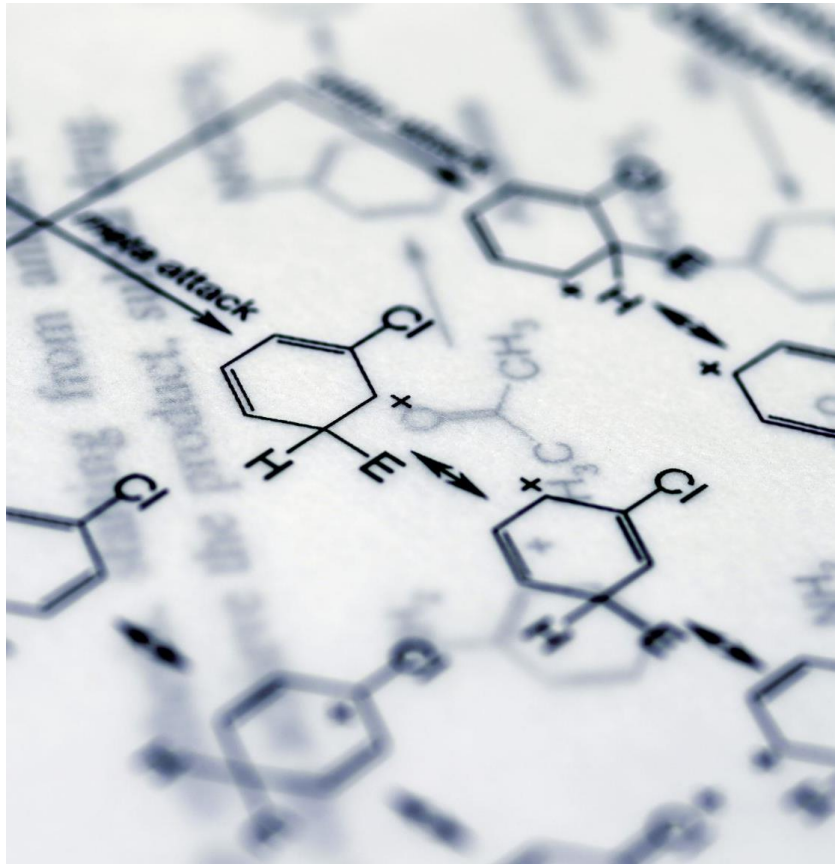
- ***General Population:*** About 12% of individuals experience elevated serum phosphate levels.
- ***End-Stage Renal Disease*** (ESRD): The incidence rises significantly, ranging from 50% to 74%
- ***Critically Ill Patients:*** Approximately 21% of critically ill patients exhibit elevated serum phosphate, as noted in a recent meta-analysis. This may be linked to factors such as tissue breakdown, cell lysis, or decreased renal function in critical illness.

Zheng WH, Yao Y, Zhou H, Xu Y, Huang HB. Hyperphosphatemia and outcomes in critically ill patients: a systematic review and meta-analysis. Front Med. 2022;9:1-11. doi:10.3389/fmed.2022.870637

Neurological Involvement

Hyperphosphatemia can affect the central nervous system (CNS) by causing:

- Hyperreflexia: Increased reflex activity.
- Muscle cramping and neuromuscular hyperexcitability.
- Severe outcomes like delirium, coma, or tetany due to disrupted calcium-phosphate balance and secondary hypocalcemia



Cognitive and Stroke Risks

Hemorrhagic Stroke in Dialysis Patients:

- Elevated phosphate levels may contribute to vascular calcification, increased arterial stiffness, and impaired cerebral perfusion, predisposing dialysis patients to intracranial hemorrhage.

Cognitive Decline:

- In pre-dialysis CKD patients, chronic phosphate retention has been associated with:
  - Accelerated cognitive decline.
  - Increased risk of incident dementia, possibly due to microvascular damage and neurotoxic effects of hyperphosphatemia

Impact in Sepsis

In septic patients, hyperphosphatemia acts as an independent risk factor for mortality.

- Mechanism: Likely related to worsening metabolic derangements, electrolyte imbalances, and systemic inflammation.
- Prognostic Implications: Higher serum phosphate levels correlate with increased mortality in septic conditions, further underscoring the systemic toxicity of hyperphosphatemia.

Pseudohyperphosphatemia

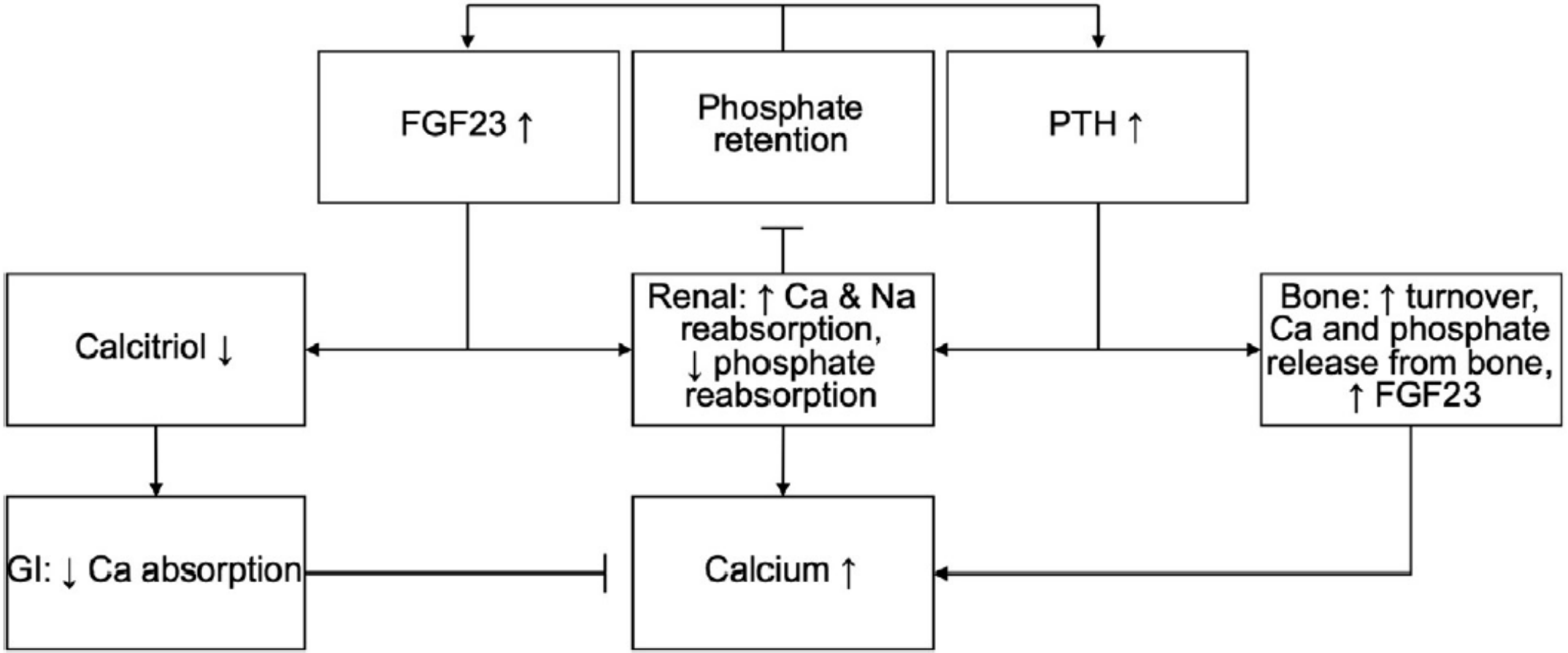
1. Hyperglobulinemia: Elevated levels of immunoglobulins can interfere with the assay.
2. Hyperbilirubinemia: High bilirubin levels, which often occur in liver disease, can interfere with some laboratory methods used to measure phosphate.
3. Hyperlipidaemia: High levels of lipids (fat particles) in the blood can lead to turbidity in the sample, which might

Phosphate excess may also indirectly exert noxious effects

- Inhibiting the renal transformation of 25(OH) vitamin D to 1,25(OH)2vitamin D
- Stimulating both FGF23 and parathyroid hormone (PTH) secretion.

