Suggested Reading

Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 7th Edition, Rosen, C.J. (Ed.); Lippincott Williams & Wilkins: Philadelphia, 2008. An excellent, short but comprehensive treatment of this area by experts in the field that includes areas not covered in this lecture, particularly details on the pathophysiology of calcium homeostasis as well as the physiology and pathophysiology of phosphate and magnesium metabolism. An excellent source of information when a short presentation of any given topic within this large field is desired.


A. Major Goals and Introduction

--To review in detail the physiology of extracellular calcium homeostasis.
--To briefly review recent advances in the physiology of phosphate homeostasis.
--To review the principles underlying the pathophysiology of calcium metabolism.
--To review the major clinical disorders causing hyper- and hypocalcemia
This lecture will cover the normal physiological regulation of the blood and extracellular calcium concentrations and will also address how calcium homeostasis goes awry in disease states. Key facts or concepts are underlined. Bone and some of its metabolic diseases are discussed in other lectures, and should be reviewed.

**B. General issues of intercellular communication and feedback regulation**

Endocrine control systems contain several essential elements, including: (1) extracellular messengers (i.e., hormones) that are produced and secreted by cells and enable them to communicate with one another, (2) either cell surface or intracellular receptors that permit target tissues to respond specifically to these messages by activating intracellular signaling systems and other effectors regulating the function of that cell and (3) elements of feedback control, such that the action of a hormone on one cell results in a response (often the secretion of another hormone) that, in turn, feeds back to regulate production and/or secretion of the first hormone. For example, thyrotropin-releasing hormone (TRH), produced by the hypothalamus, stimulates the production of thyrotropin (TSH) by the pituitary, which, in turn, stimulates production of thyroid hormones by the thyroid gland. T4 and T3 (produced both by the thyroid and by peripheral conversion from T4) then feed back to inhibit the release of TRH and TSH. The resulting dynamic balance between the actions of two or more tissues upon one another’s functions constitutes a system that can maintain a state of homeostasis. In the case of the extracellular calcium (Ca$^{2+}$) homeostatic system specifically, three elements are needed to construct the system: (1) tissues (kidney, intestine and bone) translocating mineral ions into and out of the ECF, (2) hormones [i.e., PTH, 1,25(OH)$_2$D$_3$] regulating those mineral ion fluxes and (3) sensors of the level of Ca$^{2+}$, which, in turn, regulate the production/secretion of those hormones or the mineral ion-translocating tissues themselves so as to maintain a normal Ca$^{2+}$. These are discussed in detail below.

**C. Normal calcium homeostasis**

Ca$^{2+}$ has multiple intra- and extracellular functions. Extracellular Ca$^{2+}$ plays key roles in the protection of vital soft tissues as well as in locomotion and the assimilation of food through its presence in the bones and teeth, respectively. It also contributes to plasma membrane integrity, regulates membrane excitability and is a crucial cofactor for blood clotting. Intracellular calcium is a key intracellular second messenger regulating processes as diverse as cell motility, muscle contraction, cell division, glycogen metabolism, hormonal secretion and many others. For these reasons, and because extracellular Ca$^{2+}$ is ultimately the source of all intracellular Ca$^{2+}$, maintaining a nearly constant extracellular ionized calcium concentration (Ca$^{2+}_{io}$) is a high priority for free-living terrestrial organisms, including humans, who only have intermittent access to dietary calcium. We maintain levels of free ionized calcium in our blood that vary by only a few percent over the course of a day, a week or, for that matter, a lifetime. The control of Ca$^{2+}_{io}$, however, must be coordinated with Ca$^{2+}$ homeostasis in other compartments (e.g., bone and soft tissues). For example, during growth,
hundreds of grams of calcium and phosphate are removed from the extracellular fluid (ECF) during the process of skeletal growth, yet $\text{Ca}^{2+}$ remains essentially unchanged.

1. Normal Calcium Balance.

Figure 1 shows how much $\text{Ca}^{2+}$ is ingested and excreted as well as how much is present in and moves between various tissues involved in mineral ion metabolism in a hypothetical normal individual. 99% of total bodily calcium is in the bones and teeth, most of the remainder is in the soft tissues, and only 0.1% (~1 gm) is present in all of the ECF. Of the latter, about 45% of the calcium in the blood is bound to albumin and other proteins, 10% is bound to small anions (phosphate, etc.), and 45% is free calcium ions available for uptake by tissues. The normal free ionized calcium concentration is about 1.1-1.3 mM.

