Chronic Kidney Disease: Mineral and Bone Disorder

Etiology, Clinical Impact, and Management

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KDIGO Terminology

- Definition of CKD–MBD
  - A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:
    - Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism.
    - Abnormalities in bone turnover, mineralization, volume, linear growth, or strength.
    - Vascular or other soft-tissue calcification.

Overview

- CKD leads to abnormalities
  - Hyperphosphatemia
  - Low active Vitamin D levels
  - Hypocalcemia
  - ➢ All lead to SECONDARY hyperparathyroidism
- CKD-MBD
- Treatment

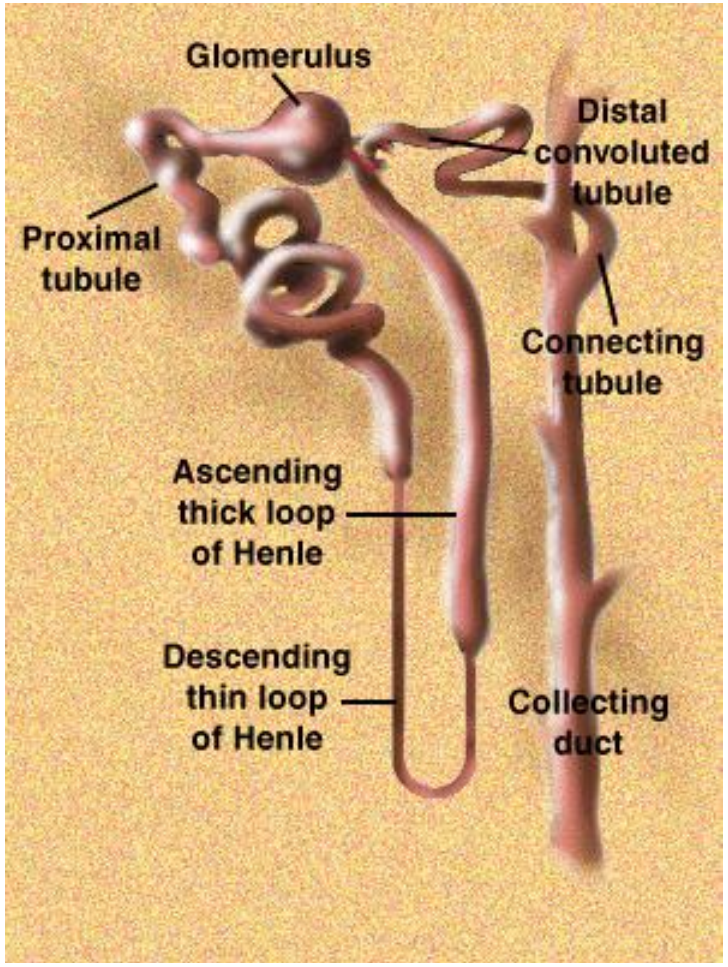
Why elevated Phosphorus in CKD? *