- Hyperphosphatemia may develop when the estimated glomerular filtration rate (eGFR) falls below 25 to 40 mL/min/1.73m2

- Kidney Int. 2012;82:737–747.


FGF23 ↑
Phosphate retention
PTH ↑
Calcitriol ↓
Renal: ↑ Ca & Na reabsorption, ↓ phosphate reabsorption
Bone: ↑ turnover, Ca and phosphate release from bone, ↑ FGF23
GI: ↓ Ca absorption
Calcium ↑

The pathophysiologic mechanisms behind mineral abnormalities

CKD-MBD definition	CKD-MBD parameters	Abnormality	Pathophysiologic mechanism
Mineral homeostasis disorder	Calcium	↓	↑ Phosphate binding to calcium, ↓ calcitriol and bone resistance to PTH actions
	Phosphorus	↑	↓ Klotho → ↓ FGF23/FGFR1 affinity → FGF23 resistance in kidney → ↓ phosphaturia
	PTH	↑	↓ Calcitriol, ↑ phosphate and hypocalcemia → ↑ PTH → parathyroid hyperplasia
	Vitamin D	↓	FGF-23 → ↓ 1a-hydroxylase and ↑ 24-hydroxylase activity ↓ kidney mass → ↓ calcitriol

Note: ↑: increase, ↓: decrease, →: results in.

Abbreviations: CKD-MBD, chronic kidney disease-mineral and bone disorder; FGF23, fibroblast growth factor 23; FGFR1, fibroblast growth factor receptor 1; PTH, parathyroid hormone.

Patients not on dialysis

- For patients with nondialysis CKD, we initiate dietary modification when the serum phosphorus level is above normal (ie, ≥4.5 mg/dL [1.45 mmol/L]) with the goal of lowering serum phosphorus into the normal range.
- We only start phosphate binders when the serum phosphorus level is persistently elevated >5.5 mg/dL despite dietary restriction .
- For patients treated with a phosphate binder in addition to dietary modification, we target a serum phosphorus ≤5.5 mg/dL

Am J Kidney Dis. 2013 Oct;62(4 Suppl 3):S1-201

Patients on dialysis

- For patients on dialysis, serum phosphorus >5.5 mg/dL (1.78 mmol/L) is an indication for treatment.
- In most patients, aim to maintain the serum phosphorus concentration between 3.5 and 5.5 mg/dL inclusive (1.13 and 1.78 mmol/L), although there are no trial data demonstrating that lowering serum phosphorus to <5.5 mg/dL improves outcomes.
- KDIGO recommendations do not provide a practical goal.

Target Serum Phosphate Levels by CKD Stage

1. **KDIGO Clinical Practice Guidelines for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)**
   - Kidney Disease: Improving Global Outcomes (KDIGO) 2017 Update.
   - Available at: https://kdigo.org/
2. **KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease**
   - National Kidney Foundation (NKF), 2003 and subsequent updates.
   - Found in the American Journal of Kidney Diseases.
3. **Block GA, et al.**
   - "Association of serum phosphorus and calcium × phosphate product with mortality risk in chronic hemodialysis patients: A national study." *American Journal of Kidney Diseases*, 1998.
   - DOI: 10.1053/ajkd.1998.v31.pm9531176
4. **Kidney Disease Outcomes Quality Initiative (KDOQI)**
   - "Clinical Practice Guidelines for Nutrition in Chronic Renal Failure."
   - NKF, 2000.
5. **US Renal Data System (USRDS)**
   - Annual Data Reports on CKD and ESRD epidemiology.
   - Website: https://usrds.org/

Target Serum Phosphate Levels by CKD Stage

- CKD Stages 1–3 (eGFR >30 mL/min/1.73 m²):

  Phosphate levels should remain within the normal laboratory reference range (2.5–4.5 mg/dL).

- CKD Stage 4 (eGFR 15–29 mL/min/1.73 m²):

  Maintain levels near the upper limit of normal (around 4.0–4.5 mg/dL).

- CKD Stage 5/ESRD (eGFR <15 mL/min/1.73 m² or on dialysis):

  Target: 3.5–5.5 mg/dL

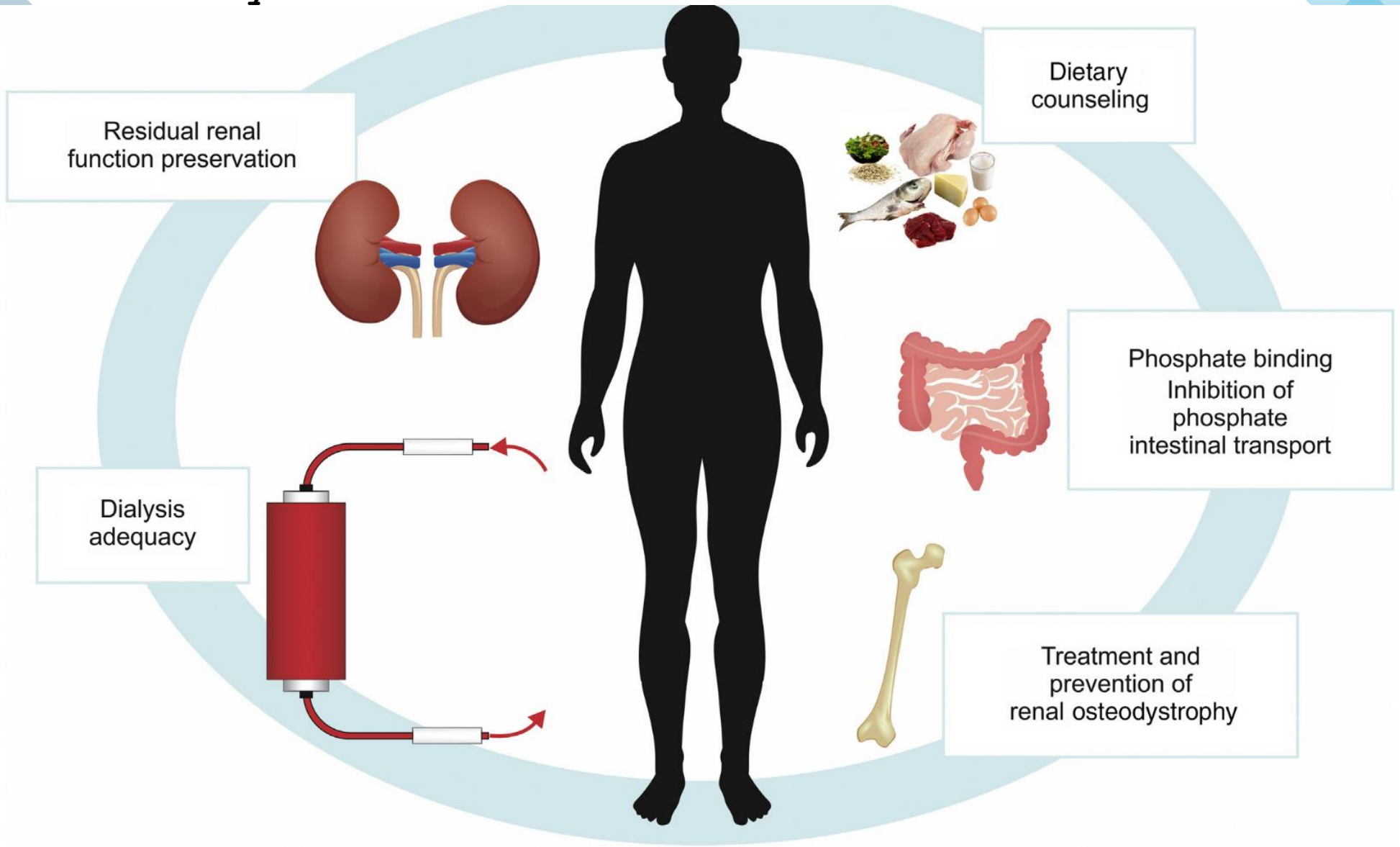
Patients on dialysis

For patients on dialysis, serum phosphorus >5.5 mg/dL (1.78 mmol/L) is an indication for treatment.

