

Calcium and phosphate homeostasis

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Calcium and phosphate play a central role in maintenance of the skeletal, cell signaling and function and provision of energy, as ATP, to cells. Excessive blood calcium levels leads to nausea, vomiting, polyuria, dehydration, hypotension, mental confusion and even coma. Excess phosphate leads to precipitation with calcium in skeletal tissues, including the cardiac conduction system and arteries, leading to failure of normal electrical conduction and vascular disease, respectively. Lack of phosphate leads to ATP deficiency, due to an inability to form ATP from ADP, and complications such as muscular weakness, respiratory failure and skeletal muscle death.

Normal calcium homeostasis reflects a balance between oral calcium intake, intestinal excretion and urinary excretion. Figure 1 summarizes the major features of whole-organ calcium homeostasis.

Dietary calcium intake averages 1000 mg/d and ~800 mg/d is excreted in the stool. GI tract calcium absorption is regulated primarily by $1,25-(\text{OH})_2\text{-vitamin D}_3$, also known as calcitriol. Calcitriol is formed through enzymatic hydroxylation of $25-(\text{OH})\text{-vitamin D}_3$ by renal tubular cells; this process is stimulated by parathyroid hormone (PTH).

Plasma calcium is ~35-40% protein bound, ~10% complexed with bicarbonate and other anions, and only ~50% is "free" in solution, and thus filterable at the glomerulus.

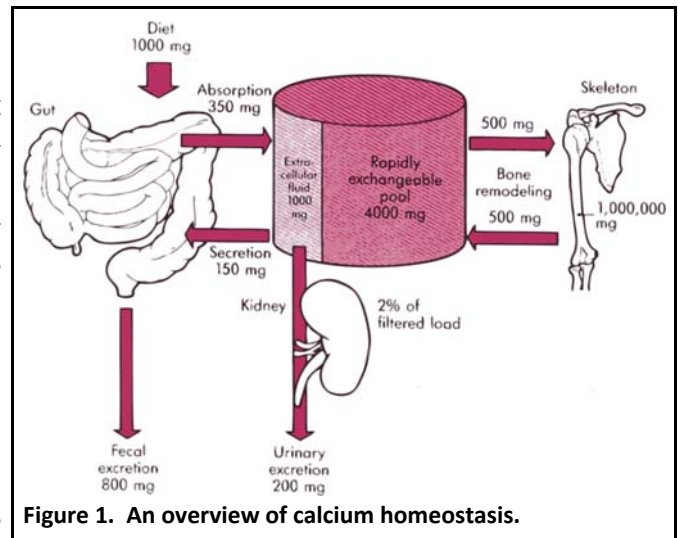


Figure 1. An overview of calcium homeostasis.

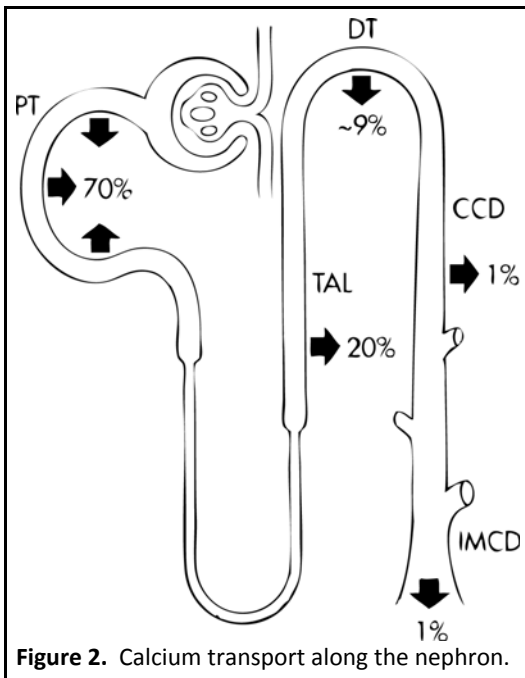


Figure 2. Calcium transport along the nephron.

The primary long-term regulation of calcium balance is through renal calcium excretion. Figure 2 summarizes the relative transport of calcium along the nephron.

The proximal tubule reabsorbs the majority of filtered calcium, ~70%. The majority occurs through paracellular routes, driven by the lumen positive voltage that develops as a result of paracellular chloride reabsorption. A small amount of calcium absorption occurs via transcellular routes.

Once again, the loop of Henle is a major site for ion transport, this time for calcium. As shown in Figure 2, ~20% of filtered calcium is reabsorbed by the thick ascending limb of the

loop of Henle. The majority of loop of Henle calcium reabsorption occurs via paracellular pathways (Figure 3). Na^+ - K^+ - 2Cl^- cotransporter-mediated Na^+ , K^+ and Cl^- reabsorption with recycling of positively charged K^+ into the luminal fluid, results in a positive voltage in the luminal fluid. This positive voltage drives paracellular Ca^{+2} movement.

