Chronic Kidney Disease

Dr. Muhannad R. M. Salih
B.Sc, M.Pharm (Clinical Pharmacy), Ph.D, RPH
Pharmacy Department, Al-Rasheed University College
muhanad_rmk@yahoo.com

Background

- **Chronic kidney disease** (CKD) is defined as abnormalities in kidney structure or function, present for 3 months or longer, with implications for health.

- Abnormalities include
  - **albuminuria >30 mg/day**
  - **presence of hematuria or red cell casts in urine sediment**
  - **electrolyte abnormalities**

CKD Classification

Stage of CKD	Glomerular filtration rate	Description
1	≥90 mL/min	Normal or high
2	60–89 mL/min	Mildly decreased
3a	45–59 mL/min	Mildly to moderately decreased
3b	30–44 mL/min	Moderately to severely decreased
4	15–29 mL/min	Severely decreased
5	<15 mL/min	Kidney failure or End Stage Renal Disease (ESRD) if requiring dialysis

Background

- Prognosis depends on
  - **cause of kidney disease**
  - **GFR at time of diagnosis**
  - **degree of albuminuria**
  - **presence of other comorbid conditions**

Pathophysiology

- **Susceptibility factors** increase the risk for kidney disease but do not directly cause kidney damage. They include
  - **advanced age**
  - **reduced kidney mass**
  - **low birth weight**
  - **racial or ethnic minority**
  - **family history**
  - **low income or education**
  - **systemic inflammation**
  - **dyslipidemia**

Pathophysiology

- **Initiation factors** directly result in kidney damage and are **modifiable** by drug therapy, they include
  - **diabetes mellitus**
  - **hypertension**
  - **glomerulonephritis**
  - **polycystic kidney disease**
  - **Wegener granulomatosis (inflammation of blood vessels)**
  - **vascular diseases**
  - **human immunodeficiency virus (HIV) nephropathy.**

Pathophysiology

- **Progression factors** accelerate the decline in kidney function after initiation of kidney damage, they include
  - **glycaemia in diabetics**
  - **hypertension**
  - **proteinuria**
  - **hyperlipidemia**
  - **obesity**
  - **smoking**

Clinical presentation

- **CKD** development and progression are **insidious**. It proceed in a gradual, subtle way, but with harmful effects.
- Patients with **stage 1** or **2 CKD** usually do not have symptoms.
- **Metabolic imbalances** seen with **stages 3** to **5**, such as
  - **anemia**
  - **secondary hyperparathyroidism**
  - **cardiovascular disease**
  - **malnutrition**
  - **fluid and electrolyte abnormalities**

Clinical presentation

- **Uremic symptoms** (fatigue, weakness, shortness of breath, mental confusion, nausea, vomiting, bleeding, and anorexia) are
  - generally absent in **stages 1** and **2 CKD**
  - minimal during **stages 3** and **4 CKD**
  - common in **stage 5 CKD** who may also experience itching, cold intolerance, weight gain, and peripheral neuropathies.

Clinical presentation

- Signs and symptoms of **uremia** are foundational to the decision to implement **renal replacement therapy**.

Treatment

- **Goal of Treatment:** The goal is to delay the progression of CKD, minimizing the development or severity of complications.

Nonpharmacologic therapy

- **Restrict protein** to 0.8 g/kg/day if GFR is <30 mL/min.
- Encourage **smoking cessation** to slow progression of CKD and reduce the risk of cardiovascular disease.
- Encourage **exercise** at least 30 minutes five times per week and achievement of a body mass index (BMI) of 20 to 25 kg/m^2.

Pharmacologic therapy

Hypertension with CKD

- Progression of CKD can be limited by optimal control of
  - **Hypertension**

- Adequate blood pressure control can reduce the decline rate in GFR and albuminuria in patients without diabetes.

Pharmacologic therapy

- Based on the KDIGO guidelines

Urine albumin excretion	Target blood pressure
<30 mg/24 h	≤140/90 mm Hg
>30 mg/24 h	≤130/80 mm Hg

Pharmacologic therapy

- Initiate **first-line** therapy with an **ACEI** or an angiotensin II receptor blocker (**ARB**).
- Add a **thiazide diuretic** in combination with an **ACEI** or **ARB** if additional reduction in **proteinuria is needed**.
- **Nondihydropyridine calcium channel blockers** (Verapamil, and Diltiazem) are generally used as **second-line antiproteinuric drugs** when ACEIs or ARBs are contraindicated or not tolerated.