In most patients, we aim to maintain the serum phosphorus concentration between 3.5 and 5.5 mg/dL inclusive (1.13 and 1.78 mmol/L), although there are no trial data demonstrating that lowering serum phosphorus to <5.5 mg/dL improves outcomes.

K/DOQI clinical practice guidelines

Therapeutic approaches to control serum phosphate in patients with chronic kidney disease.



Class	Examples	Mechanism of Action	Advantages	Potential Side Effects
Calcium-Based	- Calcium acetate (PhosLo) - Calcium carbonate (Tums, Caltrate)	Binds phosphate in the gut, forming insoluble complexes	Effective and inexpensive Provides calcium	Hypercalcemia Vascular calcification
Non-Calcium, Non-Metal-Based	- Sevelamer carbonate (Renvela) - Sevelamer hydrochloride (Renagel)	Binds phosphate in the intestine without calcium or metal involvement	No risk of hypercalcemia Lowers LDL cholesterol	GI side effects (nausea, bloating, constipation)
Lanthanum-Based	- Lanthanum carbonate (Fosrenol)	Forms insoluble lanthanum-phosphate complexes	No systemic absorption Lower pill burden	GI upset Rare lanthanum accumulation
Iron-Based	- Ferric citrate (Auryxia) - Sucroferric oxyhydroxide (Velphoro)	Binds phosphate and provides iron for absorption	Iron supplementation Lowers IV iron needs	GI issues Dark stools
Aluminum-Based (Rarely Used)	- Aluminum hydroxide	Forms insoluble aluminum-phosphate complexes	Very potent phosphate binder	Aluminum toxicity (encephalopathy, bone disease)

Table 1. Main advantages and disadvantages of currently used phosphate binders

Drug	Usual dose (pill burden)[a]	Advantages	Disadvantages
Calcium carbonate	500–1250 mg (3–6 tablets)	Lower pill burden	Calcium overload
Calcium acetate	667 mg (6–12 capsules)	As effective as calcium carbonate	Calcium overload High pill burden
Magnesium carbonate	63 mg (2–6 capsules)	Good GI tolerance, lower pill burden	Hypermagnesemia
Sevelamer hydrocloride	800 mg (6–12 capsules)	↓ LDL-cholesterol levels, better survival in HD	High pill burden, GI side effects, metabolic acidosis
Sevelamer carbonate	800 mg (6–12 capsules)	↓ LDL-cholesterol levels, better survival in HD	High pill burden, GI side effects
Bixalomer	250 mg (6–14 capsules)	Good GI tolerance	High pill burden
Lanthanum carbonate	250–1000 mg (3–6 chewable tablets)	Lower pill burden, good GI tolerance	Low solubility Tissue accumulation, eg, bone
Ferric citrate	210 mg (4–5 tablets)	Lower pill burden, ↓ iron suplementation ↓ ESA doses	GI side effects (mild)
Sucroferric oxyhydroxide	500 mg (2–6 chewable tablets)	Lower pill burden	GI side effects (mild)

ESA, erythropoiesis stimulating agents; GI, gastrointestinal; HD, hemodialysis; LDL, low-density lipoprotein.
[a]Based on package leaftlet information or cited clinical trials.

ADVERSE EFFECTS

Drug	Hypercalcemia	Diarrhea	Constipation	Nausea	Vomiting
calcium acetate*	12.6	nr	reported	3.6	2.4
calcium acetate† n=167	12.6	nr	reported	3.6	2.4
calcium acetate (Phoslyra)‡	12.6	reported	nr	3.6	2.4
ferric citrate (Auryxia)	nr	21	8	11	7
lanthanum carbonate (Fosrenol) n=180	nr	reported	reported	11	9
sevelamer carbonate (Renvela)§	nr	nr§	nr§	nr§	nr§
sevelamer hydrochloride (Renagel) n=99	nr	19	8	20	22
sucroferric oxyhydroxide (Velphoro)	nr	4-24	nr	2-10	nr

Sucroferric oxyhydroxide(Velphporo)

- Sucroferric oxyhydroxide is a chewable phosphate binder for patients with eGFR <15 mL/min/1.73 m^2.
- Sucroferric oxyhydroxide appears to be comparable with sevelamer in efficacy and safety and may be associated with a lower pill burden.
- Adverse effects are primarily gastrointestinal, including diarrhea, nausea, abnormal product taste, constipation, and vomiting

- Kidney International (2014) 86, 638–647

Sucroferric oxyhydroxide

The starting dose of sucroferric oxyhydroxide is 2.5 g three times daily with meals or, if dosing is expressed in terms of elemental iron, 500 mg three times daily with meals.

The majority of iron from sucroferric oxyhydroxide is not systemically absorbed, although small increases in transferrin saturation and ferritin have been observed

Nephrol. 2017 Dec;30(6):755-765. doi: 10.1007/s40620-017-0421-y. Epub 2017 Jul 17.

Ferric citrate

- Ferric citrate is effective in reducing serum phosphate concentration by approximately the same degree as other phosphate binders .
- In addition, ferric citrate raises hemoglobin, serum iron, transferrin saturation, and ferritin .
- Patients on dialysis who take ferric citrate also may be receiving parenteral iron as part of an anemia management regimen; serum iron, transferrin saturation, and ferritin should be carefully monitored in such patients to avoid iron overload.

- Am J Kidney Dis. 2015 Sep;66(3):479-88. doi: 10.1053/j.ajkd.2015.03.013

Uncertain role for combination therapy

hard to control phosphorus, concurrent treatment with two types of phosphate binder (eg, sucroferric oxyhydroxide plus sevelamer or calcium acetate) may be effective.