Because TAL Na^+ reabsorption determines luminal voltage, which “drives” Ca^{+2} reabsorption, changes in TAL Na^+ reabsorption induce parallel changes in Ca^{+2} reabsorption. Thus, anything that decreases Na^+ reabsorption, whether intravascular volume expansion or inhibitors of Na^+ - K^+ - 2Cl^- cotransport, i.e., “loop diuretics,” decreases calcium reabsorption and thereby increases urinary calcium excretion.

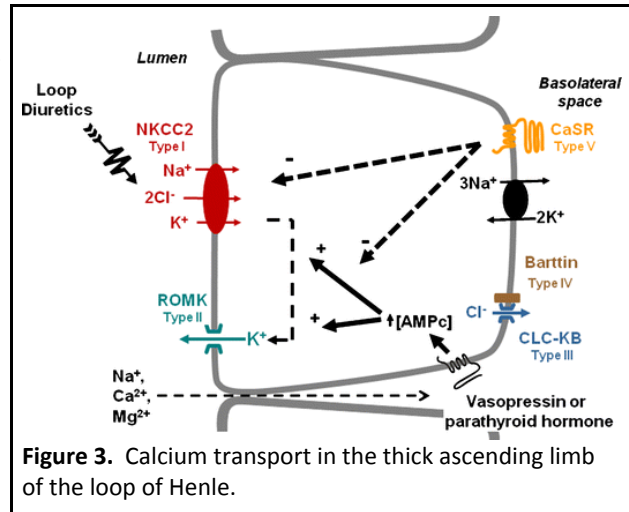


Figure 3. Calcium transport in the thick ascending limb of the loop of Henle.

The distal tubule reabsorbs ~9% of filtered calcium. In these segments and the collecting duct, see below, paracellular calcium transport is small, and essentially all calcium transport occurs via transcellular mechanisms. Most evidence suggests that calcium enters the cell from the luminal fluid via an apical calcium channel. Intracellular calcium concentration is very low, ≤ 100 nM, resulting in a steep gradient for calcium entry. There is a general consensus that basolateral calcium transport is active, mediated by a Ca^{2+} -ATPase and a Na^+ / Ca^{2+} exchanger.

Medications that inhibit distal tubule Na^+ reabsorption, “thiazide diuretics,” increase calcium reabsorption. This occurs because of indirect effects on calcium transport in sites other than the distal tubule. Inhibiting distal tubule sodium reabsorption leads to increased urinary sodium and water losses, and mild intravascular volume depletion. This stimulates proximal tubule sodium and water reabsorption, which then increases passive proximal tubule calcium reabsorption. This also increases thick ascending limb loop of Henle sodium reabsorption, which increases calcium reabsorption in this segment. The net effect is substantial increases in calcium reabsorption in sites other than the distal tubule.

Collecting ducts reabsorb ~1-3% of filtered Ca^{2+} . The exact mechanisms are unknown, but generally believed to be similar to those in the distal convoluted tubule.

MECHANISMS OF PHOSPHATE TRANSPORT

Inorganic phosphate is an important component of many organic molecules, including DNA, RNA, and ATP. It also is an important component of bone mineral matrix and is an important buffer in the urine for proton excretion. The major sites of phosphate are bone (86%) and intracellular fluid (14%), with only ~0.03% present in the extracellular fluid.

Figure 4 summarizes the major pathways for phosphate homeostasis. An average dietary phosphate intake is 1400 mg/d, with ~500 mg/d excreted in the stool. The remainder is either excreted into the urine or stored into bone and other soft tissues.

Figure 5 summarizes phosphate's reabsorption along the nephron.

As typical of other ions, the majority of inorganic phosphate reabsorption occurs in the proximal tubule.

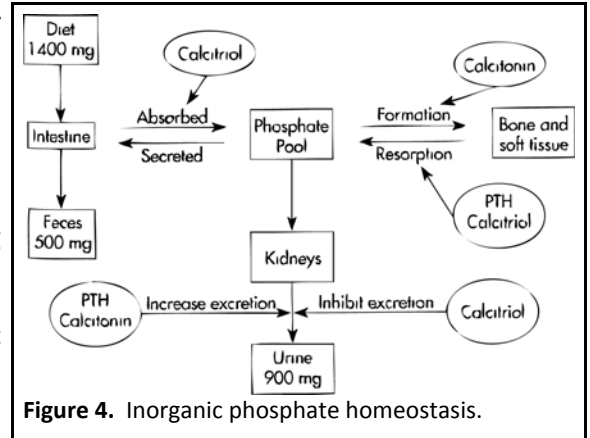


Figure 4. Inorganic phosphate homeostasis.

