Calcium and Phosphate Disorders: Core Curriculum 2024

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Maintaining normal calcium and phosphate homeostasis is essential for optimal cellular, metabolic, and organ function. Parathyroid hormone, fibroblast growth factor 23, and 1,25-dihydroxyvitamin D regulate calcium and phosphate homeostasis via multiple interlinked feedback loops, receptors, ion channels, and transporters. Following an initial overview of the stimuli and effects of the different hormonal regulators, this installment of *AJKD*'s Core Curriculum in Nephrology reviews the physiology and pathophysiology of calcium and phosphate disorders through the lens of a series of illustrative cases. The cases span clinical conundrums commonly encountered by nephrologists in their daily clinical practice and other less common disorders. Some of the cases present in the outpatient clinic setting and others in the inpatient hospital setting. Patients with normal kidney function, chronic kidney disease, kidney failure, and acute kidney injury are all represented. Some of the disorders are iatrogenic, and some are due to native disease. All demonstrate key aspects of pathophysiology that are essential knowledge for nephrology clinicians of all career stages.

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Am J Kidney Dis. 83(2):241-256. Published online December 13, 2023.

doi: 10.1053/j.ajkd.2023.04.017

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Parathyroid hormone (PTH), fibroblast growth factor 23 (FGF-23), and the active form of vitamin D, calcitriol, also known as 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], are the 3 main endocrine hormones that regulate calcium and phosphate homeostasis through their effects on the kidney, bone, and intestine (Table 1). The most fundamental effects of these hormones are:

1. PTH regulates the serum ionized calcium on a minute-to-minute basis.
2. FGF-23 governs phosphate homeostasis.
3. $1,25(OH)_2D$ is responsible for importing calcium and phosphate from the environment via intestinal absorption.

All 3 hormones have multiple other functions that are interconnected via classic negative endocrine feedback loops. As a result, changes in one will trigger downstream alterations in others, either directly or indirectly via effects on calcium and phosphate (Fig 1). The main physiological functions of these hormones can be best understood by examining their responses to different perturbations to the system.

Response to Hypocalcemia

Reductions in serum ionized calcium are sensed by the calcium-sensing receptor (CaSR) in the parathyroid glands, resulting in increased PTH secretion. PTH has the following major effects:

1. PTH enhances bone resorption, which releases calcium and phosphate into circulation.
2. PTH stimulates urinary calcium reabsorption in the distal nephron to reduce urinary calcium losses.
3. PTH up-regulates circulating $1,25(OH)_2D$ levels by stimulating the enzyme responsible for its production (CYP27B1, also known as 1α-hydroxylase) and by down-regulating the enzyme responsible for its degradation (CYP24A1, also known as 24-hydroxylase). Augmenting $1,25(OH)_2D$ levels increases intestinal calcium absorption, which supports PTH-mediated increases in serum calcium.
4. PTH stimulates urinary phosphate excretion by down-regulating phosphate reabsorption by the sodium-phosphate cotransporters of the proximal tubule, NaPi-2a and NaPi-2c. This ensures that PTH-mediated bone resorption in response to hypocalcemia results in an increase in serum calcium without a corresponding increase in phosphate because the excess phosphate is excreted in the urine.

By contrast, factors that increase serum calcium elicit the opposite PTH response and downstream effects to prevent hypercalcemia.

Response to Dietary Phosphate Loading

Chronically increased dietary phosphate intake results in increased secretion of FGF-23 into circulation by bone. This was recently discovered to be mediated by glycerol-3-phosphate production from phosphate-driven glycolysis in the proximal tubule. FGF-23 has the following major effects that result in maintenance of a normal serum phosphate level despite increased phosphate loading:

Table 1. Effects of Parathyroid Hormone, Fibroblast Growth Factor-23 and $1,25(OH)_2D$ on Calcium and Phosphate Homeostasis

	PTH	FGF-23	$1,25(OH)_2D$
Main stimulus	Hypocalcemia	$1,25(OH)_2D$, dietary phosphate	PTH
Main inhibitor	Hypercalcemia	Unknown	FGF-23
Primarily regulates	Ionized calcium	Unknown	Intestinal mineral absorption
Main effects	• Stimulates bone resorption • Inhibits calciuria • Stimulates phosphaturia • Increases $1,25(OH)_2D$ levels: ◇ Stimulates CYP27B1 ◇ Inhibits CYP24A1	• Stimulates phosphaturia • Lowers serum phosphate • Inhibits PTH • Decreases $1,25(OH)_2D$ levels: ◇ Inhibits CYP27B1 ◇ Stimulates CYP24A1	• Increases intestinal calcium, phosphate absorption • Suppresses PTH: ◇ Indirectly via calcium ◇ Direct feedback inhibition • Stimulates FGF-23 • Decreases $1,25(OH)_2D$ levels: ◇ Stimulates CYP24A1

Abbreviations: FGF-23, fibroblast growth factor 23; 1,25(OH)2D, 1,25-dihydroxyvitamin D; PTH, parathyroid hormone.

1. FGF-23 stimulates urinary phosphate excretion by down-regulating NaPi-2a and NaPi-2c in the proximal tubule (like PTH). As a result, dietary phosphate that is absorbed in excess of physiological need is lost in the urine.
2. Opposing the effects of PTH, FGF-23 reduces $1,25(OH)_2D$ levels by inhibiting CYP27B1 and stimulating CYP24A1. Although $1,25(OH)_2D$ is not as critical for intestinal absorption of phosphate as it is for calcium, suppressing $1,25(OH)_2D$ levels reduces the efficiency of intestinal phosphate absorption. As a result, less phosphate enters the circulation.
3. A less clinically important effect of FGF-23 is to directly suppress PTH secretion. This likely contributes

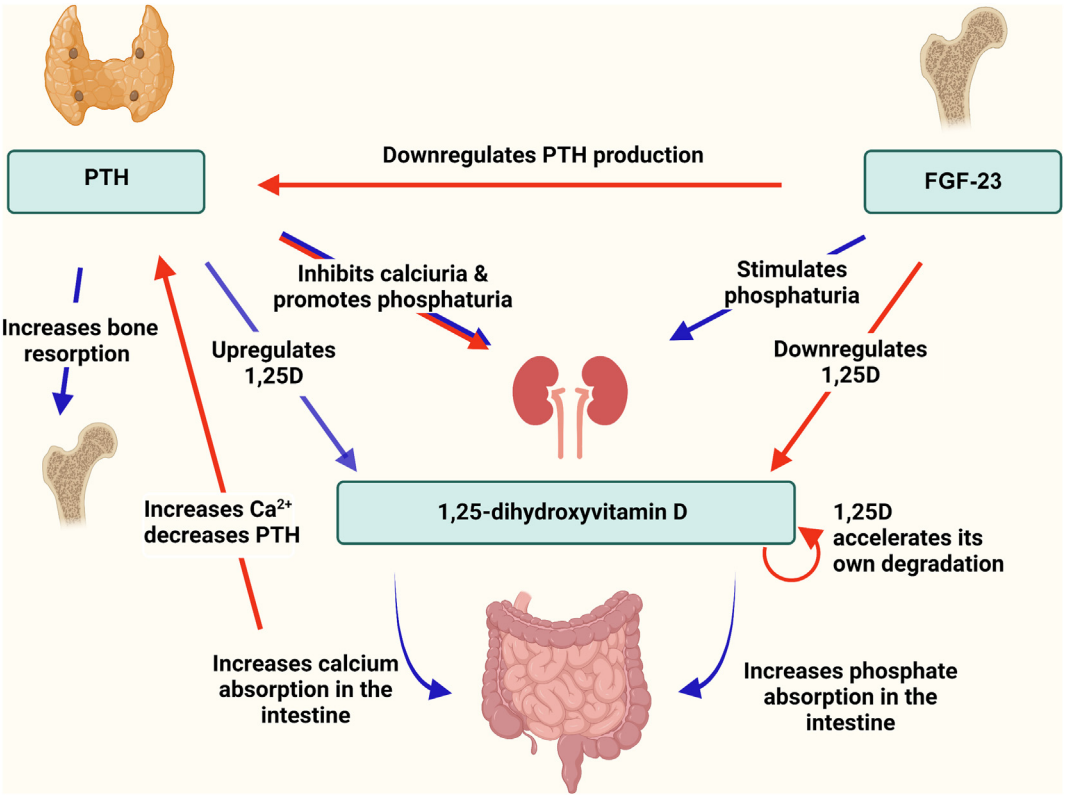

Figure 1. Axis of PTH, FGF-23, and 1,25-dihydroxyvitamin D. PTH, FGF-23, and $1,25(OH)_2D$ interact and regulate one another via classic negative endocrine feedback loops that affect calcium and phosphate transport in the kidney, bone, and intestine. Created with Biorender. Abbreviations: 1,25D, 1,25-diydroxyvitamin D; FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone.

indirectly to FGF-23–mediated reductions in $1,25(OH)_2D$ by reducing the main driver of increased $1,25(OH)_2D$. However, this effect is likely modest given that any effects of FGF-23 to suppress PTH are superseded by parallel changes in calcium-driven effects on PTH.