Kidney Function (GFR) wnl:
200 mm/d filtered

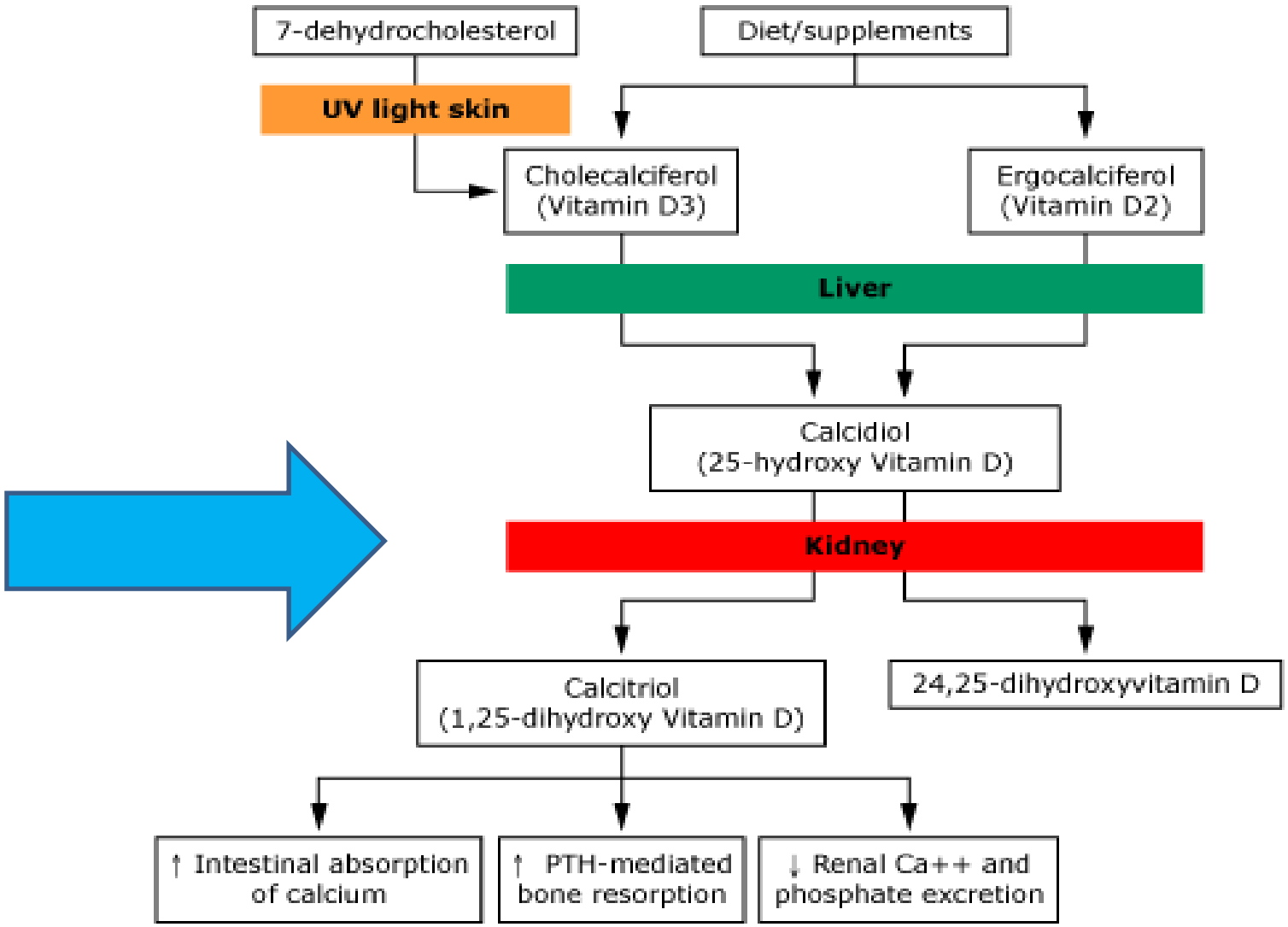
- 175 mmol reabs. (80-95%)
- 25 mmol are excreted

With ↓ Kidney Function:

- Decrease filtered load at glomerulus
- Decrease phosphorus excretion
- Kidney excretion less than gut reabsorption
- 'Positive' phos. balance



Why Decreased Vitamin D in CKD?



Why Decreased Serum Calcium in CKD?

$Ca^{2+} + HPO_4^{2-} \quad < --- > \quad CaHPO_4$

- Increased phos drives equation to the right
- Results in hypocalcemia

Less renal mass → less active Vitamin D

- Less gut calcium reabsorption

High phos → less 1∝hydroxylase

- Less active Vitamin D and hypocalcemia

Why is this a problem?