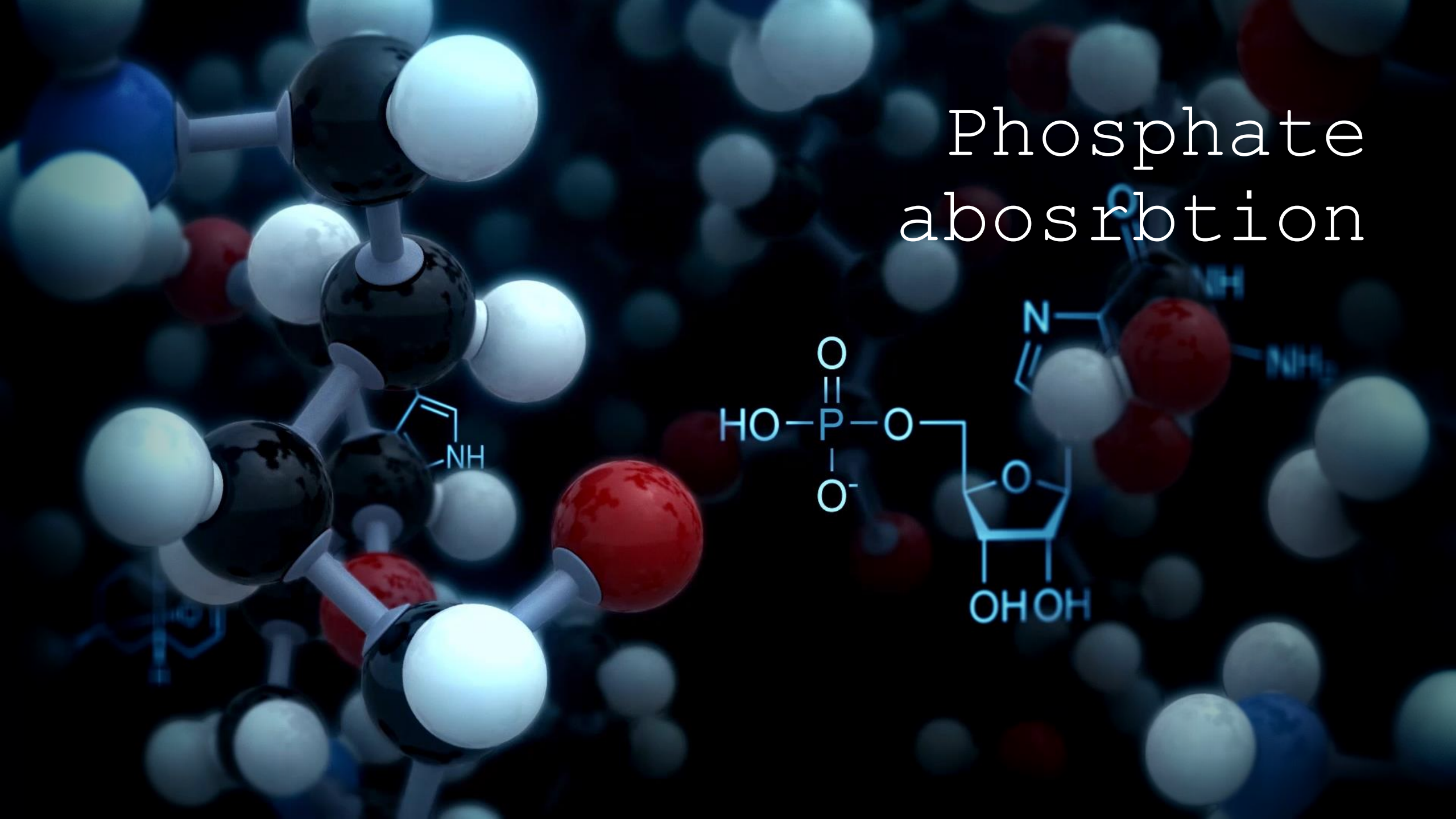
- The major downsides of combination phosphate binder therapy are an increased pill burden at mealtime, cost, and, potentially, an increase in gastrointestinal side effects.
- **With the advent of tenapanor as add-on therapy for patients on dialysis who are taking an appropriately up-titrated phosphate binder, the role of combination phosphate binder therapy is uncertain.**

- Kidney360. 2020 Mar 23;1(4):263-272. doi: 10.34067/KID.0000332019.

Refractory hyperphosphatemia

Drugs Targeting Intestinal Phosphate Transporters

Phosphate abosrbtion



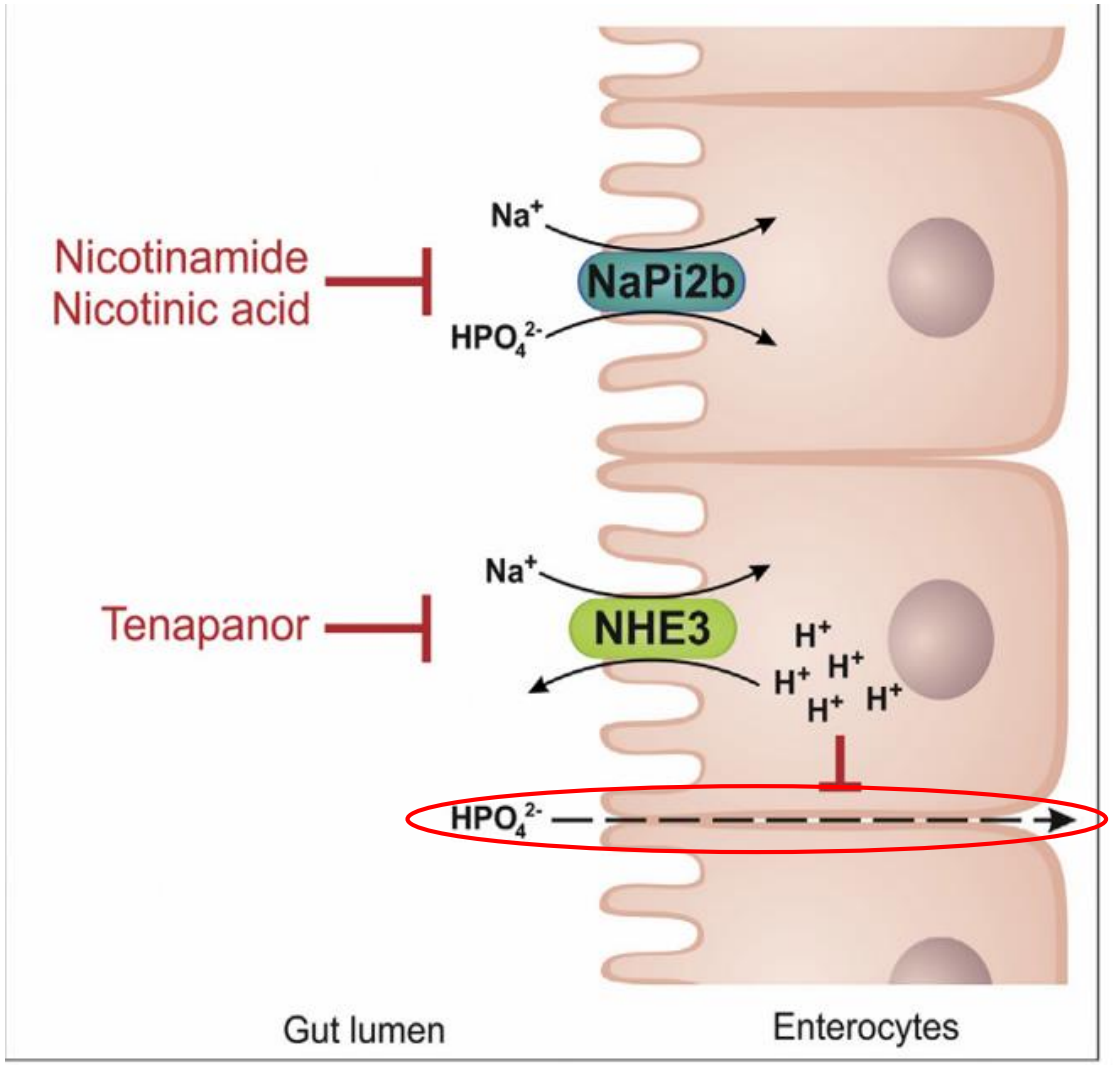
Passive Paracellular Transport (Major Route - ~70%)

Location: Mostly in the jejunum.

Mechanism:

Phosphate diffuses passively through tight junctions between intestinal epithelial cells.

This process depends on the phosphate concentration gradient between the intestinal lumen and the blood.