In contrast to oral phosphate loading, severe dietary phosphate restriction has the opposite effect. Decreased FGF-23 increases renal avidity for phosphate reabsorption and increases $1,25(OH)_2D$ levels. Collectively, these effects maintain normal serum phosphate levels despite reduced intake.

FGF-23 mediates its effects on the kidney by binding to heterodimeric receptors made of FGF receptor 1 and α-klotho. Aside from serving as a coreceptor for FGF-23, α-klotho has additional effects on phosphate homeostasis as well as other non-mineral metabolism effects that are the subject of ongoing investigation along with the non-mineral metabolism effects of FGF-23. These are beyond the scope of this installment of the *AJKD* Core Curriculum.

Calcium Homeostasis

Case 1: A 52-year-old woman with kidney failure due to autosomal dominant polycystic kidney disease received a living donor kidney transplant after having been maintained on hemodialysis for 3 years. Her pretransplant medications included aspirin, carvedilol, sevelamer, and cinacalcet at 60 mg daily. Transplantation was uncomplicated, and cinacalcet and sevelamer were stopped; she commenced standard triple immune suppression. At 1 month after transplant, her laboratory testing revealed creatinine, 1.0 mg/dL; serum urea nitrogen (SUN), 45 mg/dL; calcium, 11.2 mg/dL; and phosphate, 2.2 mg/dL.

Question 1: What is the most likely cause of her hypercalcemia?
(a) FGF-23 suppression
(b) PTH excess
(c) Vitamin D intoxication
(d) Immune suppression medications

For the answer to this question, see the following text.

Calcium Economy

Calcium is essential for survival. It is the main component of the skeleton and has vital roles in the neural, cardiac, and musculoskeletal systems that necessitate tight, minute-to-minute regulation of ionized calcium within a narrow range. The vast majority of calcium is found in bone. Of the 1% of total body calcium that circulates in blood, 40% is protein-bound, 10% is complexed to other anions, and the remaining 50% is free "ionized" calcium. Dietary calcium comes from dairy, green vegetables, almonds, and soy and is absorbed in the duodenum and upper jejunum by both 1,25-dependent transcellular and vitamin D-independent paracellular processes. Dietary calcium absorption is relatively inefficient and is markedly enhanced by $1,25(OH)_2D$.

Renal Calcium Handling

Only free or anion-bound calcium can be freely filtered by the kidney. Approximately 95% of filtered calcium is reabsorbed by the renal tubule, including 60% in the proximal convoluted tubule (PCT), 25% in the thick ascending limb (TAL) of Henle, and 15% in the distal convoluted tubule (DCT) (Fig 2).

Hormone-independent, paracellular calcium reabsorption occurs in the PCT and TAL. In the PCT, reabsorption of sodium via the sodium/proton exchanger 3 (NHE3) is the driving force for calcium reabsorption via a paracellular channel formed by claudins 2 and 12. Generation of intracellular H_2CO_3 by carbonic anhydrase generates H^+ ions; extrusion of these ions into the lumen drives NHE3. In the TAL, claudins 16 and 19 form a paracellular channel that allows calcium ions to move out of the tubular lumen driven by an electrochemical gradient generated by activity of the sodium-potassium-chloride cotransporter (NKCC2) that is coupled to back leak of potassium into the tubular lumen via the renal outer medullary potassium (ROMK) channel. Back leak of potassium into the tubular lumen provides the potassium substrate needed for the NKCC channel to function and also generates a transtubular electrochemical gradient in which the tubular lumen is relatively positively charged and the tubular cell and interstitium are negatively charged. The gradient drives paracellular reabsorption of positively charged calcium (and magnesium) ions.

In the setting of hypercalcemia, elevated interstitial calcium activates the CaSR, which inhibits ROMK. This attenuates the transtubular voltage gradient, which reduces calcium reabsorption and enhances calciuria as part of a feedback loop to reduce the serum calcium. Simultaneously, lack of sufficient potassium in the lumen due to reduced potassium efflux across ROMK paralyzes NKCC2, which leads to reduced NaCl reabsorption. The resulting diuresis, which co-opts the pathogenic pathways of Bartter's syndrome and mimics the effects of furosemide administration, is a major contributor to the severe volume depletion caused by hypercalcemia.

Fine-tuning of tubular calcium handling occurs via PTH- and $1,25(OH)_2D$-dependent transcellular reabsorption in the DCT. Calcium enters the cell from the luminal side via transient receptor potential cation channel subfamily V (TRPV5), binds intracellularly to calbindin D-28k, and exits via basolateral calcium transporters.

Hypercalcemia

Hypercalcemia may present acutely or insidiously and is most commonly first detected via routine biochemical screening. Patients may experience polydipsia and polyuria, bone and abdominal pain, volume depletion, acute kidney injury, depressed mood, and kidney stones. Severe

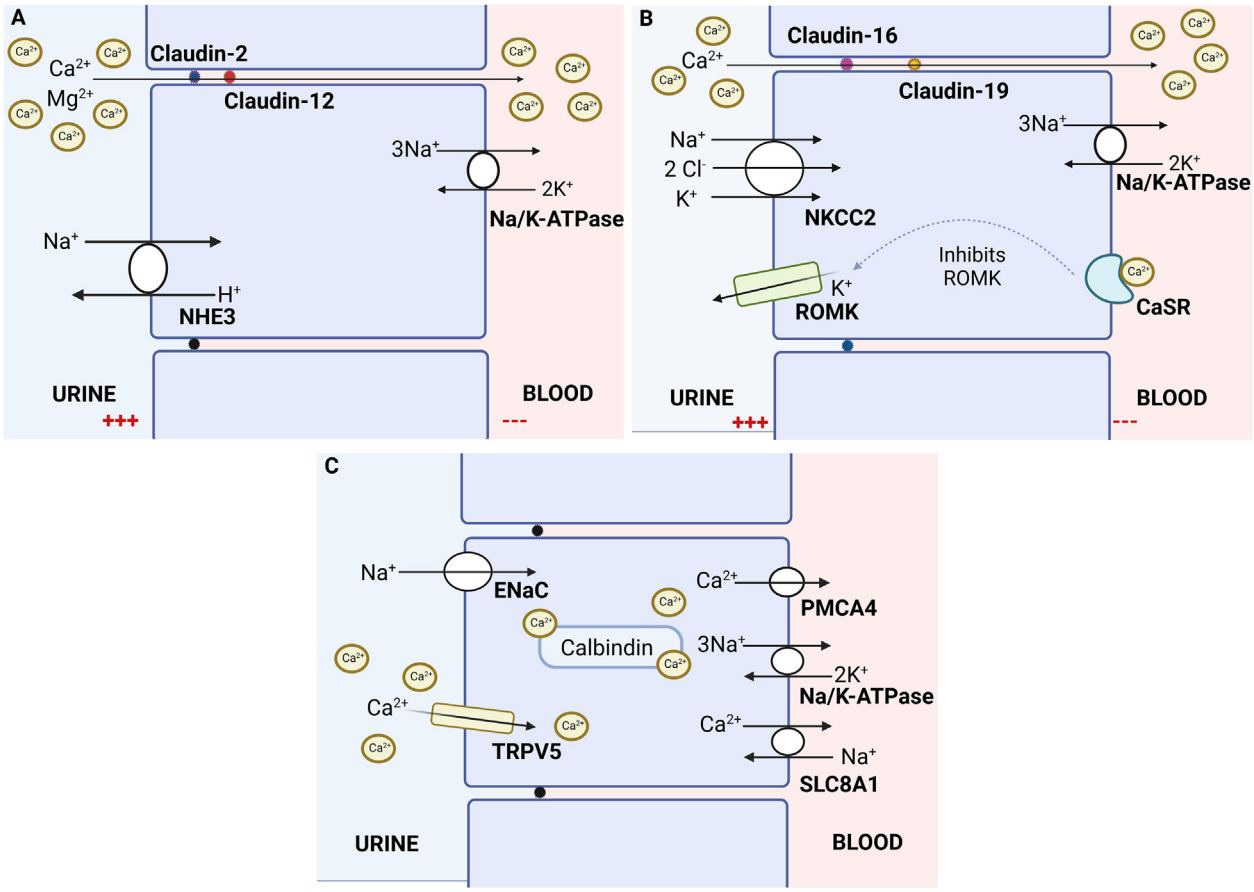

Figure 2. Calcium transport in the renal tubule. (A) In the proximal convoluted tubule, calcium reabsorption is mainly achieved via passive diffusion and solvent drag across pores formed by claudin-2 and claudin-12. The electrochemical gradient for calcium transport is generated by secretion of protons into and reabsorption of sodium ions from the lumen via the NHE3. (B) In the TAL of the loop of Henle, claudin-16 and claudin-19 form pores to allow paracellular calcium reabsorption. The electrochemical driving force in the TAL is the sodium-potassium-chloride cotransporter (NKCC2). For NKCC2 to function, it requires back leak of potassium into the tubular lumen via the ROMK channel. Back leak of potassium results in a transtubular voltage gradient that drives calcium reabsorption. In hypercalcemia, activation of the CaSR inhibits ROMK, which reduces potassium back leak and eliminates the transtubular voltage gradient, thereby decreasing calcium reabsorption. (C) In the distal convoluted tubule, calcium is reabsorbed exclusively via the transcellular route. Calcium enters the cell from the luminal side, via TRPV5. It binds intracellularly to calbindin D-28k and exits basolaterally via either the calcium ATPase PMCA4 or the sodium-calcium exchanger SLC8A1 (or NCX1). Created with Biorender. Abbreviations: CaSR, calcium sensing receptor; ENaC, epithelial sodium channel; NHE3, sodium/proton exchanger 3; NKCC2, sodium-potassium-chloride cotransporter 2; PMCA4, plasma membrane calcium pump; ROMK, renal outer medullary potassium; SLC8A1, solute carrier family 8 member A1; TAL, thick ascending limb; TRPV5, transient receptor potential cation channel subfamily V.

cases may result in QT shortening, obtundation, and coma. There are many causes of hypercalcemia, so a structured approach to diagnosis is essential (Fig 3).