Pharmacologic therapy

- **ACEI clearance is reduced in CKD**; therefore, treatment should begin with the lowest possible dose followed by gradual titration
  - **to achieve target BP**
  - **to minimize proteinuria**

- No individual ACEI is superior to another.

Pharmacologic therapy

Diabetes with CKD

- Progression of CKD can be limited by optimal control o
  - **hyperglycemia**

- Target HgbA1C is **~7%** but consider **>7%** if there is a risk of **hypoglycemia** or a **limited life expectancy**.

Pharmacologic therapy

- **Anemia of CKD**
- KDIGO definition of anemia:
  - **Hemoglobin (Hb) <13 g/dL for adult males**
  - **Hemoglobin (Hb) <12 g/dL for adult females**

- Initiate **erythropoietic-stimulating agent** therapy in all CKD patients with **Hb** is between **9** to **10 g/dL**.

Pharmacologic therapy

- **Iron deficiency** is the primary cause of resistance to treatment of anemia with **erythropoietic-stimulating agent**.

- **Iron supplementation** is required by most CKD patients to replete iron stores depleted by ongoing blood loss and increased iron demands.

Pharmacologic therapy

- **Parenteral iron therapy** improves response to **erythropoietic-stimulating agent** therapy and reduces the dose required to achieve and maintain target indices.

- In contrast, **oral therapy** is limited by
  - **poor absorption**
  - **non-adherence with therapy primarily due to adverse effects**

Pharmacologic therapy

- **Adverse effects of IV iron** include allergic reactions, hypotension, dizziness, dyspnea, headaches, lower back pain, arthralgia, syncope, and arthritis.

- Some of these reactions can be minimized by decreasing the dose or rate of infusion.

- Sodium ferric gluconate, iron sucrose, and ferumoxytol have a better safety record than iron dextran products.

Pharmacologic therapy

- **Epoetin alfa** and **Darbepoetin alfa** are erythropoietic stimulating agents
- **Darbepoetin alfa** has a longer half-life than **epoetin alfa** and prolonged biologic activity.
- **Darbepoetin alfa** doses are administered less frequently, starting at once a week when administered IV or SC.
- **Hypertension** is the most common adverse event.

Evaluation of Anemia Therapeutic Outcomes

- Iron indices (**transferrin saturation** and **ferritin**) should be evaluated before initiating an **erythropoietic-stimulating agent**.

- **Transferrin saturation** and **ferritin test** gives an idea about iron body store. If the values are lower than normal, it indicates that iron stores are low and there is an iron deficiency.

Evaluation of Anemia Therapeutic Outcomes

- Iron status should be reassessed
  - **every month** during initial **erythropoietic-stimulating agent** treatment
  - **every 3 months** for those on a stable **erythropoietic-stimulating agent** regimen

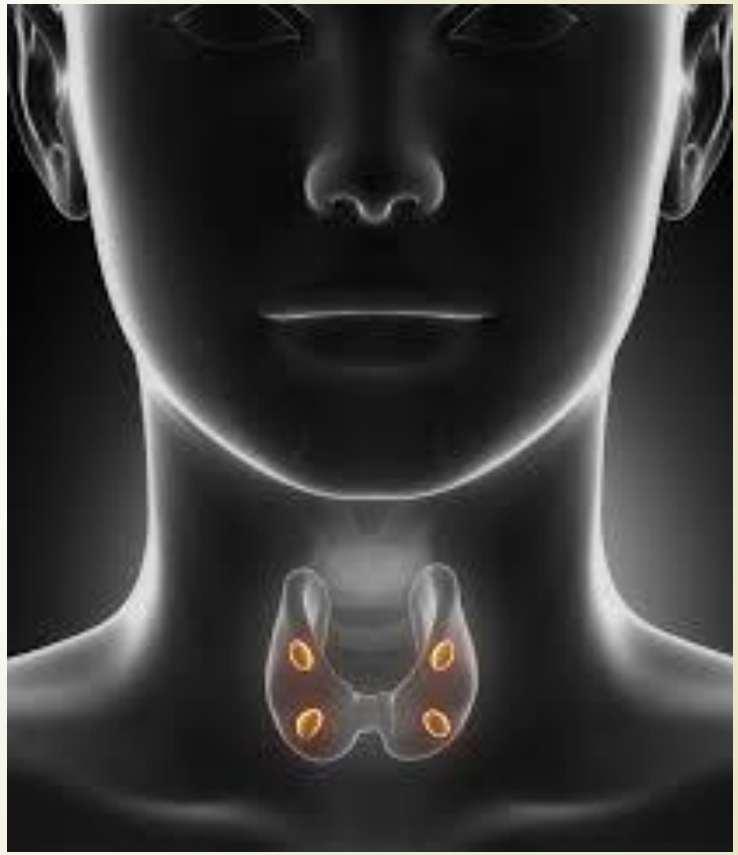
Evaluation of Anemia Therapeutic Outcomes