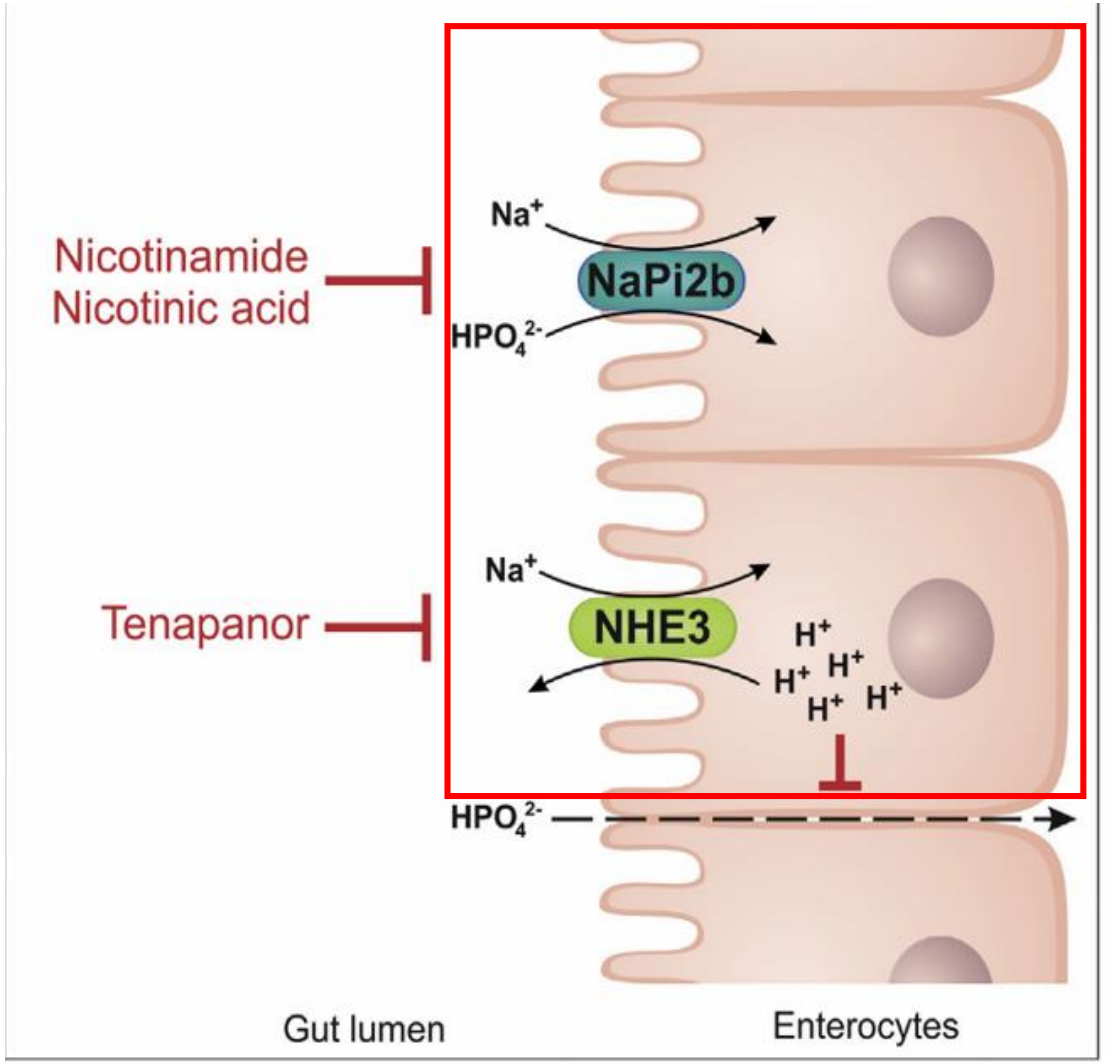


Active Transcellular Transport (Regulated - ~30%)

Occurs via sodium-dependent phosphate transporters (NaPi-IIb) in enterocytes.

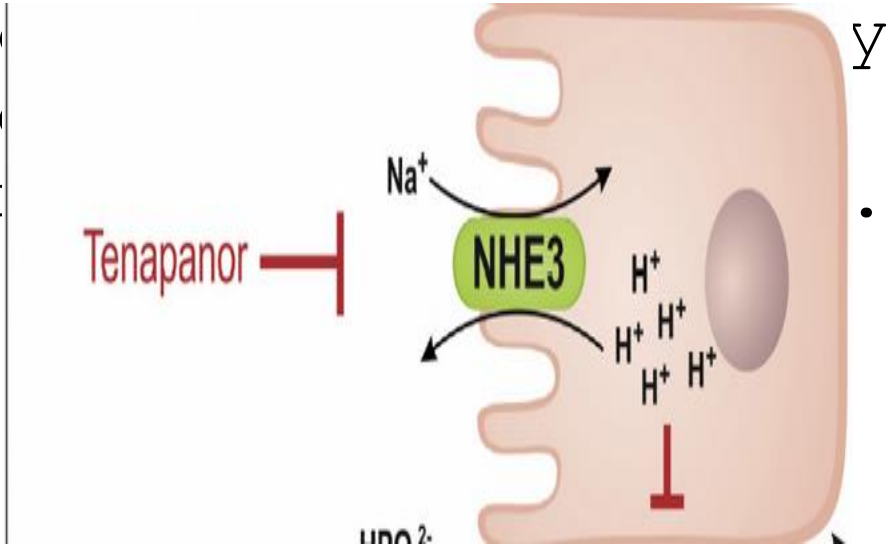
Requires energy and is upregulated by Vitamin D (1,25-dihydroxyvitamin D3).

Plays a crucial role during phosphate deficiency

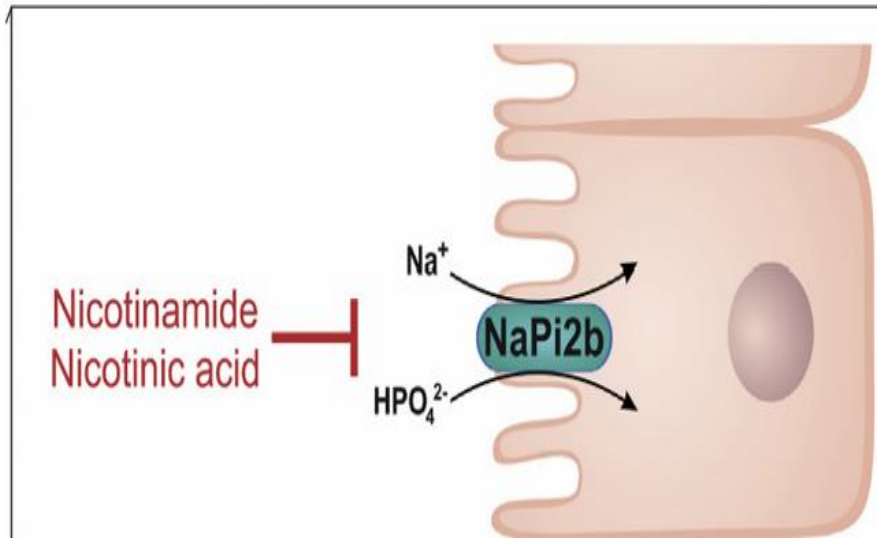


In addition, the sodium/hydrogen ion-exchanger isoform 3 (NHE3)

plays a role in secondary active phosphate absorption. This role role in ph y mo ju .



The sodium-dependent inorganic phosphate cotransporter NaPi2b is primarily responsible for phosphate absorption in the gut. (Nicotinic Acid and Nicotinamide)



Nicotinic Acid and Nicotinamide

- Nicotinic acid (niacin): A water-soluble organic compound that can be metabolized to nicotinamide (also known as niacinamide). It lowers sodium-dependent intestinal phosphate absorption via a reduction in NaPi2b expression.
- Degree of Reduction: The reduction in serum phosphate levels was generally modest, and side effects were frequent, leading to high dropout rates.
- Adverse Effects: These include flushing, nausea, diarrhea, thrombocytopenia, and

Nephrol Dial Transplant. https://doi.org/10.1093/ndt/gfz057. Accessed June 21, 2019
Nephrol Dial Transplant. 2005;20:1378-1384.