Investigating the cause of hypercalcemia begins by measuring ionized calcium to establish whether true hypercalcemia is present; adjusting for serum albumin is imprecise and not recommended. Pseudohypercalcemia is less common than pseudohyponatremia, but it has been reported in patients with IgG, IgM, and IgA multiple myeloma in whom calcium binds ex vivo to the high levels of nonalbumin protein. By contrast, high levels of protein do not interfere with the method used to measure ionized calcium.

Once true hypercalcemia is established, the diagnostic algorithm dichotomizes into PTH-dependent and PTH-independent mechanisms. Testing for PTH is the most important next step. An overtly elevated or inappropriately elevated PTH for the degree of hypercalcemia implicates hyperparathyroidism. When interpreting PTH levels, it is critical to remember that "normal" is relative. PTH should be suppressed in patients with hypercalcemia. In that setting, even a PTH within the normal range is abnormal and consistent with hyperparathyroidism.

In the general population, hypercalcemia that is PTH driven is most commonly caused by primary hyperparathyroidism due a parathyroid adenoma that secretes excess

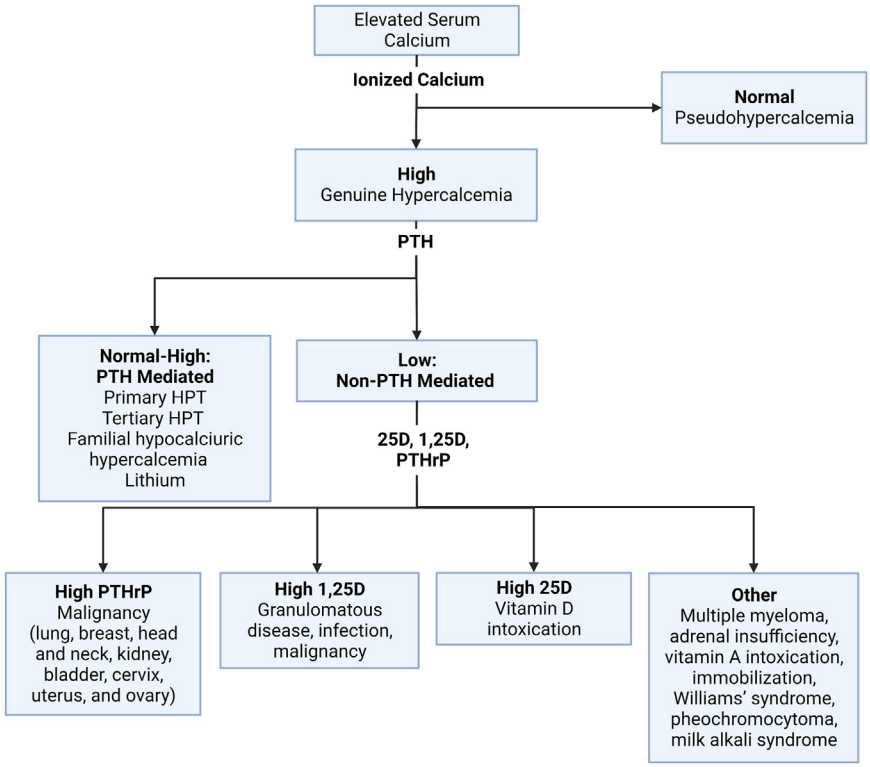

Figure 3. Diagnostic algorithm for hypercalcemia. Abbreviations: 1,25D, 1,25-dihydroxyvitamin D; 25D, 25-hydroxyvitamin D; PTH, parathyroid hormone; HPT, hyperparathyroidism; PTHrP, parathyroid hormone-related peptide.

PTH. Other less common causes include 4-gland hyperplasia as seen in multiple endocrine neoplasia, and more rarely, parathyroid carcinoma. The preferred treatment for primary hyperparathyroidism due to a parathyroid adenoma is surgical excision; however, before referring a patient for surgery, familial hypocalciuric hypercalcemia (FHH) must be ruled out.

FHH is a rare autosomal dominant disorder caused by heterozygous inactivating mutations of the calcium-sensing receptor gene *CaSR*. These mutations cause an upward reset of the calcium setpoint, leading to continued secretion of PTH despite hypercalcemia. Increased PTH augments tubular calcium reabsorption such that FHH is characterized by hypocalciuria that accompanies mild hypercalcemia (hypermagnesemia and hypophosphatemia may also be present), which distinguishes FHH from primary hyperparathyroidism, which causes hypercalciuria. Although excess PTH stimulates renal calcium reabsorption in both diseases, more severe hypercalcemia in primary hyperparathyroidism due to adenomas results in marked increases in the filtered load of calcium such that, even with augmented tubular reabsorption, hypercalciuria results. In addition, the partially inactive CaSR receptor in FHH results in less calcium-driven down-regulation of calcium reabsorption in the TAL, leading to hypocalciuria.

If PTH is appropriately suppressed in a patient with hypercalcemia, non-PTH-dependent mechanisms are the cause. In older adults, malignancy is most common and can be caused by ectopic tumor production of PTH-related peptide (PTHrP), $1,25(OH)_2D$, or multiple myeloma, which stimulates excessive osteoclastic-driven bone resorption. Excess $1,25(OH)_2D$ can also drive hypercalcemia, as seen in exogenous vitamin D intoxication or granulomatous diseases such as sarcoidosis. Other less common conditions are shown in Figure 3.

Review of Case 1

Virtually all patients with chronic kidney disease (CKD) eventually develop secondary hyperparathyroidism that is driven by FGF-23–mediated suppression of $1,25(OH)_2D$ that threatens serum calcium. The other main cause of secondary hyperparathyroidism is vitamin D deficiency (marked by low 25-hydroxyvitamin D [25(OH)D] levels), which is also common in patients with CKD. Low or low-normal serum calcium distinguishes secondary hyperparathyroidism from primary hyperparathyroidism. During months to years of CKD-associated secondary hyperparathyroidism, patients develop significant hyperplasia of the parathyroid glands. Against that backdrop, kidney transplantation rapidly reduces FGF-23 levels, restores normal $1,25(OH)_2D$ production, and provides a kidney allograft that is capable of responding to the PTH excess that can persist long after transplantation. Hypercalcemia that appears in this setting is termed tertiary hyperparathyroidism. It is often self-limited, but some

patients require treatment, which can include calcimimetics and parathyroidectomy. In case 1, follow-up testing in response to hypercalcemia revealed elevated PTH of 766 pg/mL, consistent with tertiary hyperparathyroidism, so the correct choice is (b).

Additional Readings

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Case 2: A 24-year-old man presents with malaise, nausea, weakness, and confusion. He has no past medical history but was told that his blood pressure was high when he was 18 years old. Both his parents have hypertension, and his grandmother has kidney failure. His laboratory results are sodium, 142 mmol/L; potassium, 6.4 mmol/L; creatinine, 14.4 mg/dL; SUN, 182 mg/dL; phosphate, 10.2 mg/dL; calcium, 6.5 mg/dL; albumin, 3.9 gm/dL; and bicarbonate, 9 mEq/L. Kidney ultrasound demonstrates small, scarred kidneys. Hemodialysis is initiated for his uremic symptoms, but 3 hours into the first session this patient develops seizures.

Question 2: What is the most likely cause of the seizures?
(a) Uremic encephalopathy
(b) Severe hyperphosphatemia
(c) Correction of metabolic acidosis
(d) Underlying renal-neurologic syndrome

For the answer to this question, see the following text.

Hypocalcemia Symptoms

Hypocalcemia can present from mild and asymptomatic to severe and life-threatening. Acute hypocalcemia can cause tetany, seizures, prolongation of the QT interval, and heart failure. Chronic hypocalcemia may lead to osteoporosis, dental caries, basal ganglia calcification, cataracts, and other ophthalmological manifestations.

Diagnosis

The broad physiological causes of hypocalcemia include hypoparathyroidism, pseudohypoparathyroidism (end-organ resistance to PTH), insufficient or resistance to $1,25(OH)_2D$, or calcium sequestration as in pancreatitis, rhabdomyolysis, tumor lysis syndrome, hungry bone syndrome, and ethylene glycol poisoning (Box 1). Severe hypomagnesemia, which is an essential cofactor for PTH secretion and action, is another condition that mimics hypoparathyroidism.