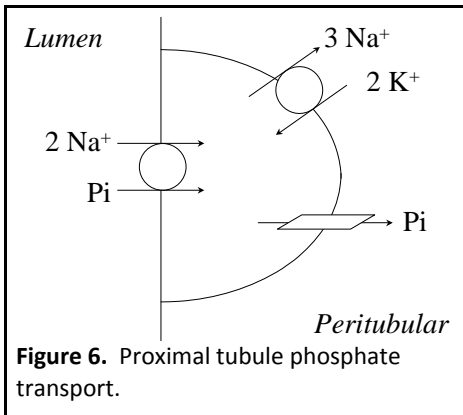


Figure 6. Proximal tubule phosphate transport.

Figure 6 summarizes proximal tubule phosphate reabsorption. Phosphate is transported into the cell in association with sodium. The low intracellular sodium concentration enables movement of sodium along with phosphate even though intracellular phosphate concentrations are greater than luminal phosphate. Phosphate then exits the cell, via a basolateral, electrogenic phosphate transporter. Intracellular electronegativity and high intracellular phosphate concentrations provides the energy for basolateral phosphate exit.

How phosphate is reabsorbed in the distal tubule (~10% filtered phosphate) is unknown.

The proximal tubule is the primary site for physiologic regulation of phosphate reabsorption. PTH decreases phosphate reabsorption, whereas phosphate depletion increases phosphate reabsorption, and is the most important hormone regulating phosphate reabsorption, Table 1 summarizes other hormones and factors that regulate phosphate transport.

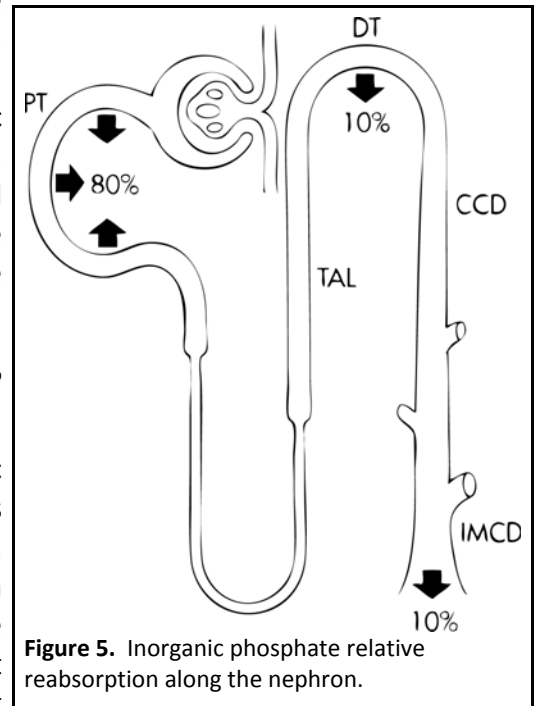


Figure 5. Inorganic phosphate relative reabsorption along the nephron.

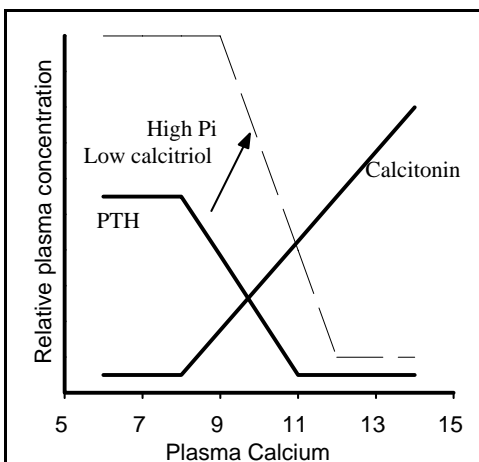


Figure 7. Relationship between plasma calcium and PTH and calcitonin release.

The primary hormones regulating calcium transport are calcitriol (1,25-(OH)₂-vitamin D₃), PTH and calcitonin. Calcitriol and

Increase excretion	Decrease excretion
↑ PTH	↓ PTH
Phosphate loading	Phosphate depletion
ECV expansion	ECV contraction
Acidosis	Alkalosis

Table 1. Regulation of renal phosphate excretion (ECV, extracellular volume).

PTH increase serum calcium while calcitonin has the opposite effect (Figures 8 and 9).

Calcitriol increases calcium levels by increasing intestinal calcium absorption, with relatively less effect on bone and kidney calcium metabolism.