Nicotinamide

Nicotinamide as a single agent is not suited for hyperphosphatemia control in CKD.

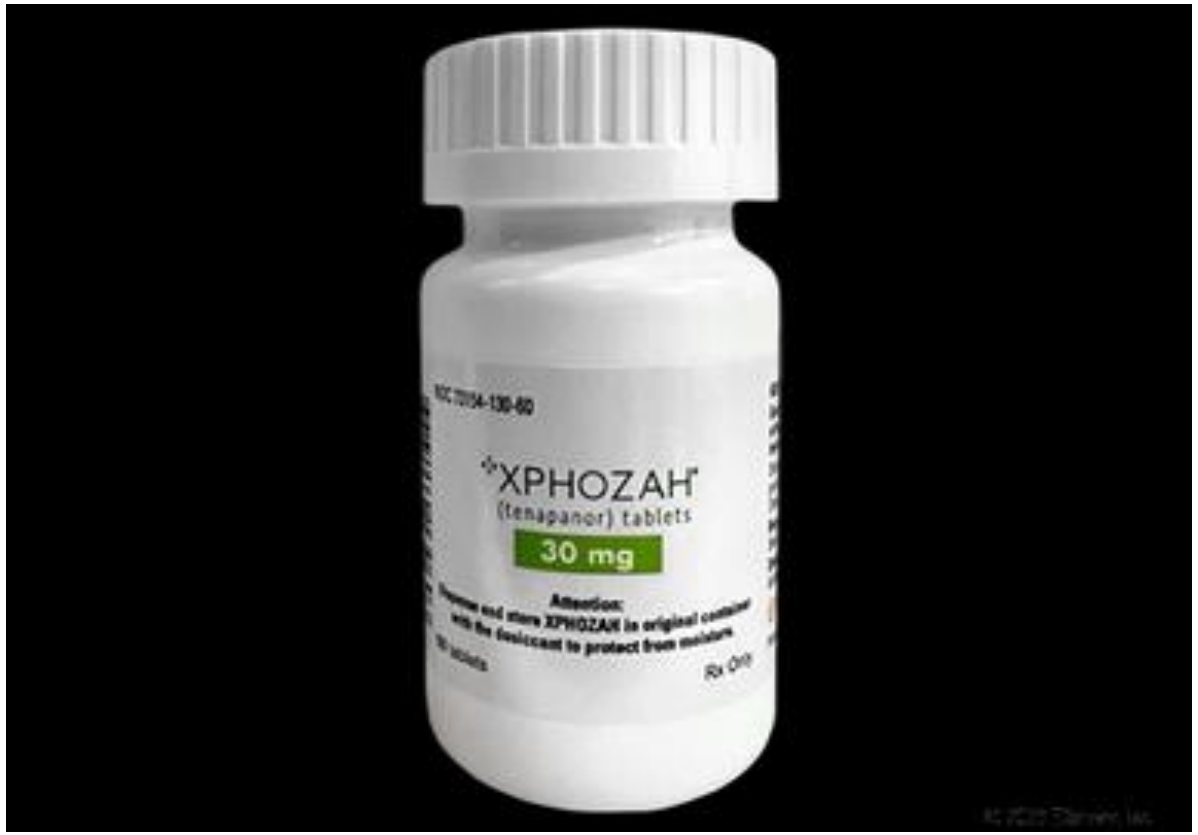
It has yet to be shown whether there remains

any place for low-dose nicotinamide treatment as add-

on therapy to established phosphate binders in patients with moderate to severe CKD or in dialysis patients

Massy ZA, Drueke TB. Vascular calcification - any place left for nicotinamide [epub ahead of print]? Nephrol Dial Transplant. June 21, 2019 https://doi.org/10.1093/ndt/gfz057

Tenapanor



XPHOZAH®
(tenapanor) tablets

Effect of Tenapanor on Serum Phosphate in Patients Receiving Hemodialysis

Block, Geoffrey A.[*]; Rosenbaum, David P.[†]; Leonsson-Zachrisson, Maria[‡]; Åstrand, Magnus[‡]; Johansson, Susanne[‡]; Knutsson, Mikael[‡]; Langkilde, Anna Maria[‡]; Chertow, Glenn M.[§]

Author Information

Journal of the American Society of Nephrology 28(6):p 1933-1942, June 2017. | **DOI:** 10.1681/ASN.2016080855

In a phase II randomized, double-blind, placebo-controlled, dose-finding study that assessed the effects of tenapanor on hyperphosphatemia in 162 patients

receiving hemodialysis therapy, this drug induced dose-dependent reductions in mean serum phosphate level from baseline, ranging from 0.47 to 1.98 mg/dl, with the largest reductions occurring in the tenapanor dosing groups, with good drug tolerability.

The most common adverse event causing discontinuation was diarrhea

CLINICAL RESEARCH www.jasn.org

Efficacy and Safety of Tenapanor in Patients with Hyperphosphatemia Receiving Maintenance Hemodialysis: A Randomized Phase 3 Trial

Geoffrey A. Block,[1] David P. Rosenbaum,[2] Andrew Yan,[2] and Glenn M. Chertow[3]

[1]Denver Nephrology Research Division, Denver Nephrology, Denver, Colorado; [2]Ardelyx Inc., Fremont, California; and [3]Division of Nephrology, Stanford University School of Medicine, Stanford, California

These findings have beenr confirmed in a phase III randomized, double-blind, placebo-controlled trial.

Tenapanor treatment for 8 weeks significantly reduced phosphate levels by a mean of 1.0–1.2 mg/dl in hyperphosphatemic hemodialysis patients.

Adverse events were mainly restricted to stool softening and increased bowel movements

CLINICAL RESEARCH www.jasn.org

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[1]Denver Nephrology Research Division, Denver Nephrology, Denver, Colorado; [2]Ardelyx Inc., Fremont, California; and [3]Division of Nephrology, Stanford University School of Medicine, Stanford, California

Study Objectives

To evaluate the potential of tenapanor, a sodium/hydrogen exchanger 3 (NHE3) inhibitor, in combination with phosphate binders to achieve better control of serum phosphorus levels compared to phosphate binders alone.

Design

Type: Randomized, double-blind, placebo-controlled, multicenter trial.

Participants: Adults on maintenance dialysis with hyperphosphatemia despite treatment with phosphate binders.

Interventions:

CLINICAL RESEARCH www.jasn.org

A Randomized Trial of Tenapanor and Phosphate Binders as a Dual-Mechanism Treatment for Hyperphosphatemia in Patients on Maintenance Dialysis (AMPLIFY)

Pablo E. Pergola,[1] David P. Rosenbaum,[2] Yang Yang,[2] and Glenn M. Chertow[3]

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JASN 32: 2021doi:https://doi.org/10.1681/ASN.2020101398

Key Findings

This double-blind phase 3 trial enrolled 236 patients undergoing maintenance dialysis with hyperphosphatemia (defined in this trial as serum phosphorus 5.5-10 mg/dl inclusive) despite receiving phosphate binder therapy (sevelamer, nonsevelamer, sevelamer plus nonsevelamer, or multiple nonsevelamer binders).