Box 1. Causes of Hypocalcemia

Low-ineffective PTH
- After thyroidectomy
- After parathyroidectomy
- After radiation therapy
- Hungry bone syndrome
- Autoimmune
- Genetic
- HIV
- PTH resistance

Insufficient Vitamin D
- Vitamin D deficiency
- Vitamin D resistance

Calcium Sequestration
- Hyperphosphatemia
- Tumor lysis syndrome
- Acute pancreatitis
- Ethylene glycol
- Acute respiratory alkalosis
- Osteoblastic metastasis

Drugs
- Bisphosphonates
- Cinacalcet
- Etelcalcetide
- Chelators: EDTA, citrate
- Foscarnet
- Phenytoin
- Fluoride poisoning
- Denosumab
- Calcitonin

Hypomagnesemia
- See Box 4

Abbreviations: EDTA, ethylenediaminetetraacetic acid; PTH, parathyroid hormone.

As in hypercalcemia, spurious conditions should be excluded first by testing ionized calcium and not relying on albumin adjustments. Spurious hypocalcemia is much less common than spurious hyperkalemia or hyponatremia, but 2 gadolinium-based contrast angiography agents, gadodiamide and gadoversetamide, are known to interfere with colorimetric calcium assays and may give spuriously low results. Once true hypocalcemia has been confirmed, further testing should include serum magnesium and PTH. Correction of hypocalcemia in response to magnesium administration establishes hypomagnesemia as the etiology. Hypocalcemia with low or inappropriately "normal" PTH suggests hypoparathyroidism, and elevated PTH suggests CKD, vitamin D deficiency, or pseudohypoparathyroidism.

Hungry bone syndrome is a condition that occurs after parathyroidectomy, primarily in patients with kidney failure undergoing dialysis or after kidney transplantation. Whereas most patients who undergo parathyroidectomy develop mild self-limited hypocalcemia, those with hungry bone syndrome can manifest severe symptomatic hypocalcemia for prolonged periods. Hungry bone syndrome is thought to be a result of prolonged periods of severe hyperparathyroidism, which is the typical antecedent of parathyroidectomy, leading to long-standing bone demineralization. When these effects of PTH on bone are acutely reversed by parathyroidectomy, rapid osteoblast-mediated uptake of calcium, phosphate, and magnesium into bone outpaces osteoclast-mediated bone resorption, resulting in hypocalcemia, hypophosphatemia, and hypomagnesemia. Hyperkalemia is also commonly observed in hungry bone syndrome, but the mechanism is unknown.

Review of Case 2

Untreated kidney failure can cause severe hypocalcemia due to prolonged $1,25(OH)_2D$ deficiency and severe hyperphosphatemia. However, concomitant severe metabolic acidosis due to long-standing kidney failure helps prop up the ionized calcium by titrating protein-binding sites on albumin and thereby reducing albumin's ability to bind calcium. In this setting, hemodialysis can rapidly raise pH, release protons from albumin, and expose anionic residues to bind calcium, which can cause the ionized calcium to plummet (in this case, to 0.49 mmol/L); seizures can ensue, making the correct choice (c).

Dialysis disequilibrium syndrome due to rapid reduction in serum urea concentrations can also contribute to seizures. In patients with untreated kidney failure complicated by severe metabolic acidosis and hypocalcemia, the risk of further decreasing ionized calcium can be mitigated by performing initially inefficient dialysis runs using low blood-flow rates and short duration times, and high calcium dialysate of 3.0 to 3.5 mEq/L. Given 2 mEq per each mole of divalent calcium, a dialysate bath of 3.0 to 3.5 mEq/L equates to an ionized serum calcium of 1.50 to 1.75 mmol/L. Using these baths will maximize the flow of calcium from the dialysate to the patient's circulation, thereby mitigating the risk of hypocalcemia.

Additional Readings

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Case 3: After a motor vehicle accident, a 44-year-old man with a history of alcohol-induced liver disease was admitted with shock, hemoperitoneum, liver lacerations, anuric acute kidney injury (AKI), hyperkalemia, and severe anion-gap metabolic acidosis. He was commenced on continuous renal replacement therapy (CRRT). Given the bleeding, regional anticoagulation with citrate was used instead of heparin to maintain patency of the CRRT circuit. On day 3 of CRRT, after normalization of hyperkalemia and closing of the anion-gap, the patient deteriorates hemodynamically, and anion-gap acidosis recurs despite normal serum potassium levels.

Question 3: Which of the following patterns best reflect this patient's current clinical status?

(a) Total calcium increasing; ionized calcium decreasing
(b) Total calcium increasing; ionized calcium increasing
(c) Total calcium decreasing; ionized calcium decreasing
(d) Total calcium decreasing; ionized calcium increasing

For the answer to this question, see the following text.

Calcium in Serious Illness

Iatrogenic hypocalcemia is common among hospitalized patients. A common cause of acute hypocalcemia encountered by nephrologists is hypocalcemia due to citrate accumulation, which most commonly occurs in the setting of either massive blood transfusion—because citrate is used as an anticoagulant in stored blood products—or regional citrate anticoagulation in patients receiving CRRT. Calcium is a crucial cofactor for normal functioning of the coagulation cascade, and citrate chelates calcium through its high affinity for divalent calcium ions. Therefore, citrate can be used as a regional anticoagulant within CRRT circuits when systemic anticoagulation is contraindicated, as in the case of trauma.

Review of Case 3

In regional citrate anticoagulation, a prefilter citrate infusion is administered to reduce ionized calcium levels sufficiently to achieve effective anticoagulation (ionized calcium < 0.35 mmol/L). A separate, postfilter infusion of calcium is administered to restore normal circulating ionized calcium concentrations. Citrate accumulation can occur when citrate administration in CRRT exceeds the capacity of the liver to convert citrate to bicarbonate, which is most commonly observed among patients with liver disease. When excess citrate is present, severe reductions in ionized calcium can result, but this is accompanied by increasing total calcium because the total calcium assay detects both ionized calcium and the calcium that is citrate bound; so (a) is the correct choice.

The total-to-ionized calcium ratio is useful in detecting early signs of citrate accumulation in patients who are receiving CRRT. A ratio of greater than 10 (when total calcium is measured in mg/dL and ionized calcium is in mmol/L) or greater than 2.5 (when total calcium and ionized calcium are both measured in mmol/L) suggests citrate accumulation. The anion gap should also be monitored in patients on CRRT because accumulation of

citrate as an "unaccounted anion" can increase the anion gap, as in the current case, in parallel with a high total-to-ionized calcium ratio.

Recommended Reading

➢ Tolwani AJ, Prendergast MB, Speer RR, Stofan BS, Wille KM. A practical citrate anticoagulation continuous venovenous hemodiafiltration protocol for metabolic control and high solute clearance. *Clin J Am Soc Nephrol*. 2006;1:79-87. https://doi.org/10.2215/cjn.00040505

Hypercalcemia and Vitamin D

Case 4: A 47-year-old man presents with fever, weight loss, and night sweats. He has a history of HIV and is known to be nonadherent with medications; he was lost to follow-up observation 18 months ago. On examination he has diffuse lymphadenopathy and hepatosplenomegaly. His laboratory results are hemoglobin, 11.4 g/dL; leukocyte count, 13,690 cells/mm^3; CD4 count, 200 cells/mm^3; creatinine, 1.4 mg/dL; calcium, 11.3 mg/dL; albumin, 2.5 mg/dL; ionized calcium, 1.50 mmol/L; and PTH, <10 pg/mL.

Question 4: What is the most likely diagnosis?
(a) PTHrP-mediated paraneoplastic syndrome
(b) HIV-associated nephropathy
(c) Fungal infection
(d) Allergic interstitial nephritis

For the answer to this question, see the following text.

Vitamin D intoxication is an important PTH-independent cause of hypercalcemia. Vitamin D is a fat-soluble hormone that is primarily responsible for intestinal absorption of calcium and, to a lesser extent, phosphate. Vitamin D precursors are synthesized in the skin from cholesterol in response to ultraviolet radiation or ingested in the form of dietary supplements (Fig 4). The liver rapidly hydroxylates vitamin D precursors at the 25-carbon position to form 25(OH)D, which is the stable storage form of vitamin D. To test for vitamin D sufficiency, 25(OH)D should be measured.

The kidney is primarily responsible for converting 25(OH)D to $1,25(OH)_2D$, which is the most active form of vitamin D based on it having the highest affinity for the vitamin D receptor (VDR); 25(OH)D can also activate the VDR to cause hypercalcemia, though it requires significantly higher levels to do so compared with $1,25(OH)_2D$. Conversion of 25(OH)D to $1,25(OH)_2D$ is regulated by the opposing effects of PTH, which acts as a "gas pedal" that enhances vitamin D activation, and FGF-23, which acts as a "brake" against vitamin D activation.