- **Hemoglobin** should be monitored at **least monthly**, although more frequent monitoring (eg, **every 1–2 weeks**) is warranted after initiation of an erythropoietic-stimulating agent or after a dose change until hemoglobin is stable.

- Patients should be monitored for potential complications, such as **hypertension**, which should be treated before starting an **erythropoietic-stimulating agent**.

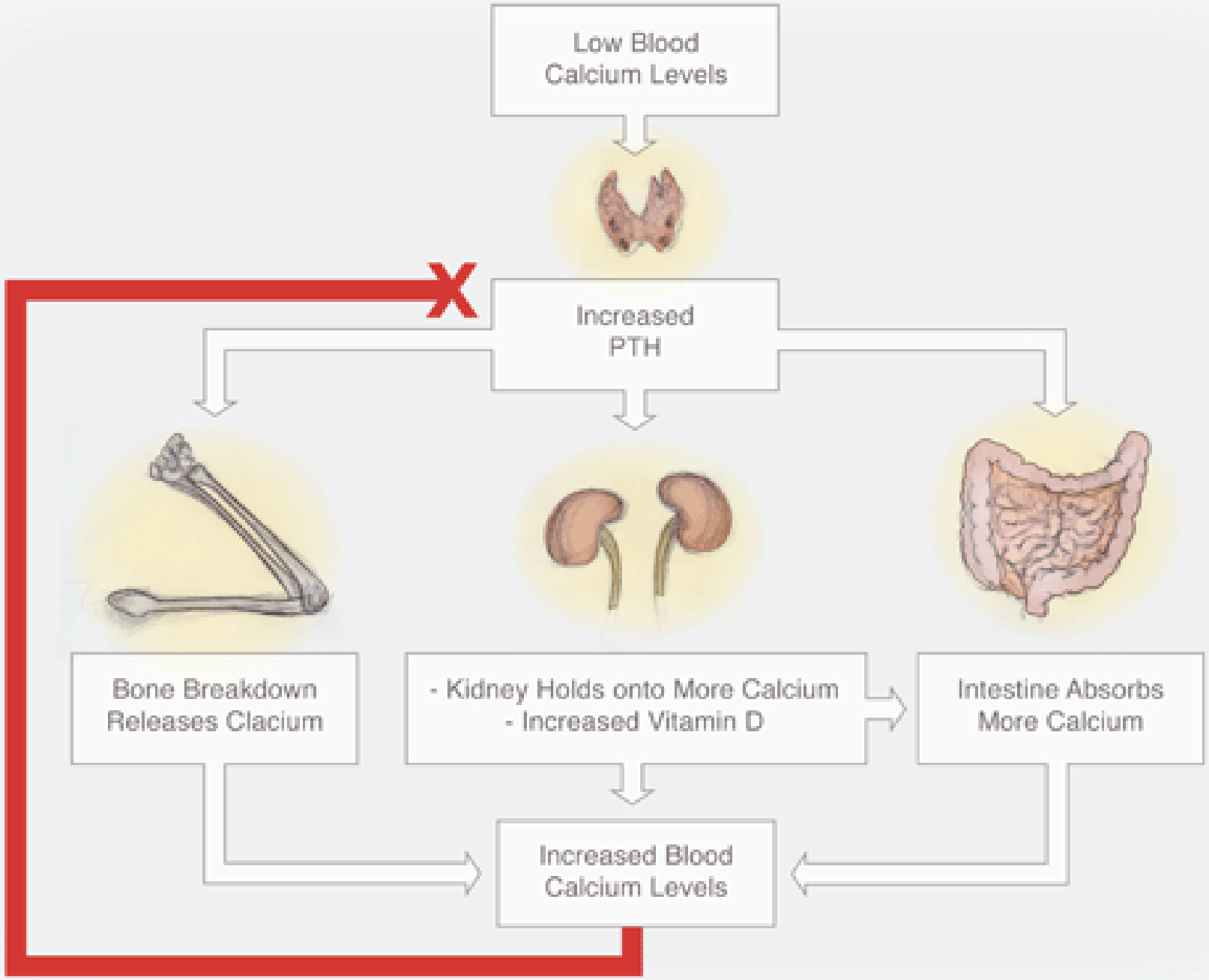
Parathyroid Glands

- The **parathyroid glands** are four tiny glands, located in the neck, that **control the body's calcium levels**.
- Each gland is about the size of a **grain of rice.**



Parathyroid Glands: Function

- The parathyroids produce a hormone called **parathyroid hormone (PTH)**. PTH raises the **blood calcium level** by:
  - breaking down the **bone**
  - increasing the body's ability to **absorb calcium from food**
  - increasing the **kidney's ability to hold on to calcium** that would otherwise be lost in the urine


Low Blood
Calcium Levels
Increased
PTH
Bone Breakdown
Releases Clacium
- Kidney Holds onto More Calcium
- Increased Vitamin D
Intestine Absorbs
More Calcium
Increased Blood
Calcium Levels

CKD-Related Mineral and Bone Disorder

- **Disorders of Mineral and Bone Metabolism** (**CKD-MBD**) are common in the CKD population.

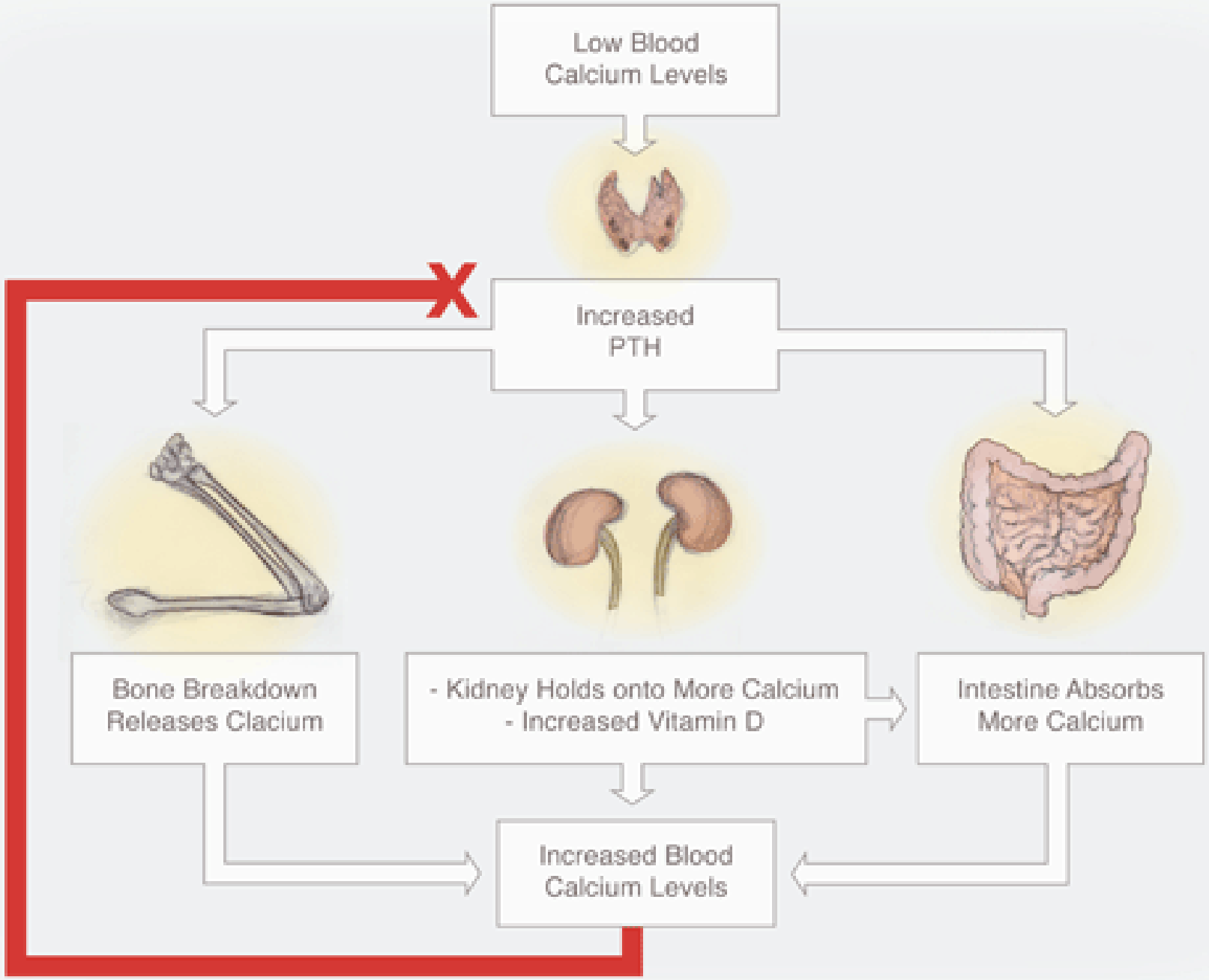
- **CKD-MBD** includes abnormalities in
  - **parathyroid hormone (PTH)**
  - **calcium**
  - **phosphorus**
  - **vitamin D**
  - **bone turnover**
  - **soft tissue calcifications**