Hypocalcemia

Low Vitamin D levels

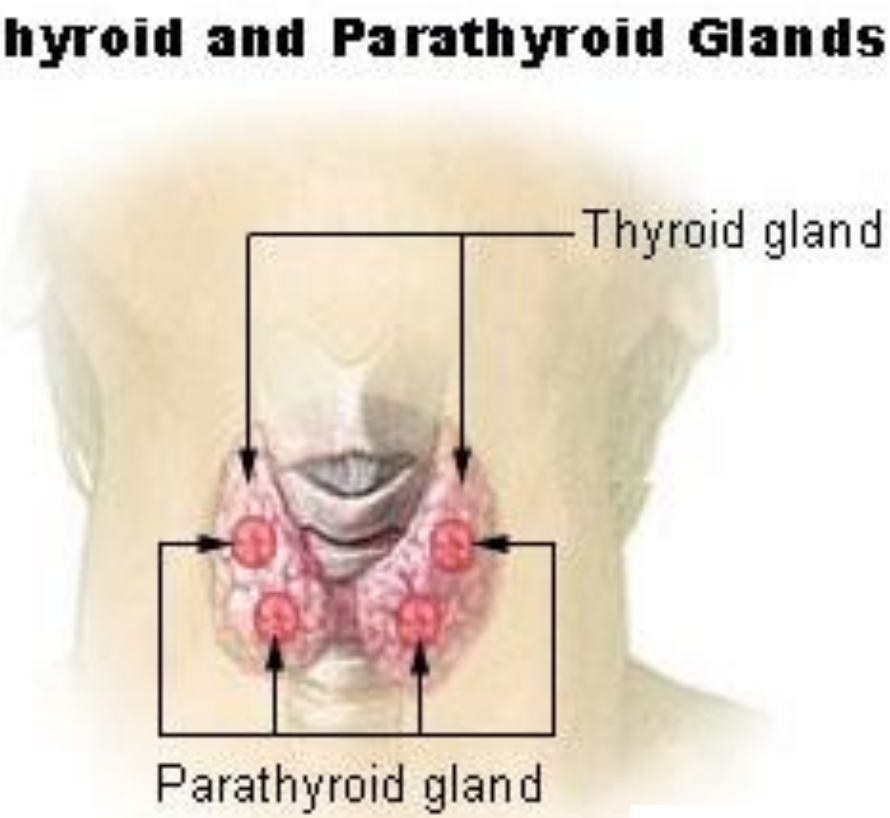
Hyperphosphatemia

ALL LEAD TO →

(Secondary)

Hyperparathyroidism!

Anatomical Location

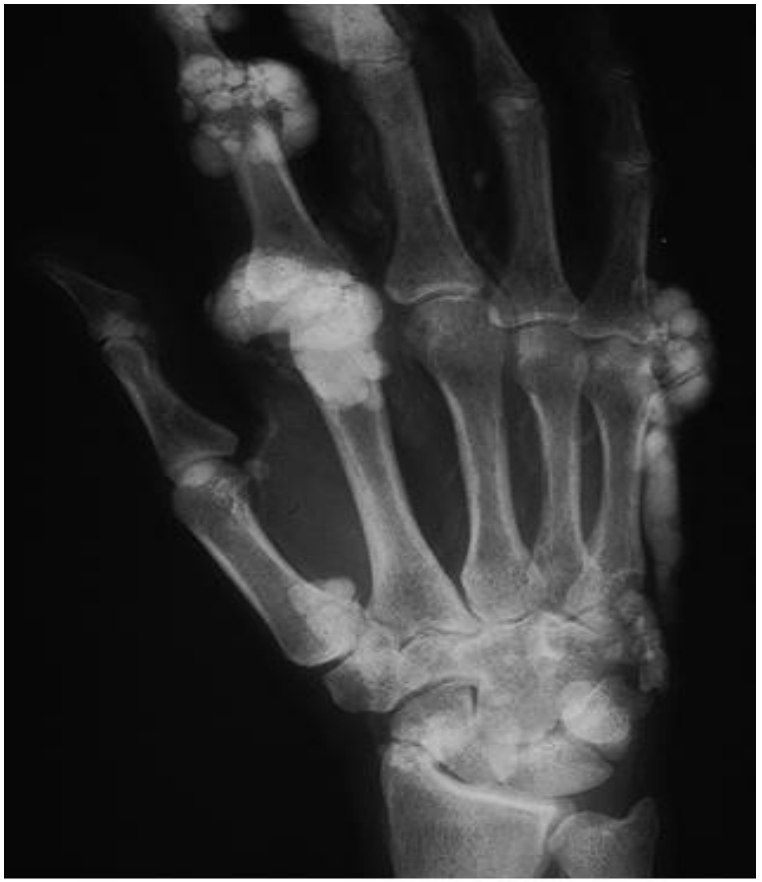


located behind thyroid gland

Front view

Metastatic Calcification*

- Arteries, joints, soft tissue, viscera
- Occurs more w/high Ca x Phos (72-80)
- KDOQI < 55 for 3-5 CKD (poor Evidence)
- Can lead to calciphylaxis (rare)



Metastatic calcification Hand radiograph showing metastatic calcification in a patient with calciphylaxis. Courtesy of Peter H Schur MD.