The main effects of $1,25(OH)_2D$ on calcium and phosphate homeostasis include stimulation of intestinal calcium absorption by up-regulating calcium transporters such as calbindin and transient receptor potential vanilloid subfamily member 6 (TRPV6), among many other proteins involved in calcium transport. $1,25(OH)_2D$ also stimulates intestinal phosphate absorption by up-regulating the $1,25(OH)_2D$-inducible NaPi-2b; however,

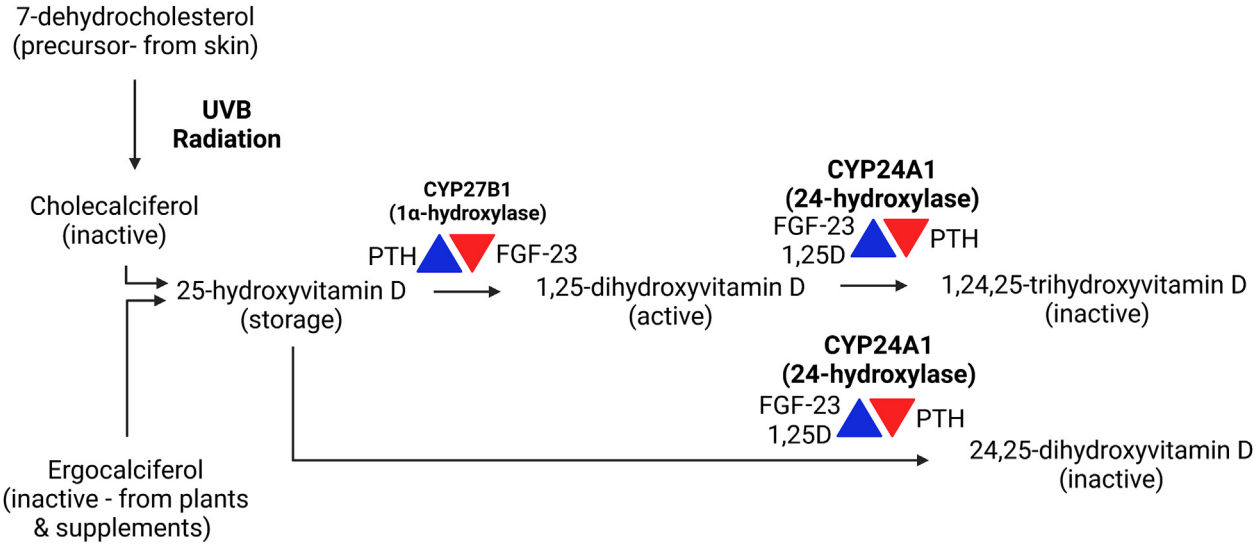

Figure 4. Synthesis and degradation of vitamin D. Vitamin D is synthesized in the skin from cholesterol in response to UVB radiation. It can also be ingested in the form of the plant- and fungi-derived ergocalciferol. Cholecalciferol and ergocalciferol undergo hydroxylation in the liver to its storage form, 25-hydroxyvitamin D. In the kidney, 25-hydroxyvitamin D is converted to the most active form of vitamin D, 1,25-dihydroxyvitamin D, by the enzyme CYP27B1 (1α-hydroxylase). PTH stimulates conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by CYP27B1, while FGF-23 inhibits CYP27B1. CYP24A1 (24-hydroxylase) is the catabolic enzyme that degrades 1,25-dihydroxyvitamin D to its inactive form, 1,24,25 trihydroxyvitamin D. It also converts 25-hydroxyvitamin D to the inactive 24,25-dihydroxyvitamin D, which can be measured to assess CYP24A1 activity. Like their opposing effects on CYP27B1, PTH inhibits and FGF-23 stimulates CYP24A1. Abbreviations: FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone; UVB, ultraviolet B.

the majority of intestinal phosphate absorption occurs via paracellular pathways that are not $1,25(OH)_2D$-dependent. Closing a feedback loop, $1,25(OH)_2D$ suppresses PTH directly by binding the VDR in the parathyroid glands, and indirectly by increasing serum calcium. Closing another feedback loop, $1,25(OH)_2D$ stimulates FGF-23 directly. Closing yet another feedback loop, $1,25(OH)_2D$ accelerates its own degradation by stimulating CYP24A1. The latter 3 effects lower $1,25(OH)_2D$ levels.

Vitamin D intoxication may be exogenous or endogenous. Exogenous vitamin D intoxication may occur due to excess intake of cholecalciferol, ergocalciferol, 25(OH)D, $1,25(OH)_2D$, or use of the topical vitamin D analogue calcipotriol for treatment of psoriasis. Hypercalcemia that is caused by exogenous $1,25(OH)_2D$ tends to resolve rapidly once therapy is stopped because of the short half-life of $1,25(OH)_2D$. Hypercalcemia due to excess intake of cholecalciferol, ergocalciferol, or 25(OH)D tends to persist longer because their half-life is longer than $1,25(OH)_2D$.

Review of Case 4

Endogenous hypervitaminosis D most commonly occurs in lymphomas or granulomatous diseases that ectopically produce $1,25(OH)_2D$. Macrophages express the 1α-hydroxylase enzyme CYP27B1, which converts 25(OH)D to the active form $1,25(OH)_2D$. Initially, excess $1,25(OH)_2D$ causes modest increases in extracellular calcium from increased intestinal absorption. As long as there is sufficient glomerular filtration rate (GFR), the kidney can excrete the excess calcium in the urine, resulting in hypercalciuria. If the burden of granulomatous disease exceeds the renal calcium excretory capacity or if some degree of kidney dysfunction develops—for example, due to prerenal azotemia or tubulointerstitial granulomatous disease—overt hypercalcemia ensues. This pathogenesis can occur in sarcoidosis, berylliosis, Sjogren's syndrome, Crohn's disease, other granulomatous diseases, and by mycobacterial infections and disseminated fungal infection (aspergillosis, candidiasis, coccidioidomycosis paracoccidioidomycosis, and histoplasmosis).

Based on the clinical history and confirmatory testing, which revealed a markedly elevated serum $1,25(OH)_2D$ level of 113 pg/mL, this patient's presentation is consistent with an infectious etiology such as a disseminated fungal infection, choice (c). HIV can be associated with hypercalcemia by predisposing individuals to disseminated granulomatous infection or lymphoma, but HIV-associated nephropathy does not directly cause hypercalcemia.

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Genetic Cause of Hypercalcemia

Case 5: A 24-year-old nulliparous woman at 28 weeks' gestation is referred for asymptomatic hypercalcemia that was identified at her 20-week prenatal visit. Her past medical history is significant for 2 episodes of nephrolithiasis, but she has no history of hypercalcemia. She only takes prenatal vitamins. Her family history includes nephrolithiasis in her father and brother. Her physical examination is unremarkable. The lab results are calcium, 12.2 mg/dL; phosphate, 3.2 mg/dL; PTH, <10 pg/mL; 25(OH)D, normal level; and $1,25(OH)_2D$, 236 pg/mL (high).

Question 5: A mutation of which gene is most likely in this patient?

(a) *CYP24A1*
(b) *CYP27B1*
(c) *NCC*
(d) *SLC34A3*

For the answer to this question, see the following text.

CYP24A1 (24-hydroxylase) is the major enzyme responsible for degrading vitamin D metabolites (Fig 4). CYP24A1 converts 25(OH)D to the inactive 24,25-dihydroxyvitamin D [$24,25(OH)_2D$] and $1,25(OH)_2D$ to 1,24,25 trihydroxyvitamin D. As in the case of CYP27B1 (1α-hydroxylase), PTH and FGF-23 also have opposing effects on CYP24A1-mediated inactivation of $1,25(OH)_2D$: PTH inhibits and FGF-23 stimulates CYP24A1.

Review of Case 5

Inactivating mutations of *CYP24A1* cause infantile hypercalcemia, characterized by severe hypercalcemia, vomiting, and failure to thrive. Carriers of pathogenic variants of *CYP24A1* can remain asymptomatic and maintain normal serum calcium in the absence of a stressor such as pregnancy in which there is increased expression of CYP27B1 by the kidney and placenta. This enables increased maternal calcium absorption to support the mineral needs of the developing fetal skeleton. As a result of increased endogenous production of $1,25(OH)_2D$, intestinal calcium absorption doubles compared with before pregnancy. The increased production of $1,25(OH)_2D$ that occurs during pregnancy may unmask genetic disorders of *CYP24A1*, as in this patient. Lack of 24-hydroxylase activity prolongs the half-life and effects of $1,25(OH)_2D$ resulting in $1,25(OH)_2D$-dependent

hypercalcemia, hypercalciuria, and increased risk of nephrolithiasis. Levels of $1,25(OH)_2D$ and 25(OH)D are variably elevated, and 24,25D levels and the ratio of 24,25D to 25(OH)D are extremely low due to CYP24A1 deficiency. In this patient, the correct answer is (a): whole exome sequencing confirmed homozygosity for a known inactivating mutation in *CYP24A1*.

Among the incorrect choices in this case, inactivating mutations of *CYP27B1*, which encodes the 1-α hydroxylase, prevents $1,25(OH)_2D$ synthesis and results in hypocalcemia and vitamin D-dependent rickets. Inactivating mutations of *NCC* cause Gitelman syndrome, which causes hypomagnesemia, hypokalemia, and hypocalciuria, but not hypercalcemia. Inactivating mutations of *SLC34A3*, which encodes NaPi-2c, cause hereditary hypophosphatemic rickets with hypercalciuria, nephrolithiasis, and occasionally hypercalcemia due to excess $1,25(OH)_2D$, but the cardinal sign is hypophosphatemia due to renal phosphate wasting.