Figure 7 summarizes the relationship between serum calcium and PTH and calcitonin levels. PTH is the primary hormone that responds to hypocalcemia to increase plasma calcium levels. PTH primarily increases plasma calcium levels by increasing intestinal calcium absorption. This occurs because PTH stimulates renal conversion of 25-(OH)-vitamin D₃ to 1,25-(OH)₂-vitamin D₃, which then acts through intestinal vitamin D receptors to stimulate intestinal calcium absorption. To a lesser extent PTH increases renal Ca⁺² reabsorption, leading to less urinary excretion and it increases Ca⁺² release from bones. However, the major effect of PTH on blood calcium levels is mediated through calcitriol-dependent increases in gut Ca⁺² absorption, which depends on PTH's stimulation of renal calcitriol production. Thus, in patients with severely disease kidneys PTH generally does not increase plasma calcium levels.

Both hyperphosphatemia and decreased calcitriol levels increase PTH levels (Figure 7). Teleologically, the reason that hyperphosphatemia increases PTH levels is because PTH inhibits renal phosphate absorption. This leads to increased urinary phosphate excretion and correction of the hyperphosphatemia. The effect of decreased calcitriol probably reflects a negative feedback system, where low calcitriol levels stimulate PTH secretion, which stimulates calcitriol production in the kidney, thereby correcting the abnormal calcitriol level. Other recently identified, and likely to prove very clinically important, regulators of renal phosphate metabolism are FGF23 and Klotho (Figure 10).

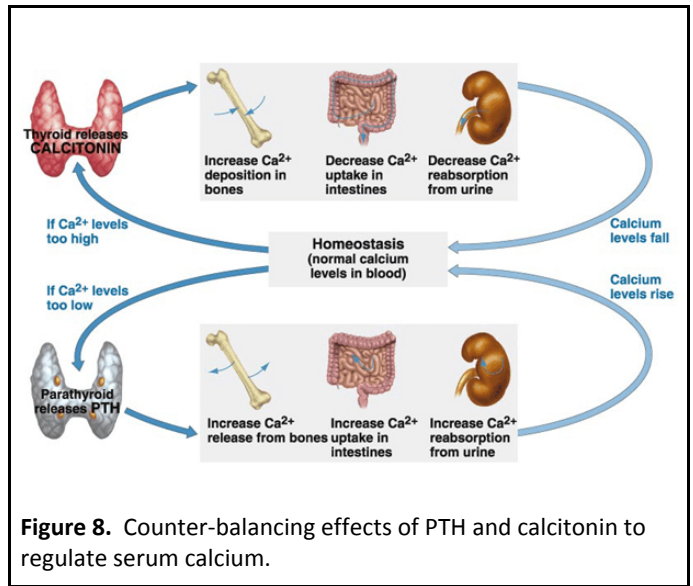


Figure 8. Counter-balancing effects of PTH and calcitonin to regulate serum calcium.

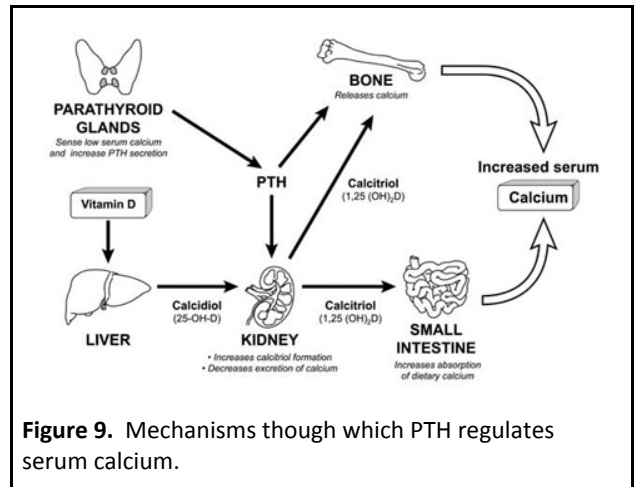


Figure 9. Mechanisms through which PTH regulates serum calcium.

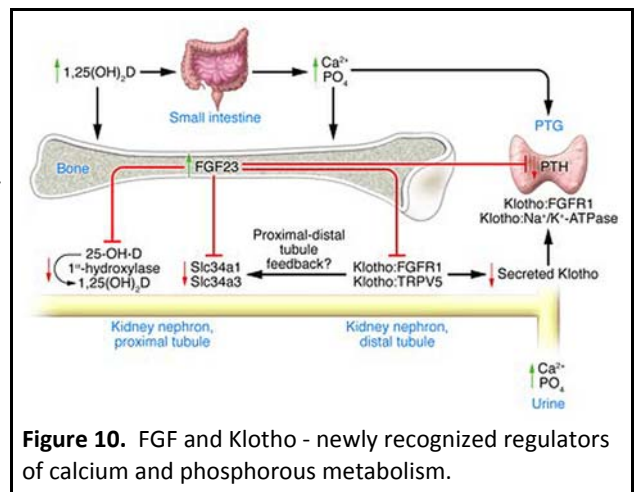


Figure 10. FGF and Klotho - newly recognized regulators of calcium and phosphorous metabolism.