Tertiary Hyperparathyroidism

- Marked refractory oversecretion of PTH
- Changes include:
  - Increased parathyroid gland mass
    - Severe hyperplasia not responsive to, eg, Ca++
  - Neoplastic transformation
    - Monoclonal parathyroid adenoma
    - Mechanisms not well understood, ?low Vit D receptor density

Additional Sequelae

- If these pathophysiologic abnormalities are not corrected:
  - Renal bone disease (CKD-MBD) will develop
  - Also, felt to contribute to cardiovascular and peripheral vascular disease

Treatment Goals: KDIGO

- Non-specific
- MOSTLY LEVEL 2C data!!!

  E.G.:

✓ iPTH 2-9 times upper limit nl

✓ Try to normalize phos (<=5.5)

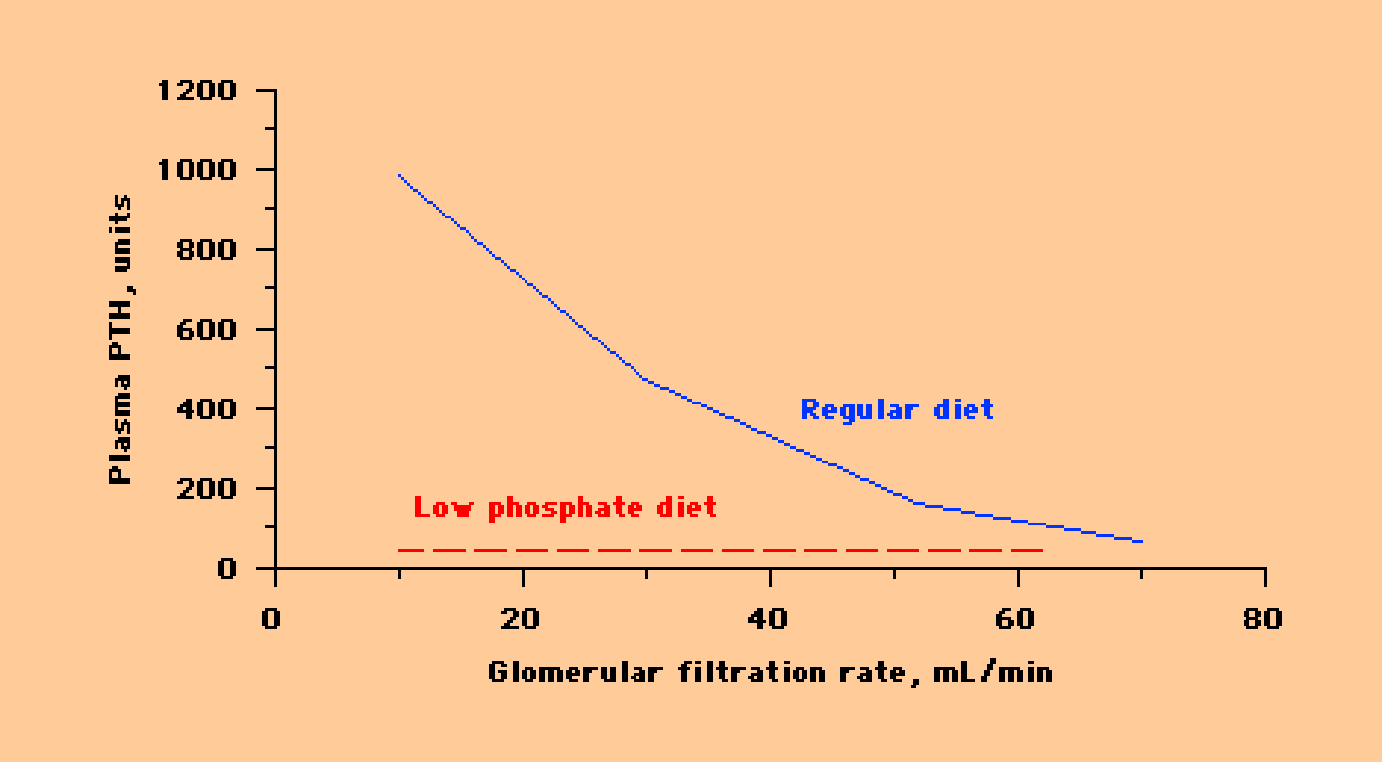
✓ Avoid Ca binders in hypercalcemia

✓ Use Vit D/analogs for high iPTH

Prevention of secondary Hyperparathyroidism

- DIET! Essential but difficult
- Phosphorus binders
- Vitamin D analogs
- Correction of metabolic acidosis
- Calcimimetics
- Bisphosphonates
- Parathyroidectomy – ? The last resort?
  - Rates decreased since calcimimetics arrived

Diet makes a difference



Phosphate restriction prevents hyperparathyroidism in renal failure Relationship between the glomerular filtration rate (GFR) and PTH

Table 2. Effects of Phosphate Binders on Clin

Drug†	Daily Dose (pill burden)	Effect on Coronary-Artery Calcification	Effects on Calcium and Phosphate	Approximate Annual Cost*	Comments
				U.S. dollars	
Calcium carbonate (Tums, Os-Cal, Caltrate)	500–1250 mg (3–6 tablets)	Unknown	Serum phosphate declines by 0.9 mg per deciliter on average, whereas serum calcium increases by 0.5 mg per deciliter on average, in comparison with no treatment	100–200	Reduction in serum phosphate and elevation in serum calcium are dose-dependent
Calcium acetate (Phoslo, Eliphos)	667 mg (6 to 12 caplets)	Unknown	Reduction in serum phosphate is slightly greater than with calcium carbonate, but serum calcium levels are similar	1,000–2,000	Phosphate control appears to be superior and hypercalcemia appears to be less frequent with calcium acetate (than with calcium carbonate), although the studies demonstrating these findings had limitations