CKD-Related Mineral and Bone Disorder

- **Calcium-phosphorus imbalance** effects on the
  - **bone**
  - **gastrointestinal tract**
  - **kidneys**
  - **parathyroid gland**

CKD-Related Mineral and Bone Disorder

- As kidney disease progresses, renal activation of vitamin D is impaired, which reduces gut absorption of calcium.
- **Low** blood **calcium** concentration stimulates **secretion of PTH**.
- As renal function declines, serum calcium balance can be maintained only at the expense of increased bone resorption, ultimately resulting in **renal osteodystrophy**.
- **Secondary hyperparathyroidism** is associated with increased morbidity and mortality and sudden death in hemodialysis patients.


Low Blood
Calcium Levels
Increased
PTH
Bone Breakdown
Releases Clacium
- Kidney Holds onto More Calcium
- Increased Vitamin D
Intestine Absorbs
More Calcium
Increased Blood
Calcium Levels

Treatment of CKD-MBD

- **Nonpharmacologic approaches** to management of hyperphosphatemia and CKD-MBD include
  - **dietary phosphorus (meats, poultry, fish, nuts, beans and dairy products) restriction**
  - **dialysis**
  - **parathyroidectomy**

Treatment of CKD-MBD

- **Phosphate-binding agents** decrease phosphorus absorption from the gut and are first-line agents for controlling both
  - **serum phosphorus concentration**
  - **serum calcium concentration**

TABLE 74–3 Phosphate-Binding Agents for Treatment of Hyperphosphatemia in CKD Patients

Drug	Brand Name	Compound Content	Starting Doses	Dose Titration[a]	Comments
Calcium carbonate[b]	Tums, Os-Cal, Caltrate	40% elemental calcium	0.5–1 g (elemental calcium) three times a day with meals	Increase or decrease by 500 mg per meal (200 mg elemental calcium)	First-line agent; dissolution characteristics and phosphate binding may vary from product to product Approximately 39 mg phosphorus bound per 1 g calcium carbonate
Calcium acetate (25% elemental calcium)	PhosLo	25% elemental calcium (169 mg elemental calcium per 667 mg capsule)	0.5–1 g (elemental calcium) three times a day with meals	Increase or decrease by 667 mg per meal (169 mg elemental calcium)	First-line agent; comparable efficacy to calcium carbonate with lower dose of elemental calcium Approximately 45 mg phosphorus bound per 1 g calcium acetate
	Phoslyra	667 mg calcium acetate per 5 mL			
Sevelamer carbonate	Renvela	800 mg tablet 0.8 and 2.4 g powder for oral suspension	800–1,600 mg three times a day with meals (once-daily dosing also effective)	Increase or decrease by 800 mg per meal	First-line agent; also lowers low-density lipoprotein cholesterol Consider in patients at risk for extraskeletal calcification Associated with a lower risk of acidosis and GI adverse events than Renagel (sevelamer hydrochloride) that is no longer available
Lanthanum carbonate	Fosrenol	500, 750, and 1,000 mg chewable tablets	1,500 mg daily in divided doses with meals	Increase or decrease by 750 mg/day	First-line agent; potential for accumulation of lanthanum due to GI absorption (long-term consequences unknown)
Aluminum hydroxide[b]	AlternaGel	Content varies (range 100–600 mg/unit)	300–600 mg three times a day with meals	Not for long-term use requiring titration	Not a first-line agent; risk of aluminum toxicity; do not use concurrently with citrate-containing products Reserve for short-term use (4 weeks) in patients with hyperphosphatemia not responding to other binders

[a]Based on phosphorus levels, titrate every 2–3 weeks until phosphorus goal reached.
[b]Multiple preparations available that are not listed.