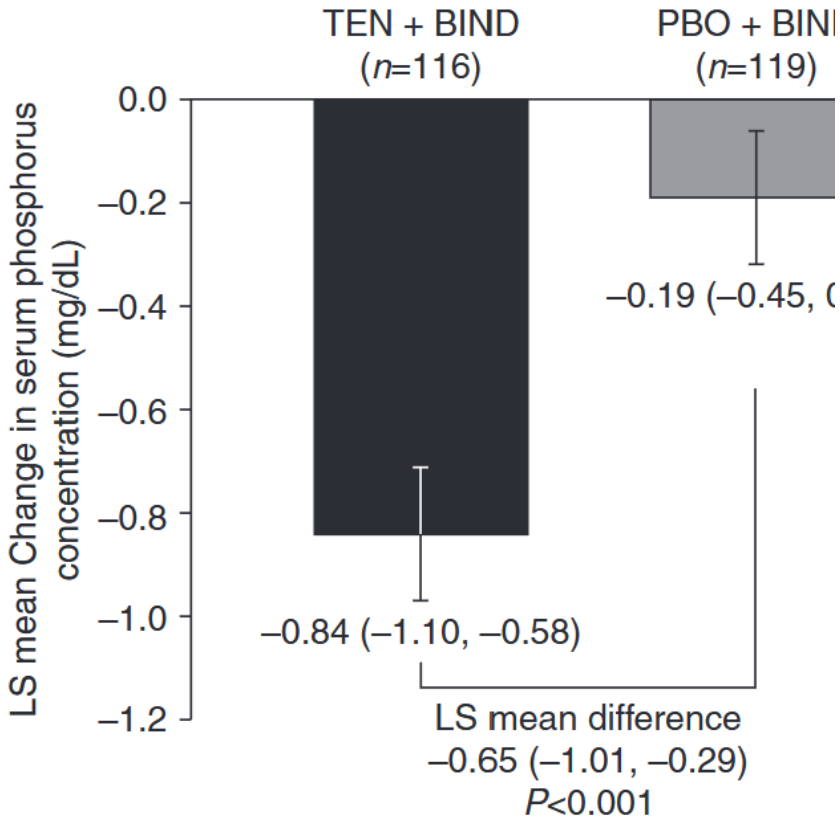
- Safety Profile:

  The most common adverse event was diarrhea, consistent with tenapanor's mechanism of action (reducing sodium and phosphate absorption in the GI tract).

  Other side effects were mild and similar between groups.

- Reduced Pill Burden:

  Tenapanor allowed for better phosphorus control with fewer phosphate binder pills, improving adherence and patient satisfaction.