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Phosphate Homeostasis

Case 6: A 25-year-old woman with a hemoglobin of 8.2 g/dL was prescribed oral iron for iron deficiency due to heavy uterine bleeding. Six months later, after struggling with constipation and persistently low ferritin and transferrin saturation, she received a course of ferric carboxymaltose consisting of 750 mg intravenously followed by a second 750 mg infusion 1 week later. Two days after the second infusion, she presented with profound weakness, reduced mental acuity, and diffuse cramps. Her hemoglobin had risen to 10.1 g/dL, but her serum phosphate level was 0.9 mg/dL. She was treated with intravenous and oral phosphate. Two months later, her hemoglobin is 11.5 g/dL, and her serum phosphate is 2.9 mg/dL after phosphate supplementation was discontinued, but she continues to have heavy menses. Six months later, her hemoglobin dropped to 8.1 g/dL due to recurrent iron deficiency. Her serum phosphate remains normal.

Question 6: What is the best treatment for her iron deficiency anemia?

(a) Subcutaneous erythropoiesis stimulating agent
(b) A second course of intravenous ferric carboxymaltose
(c) An alternative intravenous iron formulation
(d) Oral iron

For the answer to this question, see the following text.

Phosphate Economy

Phosphate homeostasis is critical for multiple cellular processes including nucleic acid and adenosine triphosphate (ATP) synthesis, cell signaling, integrity of phospholipid bilayers, and skeletal health. Between 80% and 85% of phosphate is present in bone, 14% is intracellular, and 1% is in the extracellular fluid. Dietary phosphate is absorbed in the duodenum and jejunum via a combination of passive paracellular and active transcellular transport. Paracellular absorption predominates, especially when phosphate levels are normal. When serum phosphate levels are low and $1,25(OH)_2D$ levels increase as a result, transcellular absorption via the $1,25(OH)_2D$-inducible type NaPi-2b cotransporter increases.

A typical dietary intake of phosphate is 800-1,200 mg/day, approximately two-thirds of which is absorbed, but dietary phosphate is absorbed at different rates depending on its source. Animal protein and dairy sources are readily absorbed, whereas much of plant-based phosphate is found in phytate, which is poorly absorbed by the human intestine due to lack of the enzyme phytase. Inorganic phosphate found in food additives is most easily absorbed. As a result, diets rich in processed foods can lead to consumption and absorption of phosphate far in excess of physiological need.

Renal Phosphate Handling

Renal excretion of phosphate is extremely efficient. Healthy kidneys can excrete up to 4,000 mg daily with only a minimal increase in serum phosphate. Most circulating phosphate is filtered by the glomerulus, and most filtered phosphate is reabsorbed in the PCT. As a result, less than 15% of filtered phosphate is typically excreted in the urine; in other words, fractional excretion is usually <15% in healthy individuals on typical diets. Three sodium-phosphate cotransporters, NaPi-2a, NaPi-2c, and the PiT-2 are expressed in the PCT (Fig 5). When NaPi-2a and NaPi-2c are situated in the apical membrane of the PCT, they reabsorb phosphate. In contrast, increases in FGF-23 or PTH cause recycling of NaPi-2a and NaPi-2c from the apical membrane leading to increased urinary phosphate excretion. Conversely, sodium-glucose transport protein-2 (SGLT2) inhibitors can increase phosphate reabsorption in the PCT, causing a modest rise in phosphate.

As GFR falls in patients with CKD, filtration of phosphate falls in parallel. In early CKD, rising FGF-23 levels maintain normal serum phosphate levels by reducing expression of NaPi-2a and NaPi-2c, thereby increasing fractional excretion of phosphate. FGF-23–mediated reduction in $1,25(OH)_2D$ levels leads to secondary hyperparathyroidism, and the rise

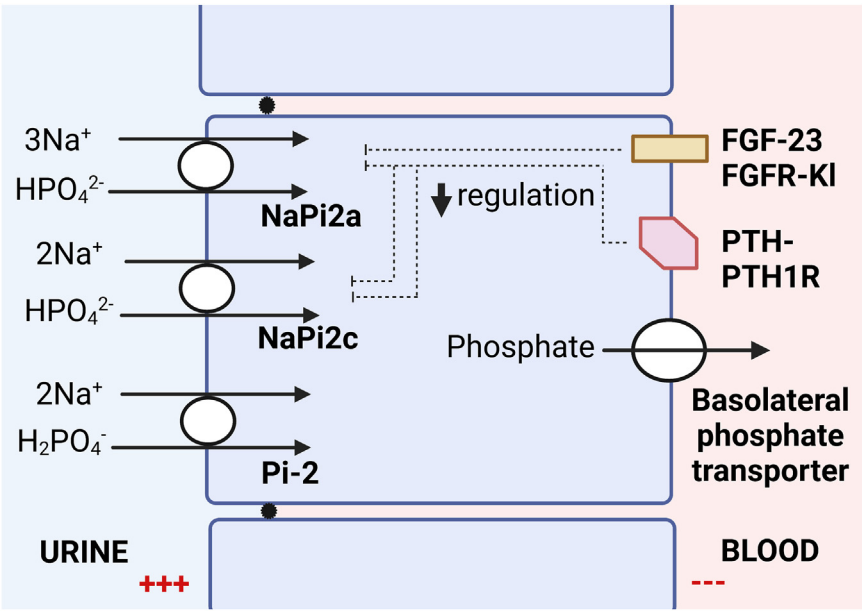

Figure 5. Phosphate transport in the proximal convoluted tubule. Phosphate is reabsorbed via transcellular transport in the proximal convoluted tubule. Three sodium-phosphate cotransporters, NaPi-2a, NaPi-2c, and PiT-2, transport phosphate from the tubular lumen into the cell. Phosphate is then transported out of the cell by an unknown basolateral phosphate transporter. Binding of FGF-23 to FGF receptor (FGFR)-klotho (Kl) complexes, and PTH to the PTH1R inhibits phosphate reabsorption by down-regulating apical expression of NaPi-2a and NaPi-2c. Created with Biorender. Abbreviations: FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone; PTH1R, parathyroid hormone 1 receptor.

in PTH further augments renal phosphate excretion. As a result of these adaptations to CKD, hyperphosphatemia does not occur until critical reductions in GFR overcome the compensatory effects of FGF-23 and PTH.

Hypophosphatemia

Mild hypophosphatemia is often asymptomatic, but severe hypophosphatemia can cause cellular ATP depletion that results in musculoskeletal symptoms such as diffuse skeletal muscle weakness, respiratory muscle weakness that can precipitate respiratory failure, and cardiac muscle weakness that can cause heart failure. Other severe complications include proximal myopathy, dysphagia, ileus, rhabdomyolysis, hemolysis, and neurological symptoms including paresthesia, delirium, generalized seizures, and coma. Chronic hypophosphatemia can lead to severe bone and dental demineralization, resulting in rickets or osteomalacia, depending on the age of onset relative to fusion of growth plates.

Diagnosis

Hypophosphatemia may occur due to redistribution of extracellular phosphate into cells or loss via renal excretion; decreased gut absorption of phosphate can exacerbate hypophosphatemia due to other causes, but rarely causes hypophosphatemia on its own (Box 2). Measurement of 24-hour urinary phosphate excretion or fractional excretion of phosphate on a spot urine test helps to establish whether hypophosphatemia is caused by renal phosphate wasting or other causes, such as transcellular shift. Because the kidney is very efficient at reabsorbing even small amounts of phosphate, urinary phosphate excretion > 100 mg/day in the setting of hypophosphatemia is inappropriate and confirms renal phosphate wasting. Likewise, fractional excretion of phosphate (100 × [Urine phosphate × Serum creatinine/Serum phosphate × Urine creatinine]) should be low in hypophosphatemia; elevation > 20% confirms renal phosphate wasting.

Most cases of chronic hypophosphatemia are due to renal phosphate wasting, either due to excess FGF-23 or PTH. When hypophosphatemia is PTH-mediated, it is accompanied by hypercalcemia, which is the primary consequence of PTH excess. Hypophosphatemia due to renal phosphate wasting in the absence of hypercalcemia suggests primary FGF-23 excess for which there are several hereditary and acquired causes.