Magnesium hydroxide (Milk of Magnesia)	311 mg (1 to 6 tablets)	Unknown	Phosphate-lowering capacity appears to be similar to that of calcium-based agents; often used as add-on therapy with calcium-based agents	120	Data are insufficient to recommend one magnesium salt over another
Magnesium carbonate (Gaviscon‡)	63 mg (2 to 6 tablets)	Unknown	Phosphate-lowering capacity appears to be similar to that of calcium-based agents; often used as add-on therapy with calcium-based agents	120	Data are insufficient to recommend one magnesium salt over another
Sevelamer hydrochloride (Renagel)	800 mg (6 to 12 caplets)	Trend toward less progression of calcification with sevelamer as compared with calcium-based binders	Serum phosphate is lower with calcium-based phosphate binders; serum calcium is lower with sevelamer	4,400–8,800	Conclusions regarding vascular calcification cannot be drawn, given methodologic limitations of the studies that assessed this outcome
Sevelamer carbonate (Renvela)§	800 mg (6 to 12 caplets)	Unknown but presumably similar to that of sevelamer hydrochloride	Effects are similar to those of sevelamer hydrochloride	5,500–11,000	As with sevelamer hydrochloride, serum bicarbonate and chloride levels and markers of vitamins D, E, and K and folic acid status should be monitored during therapy
Lanthanum (Fosrenol)	250–1000 mg (3 to 6 chewable tablets)	Unknown	Effects are similar to those of calcium-based phosphate binders, but with fewer episodes of hypercalcemia	7,000–14,000	

Tonelli, NEJM,362:1312-24 2010

Vitamin D analogs

- Administered to correct Vitamin D deficiency
- Suppresses PTH release
- Improves PTH-induced osteitis fibrosa
- Can slightly increase calcium levels

Calcimimetics

- Increases the sensitivity of the CaSR in the parathyroid gland to calcium
- Leads to **acute suppression of PTH**
  - Cinacalcet (Sensipar) – oral – generic now ($1s)
  - Etelcalcetide (Parsabiv) – IV – non-generic (>$1000+)
    - Don’t start if Ca too low
    - N/v and GI sxs most common side effects
    - IV not better than oral (CMO approval)
    - Currently, 7 patients on Parsabiv cost more than the 200+ on Sensipar.