Treatment of CKD-MBD

- **KDIGO guidelines** recommend that **elemental calcium** from
  - calcium-containing binders should **not exceed 1500 mg/day**
  - the total daily intake from all sources should **not exceed 2000 mg**
- This may necessitate a combination of calcium- and non–calcium-containing products (e.g, sevelamer HCL and lanthanum carbonate).

Treatment of CKD-MBD

- Adverse effects of **all phosphate binders** are generally limited to **GI effects**, including constipation, diarrhea, nausea, vomiting, and abdominal pain.

- Risk of **hypercalcemia** may necessitate restriction of calcium-containing binder use and/or reduction in dietary intake.

Treatment of CKD-MBD

- **Aluminum** and **magnesium binders** are not recommended for regular use in CKD
- **Aluminum binders** have been associated with
  - **CNS toxicity**
  - **worsening of anemia**
- Whereas **magnesium binders** may lead to
  - **Hypermagnesemia**
  - **hyperkalemia**

Vitamin D therapy

- Reasonable control of **calcium** and **phosphorus** must be achieved before initiation and during continued **vitamin D therapy**.
- **Calcitriol, 1,25-dihydroxyvitamin D3**, directly suppresses PTH synthesis and secretion and up regulates vitamin D receptors.
- The dose depends on the stage of CKD

Vitamin D therapy

- The newer **vitamin D** analogues **paricalcitol** and **doxercalciferol** may be associated with **less hypercalcemia** and, for paricalcitol, less **hyperphosphatemia**.

- **Vitamin D therapy**, regardless of agent, is associated with **decreased mortality**.

Generic Name	Brand Name	Form of Vitamin D	Dosage Forms	Initial Dose	Dosage Range	Frequency of Administration
Nutritional Vitamin D						
Ergocalciferol[a]	Generic	D_2	po	Varies based on 25OHD levels	400–50,000 international units	Daily (doses of 400–2,000 international units)
Cholecalciferol[a]	Generic	D_3	po			Weekly or monthly for higher doses (50,000 international units)
Active Vitamin D						
Calcitriol	Calcijex	D_3	IV	1–2 mcg	0.5–5 mcg	Three times per week
	Rocaltrol		po	0.25 mcg	0.25–5 mcg	Daily or three times per week
Vitamin D Analogs						
Paricalcitol	Zemplar	D_2	po	CKD nondialysis: 1 mcg daily or 2 mcg three times per week if PTH ≤500 pg/mL (≤500 ng/L; ≤54 pmol/L); 2 mcg daily or 4 mcg three time per week if PTH >500 pg/mL (>500 ng/L; >54 pmol/L) Stage 5 CKD: mcg dose based on ratio of PTH/80 and administered three times per week	1–4 mcg	Daily or three times per week
			IV	Stage 5 CKD: 0.04–1 mcg three times per week	2.5–15 mcg	Three times per week
Doxercalciferol	Hectorol	D_2	po	CKD nondialysis: 1 mcg daily Stage 5 CKD: 10 mcg three times per week	5–20 mcg	Daily or three times per week
			IV	Stage 5 CKD: 4 mcg three times per week	2–8 mcg	Three times per week

[a]Multiple preparations are available that are not listed.

Calcimimetics

- **Cinacalcet** reduces **PTH secretion** by increasing the sensitivity of the calcium sensing receptor.
- The most common adverse events include **nausea** and **vomiting**.
- The starting dose is **30 mg daily**, which can be titrated to the desired PTH and calcium concentrations every **2** to **4 weeks** to a **maximum of 180 mg daily**.

Hyperlipidemia

- The prevalence of **hyperlipidemia** increases as **renal function declines**.

- **KDIGO** guidelines recommend treatment with a **statin** in adults ≥50 years with stage 1 to 5 CKD.
- for example;
  - **atorvastatin 20mg**
  - **fluvastatin 80mg**
  - **rosuvastatin 10mg**
  - **simvastatin 20 mg**

Thank You