Tumor-induced (previously termed "oncogenic") osteomalacia (TIO) is a rare paraneoplastic syndrome caused by ectopic FGF-23 secretion, which presents with hypophosphatemia, bone pain, fractures, and muscle weakness. Although reports of TIO caused by carcinoma seem to be increasing, TIO is most commonly caused by benign mesenchymal tumors, the small size of which can make them difficult to locate for curative resection. A combination of computed tomography (CT), magnetic resonance imaging, functional imaging (gallium-68 Dotatate positron emission tomography and octreotide

Box 2. Causes of Hypophosphatemia

Gastrointestinal Loss
- Insufficient intake
- Chronic diarrhea
- Steatorrhea
- Magnesium, aluminum-based antacids
- Niacin intake

Redistribution Into Cells
- Refeeding syndrome
- Treatment of diabetic ketoacidosis
- Treatment of nonketotic hyperglycemia
- Acute respiratory alkalosis
- Hungry bone syndrome

Renal Loss
- Hyperparathyroidism
- After kidney transplant
- Fanconi syndrome
- X-linked hypophosphatemic rickets
- Tumor-induced osteomalacia
- Intravenous iron
- NPT2a, NPT2c mutations
- Acetazolamide
- Tyrosine-kinase inhibitors
- VEGF inhibitors
- mTOR inhibitors
- Intensive hemodialysis and CRRT

Abbreviations: CRRT, continuous renal replacement therapy; mTOR, mammalian target of rapamycin; NPT, sodium-phosphate cotransporter; VEGF, vascular endothelial growth factor.

scintigraphy), and sampling of major venous beds with testing for an FGF-23 "step up" can be used to locate these tumors. When the tumor has been successfully identified and excised, the signs and symptoms usually rapidly subside. When the tumor cannot be located or cannot be excised (eg, metastatic carcinoma), burosumab, a monoclonal anti-FGF-23 antibody, can be used as an effective but expensive alternative.

Hypophosphatemia can affect up to 85%-90% of patients with functioning kidney allografts in the early posttransplant period because the immediate restoration of GFR enables marked urinary phosphate excretion in response to residual elevations of FGF-23 and PTH from the kidney failure period. It can take weeks for FGF-23 elevation to revert to normal and much longer for PTH, which can remain elevated for years after transplantation. Hypophosphatemia also occurs in many patients receiving CRRT or intensive hemodialysis due to excess phosphate clearance. Supplementation of phosphate effectively treats hypophosphatemia in these settings.

Review of Case 6

Via unknown mechanisms, intravenous ferric carboxymaltose causes acute increases in biologically active levels of FGF-23, which results in hypophosphatemia in over 50% of patients who receive the drug. Randomized clinical trials have demonstrated that other iron preparations such as ferumoxytol, ferric derisomaltose, iron sucrose, and iron dextran have a significantly lower risk of severe hypophosphatemia compared with ferric carboxymaltose. Phosphate levels generally recover over the course of 1-3 months, but some patients can experience hypophosphatemia for 3-6 months after a single course of ferric carboxymaltose. Repeated courses can result in protracted periods of hypophosphatemia that have been complicated by severe musculoskeletal complications, including osteomalacia and fractures. In this patient who previously developed ferric carboxymaltose–induced hypophosphatemia, the correct choice is (c): it would be prudent to treat recurrent iron deficiency anemia with a formulation of intravenous iron other than ferric carboxymaltose to avoid recurrent hypophosphatemia.

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Hyperphosphatemia

Case 7: A 46-year-old woman was treated with cytarabine and doxorubicin for newly diagnosed acute myeloid leukemia. Day 1 of her chemotherapy laboratory results yielded sodium 142, mmol/L; potassium, 4.1 mmol/L; SUN, 32 mg/dL; creatinine, 0.7 mg/dL; calcium, 9.4 mg/dL; phosphate, 3.2 mg/dL; and albumin, 3.9 mg/dL. Week 2 of her treatment was complicated by aspiration pneumonia, which required intubation for 7 days. She was treated with vancomycin for *Staphylococcus aureus* pneumonia and liposomal amphotericin B for possible invasive candidiasis. Day 21 of admission laboratory results yielded sodium, 144 mmol/L; potassium, 4.9 mmol/L; SUN, 42 mg/dL; uric acid, 6.8 mg/dL; creatinine, 1.2 mg/dL; calcium, 9.3 mg/dL; phosphate, 9.7 mg/dL; and albumin, 2.3 g/dL.

Question 7: What is the most likely cause of this patient's hyperphosphatemia?
(a) Amphotericin B
(b) Chemotherapy-induced hypoparathyroidism
(c) Immobility
(d) Tumor lysis syndrome

For the answer to this question, see the following text.

Acute Hyperphosphatemia

Acute hyperphosphatemia can be life threatening, primarily by inducing severe, concomitant hypocalcemia. Calcium-phosphate deposition in the kidney, heart, joints,

and vasculature may occur. Acute onset of calcium-phosphate deposition in the renal tubules and interstitium can cause severe AKI that exacerbates the hyperphosphatemia, as observed in patients with some degree of CKD who receive phosphate-based enemas as bowel preparation for colonoscopy and develop acute phosphate nephropathy.

Acute hyperphosphatemia can occur due to phosphate loading or rapid shifting of phosphate from the intracellular to extracellular space (Box 3). Preexisting or concurrent reductions in GFR exacerbate each of these mechanisms by reducing filtration and thus excretion of phosphate. Phosphate excretion becomes progressively more impaired as the kidneys fail, so patients with advanced CKD have a tendency toward chronic hyperphosphatemia and are also more vulnerable to acute changes in phosphate precipitated by other mechanisms.

Tumor lysis syndrome is one of the most common causes of emergent hyperphosphatemia. It occurs after massive lysis of tumor cells, either spontaneously or, more commonly, in response to initiation of cytotoxic therapy in highly proliferative tumors such as high-grade lymphoma or leukemia. Acute cell lysis leads to the release of large quantities of potassium, nucleic acids, and phosphate from the intracellular space, which results in hyperkalemia, hyperuricemia, and hyperphosphatemia with secondary hypocalcemia. Rhabdomyolysis, especially when complicated by AKI, can cause similar changes due to lysis of muscle cells.

Box 3. Causes of Hyperphosphatemia

Acute Phosphate Load
- Phosphate-containing laxatives
- Fosphenytoin

Redistribution Out of Cells
- Rhabdomyolysis
- Tumor lysis syndrome
- Severe lactic acidosis
- Severe ketoacidosis

Reduced Renal Excretion
- Advanced kidney failure
- Hypoparathyroidism
- Vitamin D toxicity
- Familial tumoral calcinosis
- Acromegaly
- Bisphosphonates
- FGF receptor inhibitors

Abbreviations: FGF, fibroblast growth factors.

Chronic Hyperphosphatemia

In the absence of kidney failure, hypoparathyroidism (or pseudohypoparathyroidism) and FGF-23 deficiency or impaired FGF-23 effects cause hyperphosphatemia by increasing the expression of sodium-phosphate cotransporters in the PCT that increase tubular reabsorption of filtered phosphate (Box 3). When hyperphosphatemia is due to insufficient PTH, it is accompanied by hypocalcemia, which is the primary consequence of PTH deficiency. Hyperphosphatemia is a class effect of the fibroblast growth factor receptor inhibitors (erdafitinib used to treat urothelial cancers; pemigatinib and infigratinib used to treat cholangiocarcinoma), which block the tubular effects of FGF-23. Like disorders of excess $1,25(OH)_2D$ (eg, granulomatous diseases), these drugs and other disorders of FGF-23 deficiency also cause hypercalciuria and sometimes hypercalcemia due to failure of FGF-23 to suppress $1,25(OH)_2D$ levels.

Other drug-induced causes of hyperphosphatemia include administration of fosphenytoin, bisphosphonates, and sodium phosphate-containing laxatives. These agents must be used with extreme caution in patients with CKD because there is a risk of inducing life-threatening hyperphosphatemia and AKI. Of course, the most common cause of chronic hyperphosphatemia is kidney failure in which ongoing dietary phosphate absorption plus PTH-mediated bone resorption result in phosphate entry into the circulation in excess of renal excretion plus clearance by standard dialysis regimens (intensive daily dialysis can remove large amounts of phosphate).

Diagnosis

Because the kidney is the sole pathway of regulated phosphate excretion, there is little utility in quantifying urinary phosphate excretion in patients with hyperphosphatemia; in this setting, any measured amount of urinary phosphate excretion is insufficient. Instead, diagnosis should focus on identifying why the kidney is not excreting the phosphate load and identifying any source of phosphate loading. Usually history, physical examination, and basic laboratory testing, including serum calcium, will establish the mechanism of hyperphosphatemia; occasionally ancillary testing of PTH, $1,25(OH)_2D$, and FGF-23 levels are needed to make a specific diagnosis.

Review of Case 7

The absence of hyperkalemia, hyperuricemia, and hypocalcemia rules out tumor lysis syndrome. This patient has pseudohyperphosphatemia due to liposomal amphotericin B, which can interfere with the laboratory analyzer and cause an artificially elevated phosphate reading: the correct choice is (a). By the same mechanism, pseudohyperphosphatemia can also be seen in multiple myeloma, hemolysis, and hyperlipidemia, and in samples contaminated by heparin or alteplase. If pseudohyperphosphatemia is suspected, alternative phosphate assays can be used.