Chronic Maintenance In-Center Standing Orders – Paricalcitol

Paricalcitol (ICD10 - N25.81)

- **Targets:** iPTH 150 – 600 pg/ml
  Calcium ≤ 10.2
- **Labs:**
- Draw monthly calcium (in NKC Profile) unless otherwise indicated by tables below.
- Draw iPTH quarterly (Jan.-Apr.-July-Oct.) unless otherwise indicated below.
- Draw labs with the routine monthly lab draws unless otherwise indicated by tables below.
- If monthly calcium >10.2, redraw calcium in 1 week
- If calcium > 10.5 notify physician for guidance on management.

- **Dosing:**

  1. Paricalcitol dosing is based on tiers that correspond to specific doses in mcg as indicated in Table 1:
  2. Give paricalcitol doses IV, 3x/week with dialysis. If patient dialyzes >3x/week, ensure doses are spaced evenly 3x/week throughout the week. If patient runs only 1 or 2 times per week administer the dose with each dialysis i.e. qweek or 2x/week respectively.
  3. Always use the most recent calcium and iPTH when applying the algorithms.

Table 1: Tier Dosing

Tier	Dose, mcg		Tier	Dose, mcg
0	0		6	6
1	1		7	8
2	2		8	10
3	3		9	12
4	4		10	14
5	5		>10	Call physician

Incident Patient Algorithm:

a. Incident patient = patient new to dialysis or established patient who has not received any paricalcitol within past 6 months.

b. Do not start paricalcitol if calcium >9.8, monitor calcium monthly

c. If calcium is ≤9.8 give paricalcitol at the dose indicated in Table 2 and draw next iPTH in one month.

Table 2: Incident Patient Paricalcitol Dosing		
iPTH (pg/ml)	Tier	Dose (mcg)
< 300	0	0
300 - 450	1	1
450 - 600	2	2
> 600	4	4

d. Once paricalcitol started and result of next iPTH draw known, proceed per Established Patient Algorithm below.

Established Patient Algorithm

a. If calcium >10.1 mg/dL, hold paricalcitol dose

b. If calcium ≤10.1 mg/dL, determine paricalcitol dose using the paricalcitol brackets in Table 3 and the following algorithm.

Table 3: Established Patient PTH Brackets	
iPTH (pg/mL)	Bracket
< 150	A
150 - 300	B
300 - 450	C
450 - 600	D
> 600	E

c. Change current paricalcitol dose based on most recent PTH result compared to the prior PTH result:

- Hold dose if PTH is in bracket (A)
- 1-tier increase if patient switched from PTH bracket (B) to bracket (C) or from bracket (C) to bracket (D) or from bracket (D) to bracket (E) or patient remains in bracket (E)
- 2-tier increase if patient had two or more PTH bracket increase
- 1-tier decrease if patient switched from PTH bracket (E) to bracket (D) or from bracket (D) to bracket (C) or from bracket (C) to bracket (B)
- 2-tier decrease if patient had two or more bracket decrease, unless patient switches to bracket (A) in which case hold dose
- In all other cases keep existing dose

d. If a paricalcitol dose change is made, or if dose is in tier 10 (14 mcg), recheck PTH in 1 month

Held Dose Algorithm (for prevalent patients)

a. If paricalcitol dose on hold, and most recent calcium <10.0 mg/dl AND iPTH > 300 pg/ml, then restart paricalcitol using the following algorithm:

- Restart with the same dose if in bracket (C) or (D)
- Restart with 1-tier increase if in bracket (E)

b. When paricalcitol restarted after a hold, recheck PTH in 1 month

THE END

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