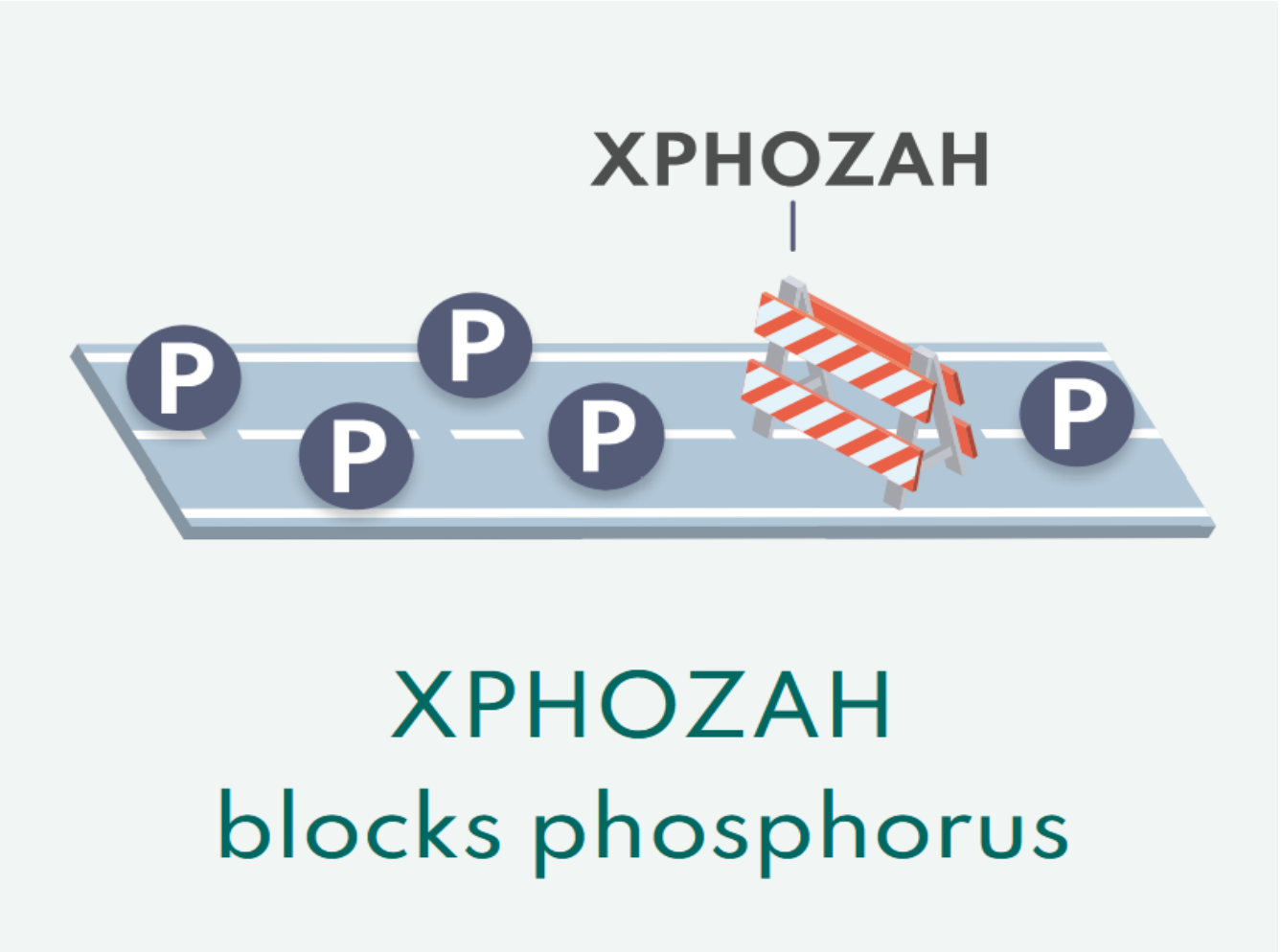


Clinical Trials Evaluating the Effects of Tenapanor in Haemodialysis Patients

Study Design	Population	Active Treatment	Control	Follow-Up Duration	Main Results
Phase 2 multicentre randomized, double-blind, placebo-controlled study	162 HD pts with hyperphosphataemia (of whom 115 completed the study)	Six tenapanor regimens (3 or 30 mg once daily or 1, 3, 10, or 30 mg twice daily)	Placebo	4 wks	• Dose-dependent reduction in serum phosphate • Most common adverse event in the active group: diarrhoea
Phase 2, double-blind, parallel-group, dose-finding study	207 HD patients with hyperphosphataemia	4 groups (Tenapanor 5 mg twice daily, 10 mg twice daily, 30 mg twice daily or 30 mg twice daily dose-titration)	Placebo	6 wks	• Dose-responsive serum phosphate-lowering action • Most common drug-related adverse event: diarrhoea, mostly mild and tolerable
Phase 3 randomized, double-blind trial	219 randomized HD pts with hyperphosphataemia (of which 152 completed both study phases)	1. Twice-daily oral tenapanor (3, 10, or 30 mg for 8 wks) 2. Rerandomization of pts to previously assigned dose or placebo for a 4-wk withdrawal period	Placebo	8 wks + 4 wks	• Significant reduction in mean serum phosphate (decrease of 1.00, 1.02, and 1.19 mg/dl in the three dose groups) • Mean increase of 0.85 mg/dl in the placebo group vs a mean increase of 0.02 mg/dl in the pooled active group • Adverse events: softened stool, slight increase in bowel movement frequency
Phase 3 double-blind trial	236 HD pts with hyperphosphatemia already treated with phosphate binders (of which 235 included in the full analysis and 228 completed treatment period)	Twice-daily oral tenapanor 30 mg plus phosphate binder	Placebo plus phosphate binder	4 wks	• Greater mean change in serum phosphorus levels in the tenapanor plus binder group compared to placebo plus binder group (−0.84 vs -0.19 mg/dl, P < 0.001) • Most common adverse events in the active group: diarrhoea, nausea
Double-blind, multicentre, randomized trial	47 HD pts with hyperphosphataemia not responding to phosphate binders	Twice-daily tenapanor 30 mg plus phosphate binder	Placebo plus phosphate binder	6 wks	• Decrease in mean serum phosphorus from 6.77 mg/dL to 4.67 mg/dL in the tenapanor group and from 7.01 mg/dL to 6.69 mg/dL in the placebo group • Most common adverse event: diarrhoea (65.2% and 8.3% of pts in the tenapanor and placebo groups, respectively)
Multicentre, phase 3 trial	564 HD pts with hyperphosphataemia and 1.5 mg/dl phosphate increase after phosphate binder washout	Twice daily tenapanor 30 mg for 26 wks, then rerandomization to tenapanor or placebo for 12 weeks and eligibility for the 14-wk safety extension period	Sevelamer carbonate	52 wks comprising three periods: - a 26-wk open-label randomized therapy period - a 12-wk double-blind placebo-controlled randomized withdrawal period - a 14-wk open-label safety extension period	• Statistically significant difference in estimated mean change in serum phosphate level between tenapanor and placebo (−1.4 mg/dl, P < 0.0001) • Most frequent adverse event in tenapanor group: loose stools; serious adverse events more common in the sevelamer carbonate group

Tenapan or

XPHOZAH is not a binder, it's a blocker



October of 2023 got FDA approval

Tenapanor

Tenapanor is a medication used primarily for the treatment of:

- Irritable Bowel Syndrome with Constipation (IBS-C): Tenapanor is approved for adults with IBS-C.
- Hyperphosphatemia in Chronic Kidney Disease (CKD): Tenapanor has been studied as a treatment to reduce serum phosphate levels in patients with CKD who are on dialysis.

CONTRAINDICATIONS

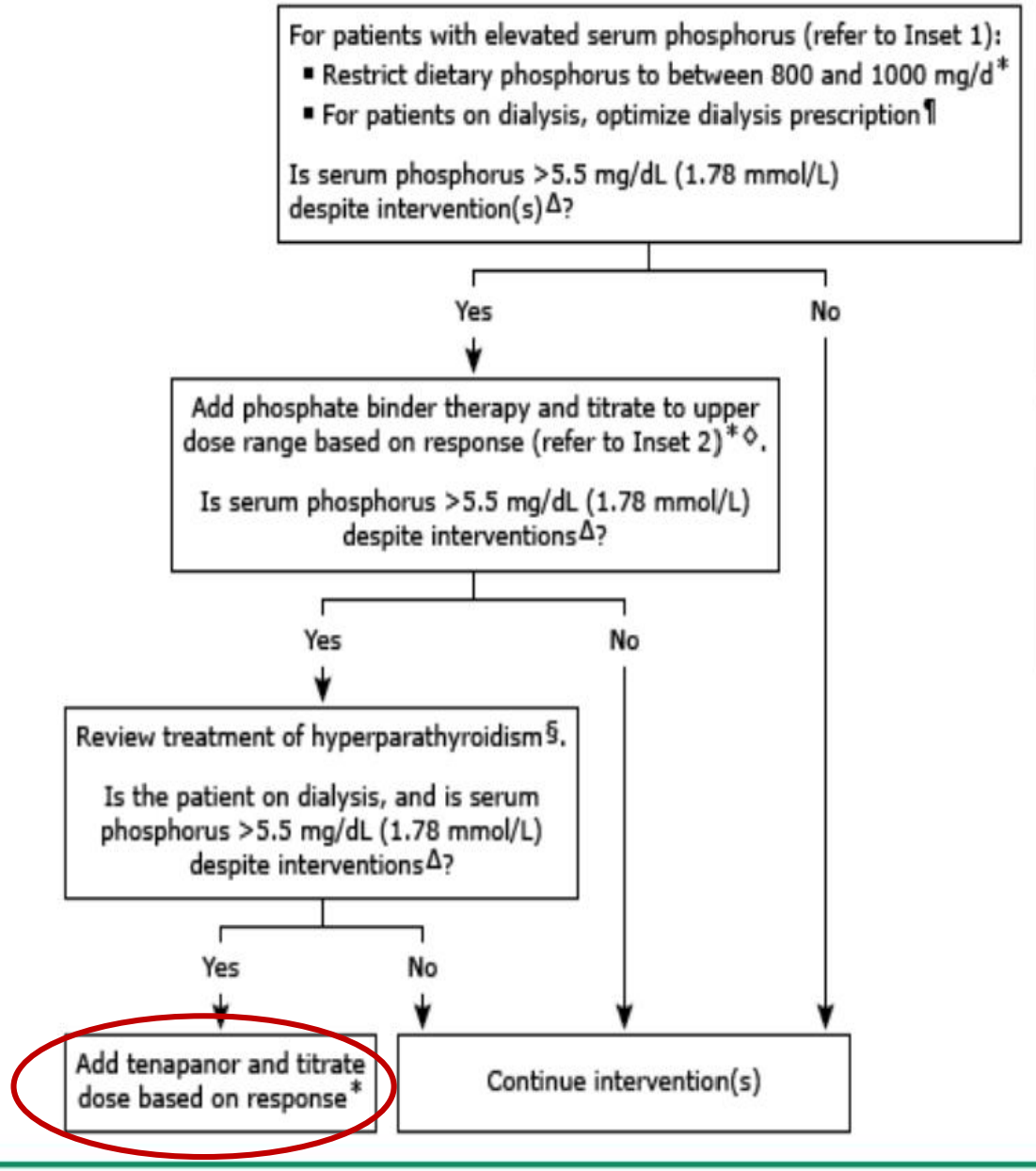
Xphozah is contraindicated in:

- Pediatric patients under 6 years of age
- Patients with known or suspected mechanical gastrointestinal obstruction

Summarizing the pharmacokinetics of Tenapanor

Absorption	Minimal systemic absorption (<1%); acts locally in the GI tract
Distribution	Limited to the intestinal lumen; negligible systemic distribution
Metabolism	Not significantly metabolized; exerts effects locally
Excretion	Primarily in feces; minimal renal clearance
Half-life	Not relevant due to lack of systemic absorption
Mechanism of Action	Inhibits sodium/hydrogen exchanger 3 (NHE3), reducing sodium absorption and increasing intestinal water content
Primary Uses	- Irritable bowel syndrome with constipation (IBS-C) - Chronic kidney disease-associated hyperphosphatemia
Common Side Effect	Diarrhea (due to increased intestinal water secretion)
Systemic Effects	Minimal due to poor absorption

Management of hyperphosphatemia in adults with chronic kidney disease



Inset 1: Treatment thresholds

- For patients with nondialysis CKD, we initiate dietary phosphorus restriction when the serum phosphorus is persistently above normal (ie, ≥4.5 mg/dL [1.45 mmol/L]), with the goal of lowering phosphorus into the normal range.
- For most patients on dialysis, serum phosphorus persistently >5.5 mg/dL (1.78 mmol/L) is an indication for treatment.

Inset 2: Treatment target

- For patients with nondialysis CKD who are treated with medical therapy in addition to dietary modification, and for most patients on dialysis, we try to maintain serum phosphorus between 3.5 and 5.5 mg/dL (1.13 and 1.78 mmol/L), inclusive.

Should be use :

Phosphate-lowering pharmacological agents

Bandar Abbas