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Magnesium Homeostasis

Case 8: A 55-year-old woman with no past medical history was diagnosed with metastatic colorectal cancer. She was treated with leucovorin, 5-fluorouracil, and oxaliplatin for palliation. Restaging after 3 months revealed disease progression, so she was switched to cetuximab. Eight weeks later, she was brought to the emergency room too weak to walk. Physical examination revealed Chvostek's and Trousseau's signs. Her laboratory results were sodium, 128 mEq/L; potassium, 3.0 mEq/L; SUN, 18 mg/dL; creatinine, 1.1 mg/dL; calcium, 6.0 mg/dL; phosphate, 4.2 mg/dL; albumin, 3.4 gm/dL; and low ionized calcium of 0.68 mmol/L. Repeat CT scans showed no evidence of further disease progression.

Question 8: Which of the following would be the next most useful test in this patient?
(a) $1,25(OH)_2D$ level
(b) PTH level
(c) Magnesium level
(d) Urinary calcium

For the answer to this question, see the following text.

Magnesium Economy

Magnesium is the fourth most abundant cation in the body. It has multiple essential roles, including synthesis of bone, protein, and DNA, and regulation of nerve and muscle function. It is involved in multiple enzymatic reactions and helps to regulate hormones, including PTH, adrenocorticotropic hormone, and cortisol.

Magnesium is absorbed from the intestine via paracellular and transcellular transport. Paracellular transport is passive and driven by concentration gradients, while transcellular transport is facilitated by transient receptor potential cation channel subfamily M member 6 (TRPM6) and transient receptor potential cation channel subfamily M member 7 (TRPM7). Magnesium is stored primarily in bone as a component of hydroxyapatite crystals.

Renal Magnesium Handling

Only 20%-25% of reabsorption occurs in the proximal tubule. The majority of reabsorption occurs in the TAL of the loop of Henle via paracellular pathways through tight junctions between epithelial cells (Fig 6). The movement of magnesium is facilitated by claudins 16 and 19. As with calcium, transport is dependent on the transepithelial voltage

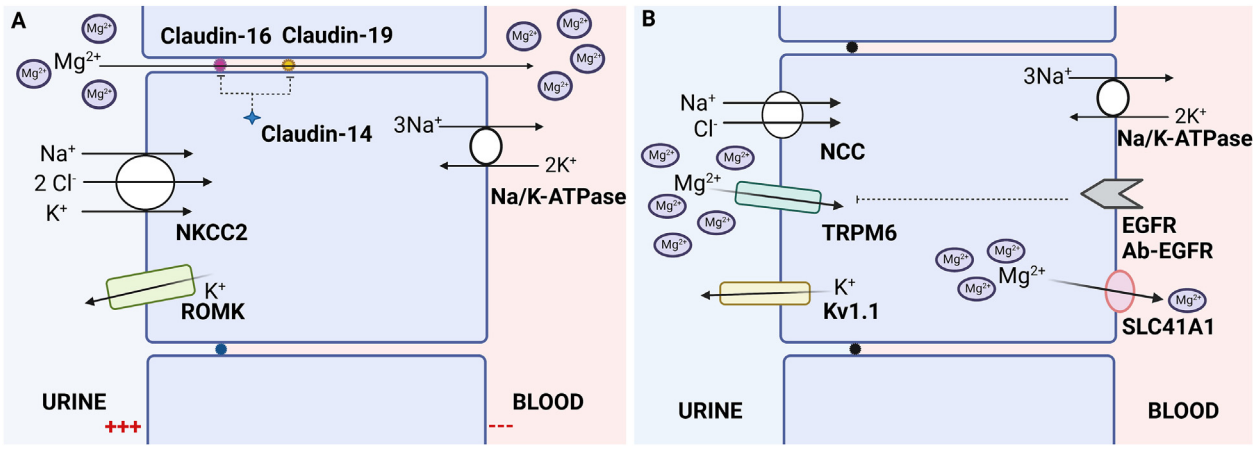

Figure 6. Magnesium transport in the renal tubule. (A) Magnesium is reabsorbed primarily in the thick ascending limb of the loop of Henle via the paracellular route. This is facilitated by claudin-16 and claudin-19. Like calcium, magnesium reabsorption depends on the transepithelial voltage gradient generated by the activity of NKCC2 and back secretion of potassium into the lumen via ROMK. In hypermagnesemia, claudin-14 interferes with claudin-16 and claudin-19, which reduces paracellular permeability to magnesium. (B) In the distal convoluted tubule, TRPM6 facilitates transcellular magnesium reabsorption. Given the neutral electrochemical effect of salt reabsorption via the NCC, extrusion of potassium into the lumen via the apical potassium channel Kv1.1 creates a favorable electrochemical gradient for magnesium reabsorption. Magnesium then passes through the basolateral membrane via SLC41A1. Created with Biorender. Abbreviations: EGFR, epithelial growth factor receptor; NCC, sodium chloride cotransporter; NKCC2, sodium-potassium-chloride cotransporter 2; ROMK, renal outer medullary potassium; SLC8A1, solute carrier family 8 member A1; TRPM6, transient receptor potential cation channel subfamily M member 6.

generated by the activity of the NKCC2 transporter and back leak of potassium into the tubule lumen via ROMK. This results in an electrochemical gradient from the more positively charged tubule lumen across the more negatively charged tubular cell, which drives paracellular magnesium reabsorption. When magnesium levels are high, claudin-14 decreases the permeability of this paracellular pathway, increasing urinary magnesium excretion. Mutations in claudins 16 and 19 cause hereditary forms of magnesium wasting, and loop diuretics cause acquired forms of decreased magnesium reabsorption by inhibiting NKCC2.

The final 10% of magnesium absorption occurs in the DCT, where TRPM6 channels mediate transcellular absorption, determining the final urinary magnesium excretion. Activation of the epithelial growth factor receptor (EGFR) increases the presence of TRPM6 in the luminal membrane.

Hypomagnesemia

Hypomagnesemia is extremely common in hospitals, affecting 12% of all hospitalized patients and 60% of patients in the intensive care unit. Severe hypomagnesemia can cause muscle weakness, tetany, confusion, seizures, arrhythmias, and heart failure. Many of these complications are due to concomitant hypocalcemia and hypokalemia.

Unlike other ions, hypomagnesemia due to intracellular shift tends not to occur, so the majority of hypomagnesemia is caused by gastrointestinal or renal loss (Box 4). Gastrointestinal loss may occur due to excessive upper or lower gastrointestinal secretions, though it more commonly occurs in diarrhea because a higher concentration of magnesium is present in lower gastrointestinal secretions. Proton pump inhibitors (PPI) decrease intestinal magnesium absorption by reducing TRPM6- and TRPM7-mediated absorption. Given the pervasiveness of their use in the population, PPI are among the most common causes of hypomagnesemia.

Renal loss of magnesium can be due to multiple causes (Box 4), including drugs, tubular dysfunction, and hereditary causes, which include dominant and recessive mutations in TRPM6, claudins 16 and 19, and Gitelman syndrome due to inactivating mutations of the sodium chloride cotransporter (NCC). Those that affect paracellular movement of magnesium through the TAL, such as familial hypomagnesemia with hypercalciuria and nephrocalcinosis, may have associated hypercalciuria whereas disorders affecting transcellular receptors may present with isolated hypomagnesemia or the Gitelman-like familial hypomagnesemia syndromes with hypocalciuria.

Review of Case 8

Anti-EGFR monoclonal antibodies, such as panitumumab and cetuximab, cause hypomagnesemia by increasing renal magnesium wasting. Severe hypomagnesemia causes hypocalcemia because the parathyroid gland depends on magnesium for the synthesis and secretion of PTH. Because the end-organ effects of PTH also require magnesium, hypomagnesemia results in hypocalcemia due to hypoparathyroidism and PTH resistance that cannot be corrected by calcium or vitamin D alone. Resolution of hypocalcemia only occurs with correction of hypomagnesemia. Therefore, in cases of refractory hypocalcemia the correct choice is (c): it is critical to check the serum magnesium level and administer magnesium repletion.

Box 4. Causes of Hypomagnesemia

GI Losses
- Diarrhea
- Vomiting
- Proton pump inhibitors

Renal Losses
- Drug-induced
  - Aminoglycosides
  - Amphotericin B
  - Cisplatin
  - Calcineurin inhibitors
  - Digoxin
  - Pentamidine
  - Antibodies targeting FGF receptors
- Genetic
  - Gitelman syndrome
  - Bartter syndrome
  - EAST syndrome
  - FHHNC
  - HNF1B mutations
  - Na-K-ATPase mutations
  - ROMK mutations
- Acquired tubular dysfunction
  - After kidney transplant
  - Hypercalcemia
  - Alcohol abuse
  - After acute tubular necrosis

Abbreviations: EAST, epilepsy, ataxia, sensorineural deafness, tubulopathy; FGF, fibroblast growth factor; FHHNC, familial hypomagnesemia with hypercalciuria and nephrocalcinosis; GI, gastrointestinal; HNF1B, hepatocyte nuclear factor 1β; ROMK, renal outer medullary potassium.

Additional Readings

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Support: None.

Financial Disclosure: Dr Wolf has equity interests in Akebia, Walden, and Unicycive, and has served as a consultant for Amgen, Bayer, Enyo, Jnana, Pharmacosmos, and Reata. Dr Murray declares that she has no relevant financial interests.

Peer Review: Received December 1, 2022 in response to an invitation from the journal. Evaluated by 2 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form April 29, 2023.