Figure 1: Normal calcium balance

\[ \text{INTESTINE} \]

\[ \text{KIDNEY} \]

\[ \text{BONES (and TEETH)} \]

\[ \text{ECF}^{++} (\sim 45\% \text{ bound}) \]

\[ \text{Ca}^{1000 \text{mg}} \]

\[ \text{Ca}^{100 \text{mg}} \]

\[ \text{Ca}^{300 \text{mg}} \]

\[ \text{Ca}^{500 \text{mg}} \]

\[ \text{Ca}^{1 \text{kg}} \]

\[ \text{Ca}^{10 \text{g}} \]

\[ \text{Ca}^{200 \text{mg}} \]

\[ \text{Ca}^{9.8 \text{g}} \]

\[ \text{Ca}^{200 \text{mg}} \]

\[ \text{a. Gastrointestinal Ca}^{2+} \text{ handling. Many of us ingest amounts of calcium (~500-1000 mg/day) that are suboptimal for skeletal health. The daily adequate intakes (AI) of calcium have been designated to be: (1) 500 mg/day for ages 1-3; (2) 800 mg/day for ages 4-8; (3) 1300 mg/day for ages 9-18; (4) 1000 mg/day for ages 19-50; (5) 1200 mg/day for >50 years; and (6) 1300 mg/day for pregnant women under the age of 19 and 1000 mg/day thereafter. Of the ~300 mg/day of ingested Ca$^{2+}$ that are absorbed, net absorption is ~200 mg because of intestinal loss/secetration, principally in the small intestine.} \]

\[ \text{b. Skeletal turnover of calcium. ~500 mg/day of Ca}^{2+} \text{ enter and leave the skeleton due to bone formation and resorption, respectively, but there is also a larger pool of more readily available skeletal Ca}^{2+}, \text{ probably at the bone surface. Bone formation and resorption are precisely in balance only for a relatively short period of time (between the ages of ~20-30), with positive skeletal Ca}^{2+} \text{ balance} \]
occurring during growth and negative balance in older age (beginning in the 30’s in women and a decade or so later in men). Because of the huge excess of Ca\(^{2+}\) in bone relative to ECF (~1000:1), an excess of bone resorption over formation is the commonest cause of hypercalcemia.

c. Renal Ca\(^{2+}\) handling. ~10 grams/day of Ca\(^{2+}\) are filtered by the kidneys, of which ~98% is reabsorbed—60-65% in the proximal tubule, 20-30% in the loop of Henle and distal convoluted tubule, and 5% in the collecting ducts. Appropriate increases and decreases in renal Ca\(^{2+}\) excretion are an essential part of the homeostatic defenses against Ca\(^{2+}\) excess and deficiency, respectively.

2. The Calcium Homeostatic System.

Figure 2 shows the principal elements of the Ca\(^{2+}\) homeostatic system. Not shown is calcitonin (CT), a hypocalcemic peptide secreted in response to hypercalcemia.

**Figure 2:** The calcium homeostatic system

![Diagram of the calcium homeostatic system](image)

that plays a lesser role in mineral ion homeostasis in humans than do PTH and 1,25(OH)\(_2\)D\(_3\), but which is important in some mammalian species (i.e., the rat) due to its antiresorptive and calciuric actions. The key elements of this system are: (1) Ca\(^{2+}\)-sensing cells that sense changes in Ca\(^{2+}\) and respond with appropriate changes in the secretion and/or biosynthesis of (2) calcitropic hormones [i.e., PTH, CT or 1,25(OH)\(_2\)D\(_3\)]; and (3) effector tissues that transport mineral ions into or out of the ECF in response to these hormones.
(1) Parathyroid cells, C-cells, and renal proximal and distal tubular cells show functional alterations over a very narrow range of Ca\(^{2+}\). The steep, inverse sigmoidal relationship between Ca\(^{2+}\) and PTH is shown in Figure 3A. It contributes importantly to the narrow range within which Ca\(^{2+}\) is maintained in vivo by ensuring large changes in PTH for small changes in Ca\(^{2+}\). The midpoint of the curve (the “set-point”) is close to the level at which Ca\(^{2+}\) is “set” in vivo, and the parathyroid cell can be viewed as a “calciostat”, e.g., thermostat for Ca\(^{2+}\).

**Figure 3A** Calcium regulated PTH release in vitro and in vivo in normal humans

(2) Ca\(^{2+}\)-sensing by parathyroid and C-cells and some renal cells involves a cell surface Ca\(^{2+}\)-sensing receptor (CaSR) (Figure 3B) that is a member of the superfamily of G-protein coupled receptors (GPCR). Three inherited diseases of Ca\(^{2+}\) homeostasis result from mutations in this receptor. Familial hypocalciuric hypercalcemia (FHH) and neonatal severe hyperparathyroidism (NSHPT) are caused by heterozygous and homozygous inactivating mutations, respectively. Activating mutations produce a form of autosomal dominant hypocalcemia. In all three conditions, the homeostatic mechanism is “reset” to maintain a stably elevated or reduced level of Ca\(^{2+}\) using the same elements of the system described below for normal persons. There can be mild hypermagnesemia in FHH and NSHPT and hypomagnesemia in autosomal dominant hypocalcemia, suggesting that the CaSR contributes to “setting” not only Ca\(^{2+}\) but also Mg\(^{2+}\). Recently, a form of Bartter’s syndrome has been described in individuals with activating CaSR mutations, presumably as a result of the “lasix-like” action of the CaSR on the TAL, where it inhibits the reabsorption of not only Ca\(^{2+}\) but also NaCl.
b. Calciotropic hormones.

(1) PTH: PTH is synthesized as a precursor (preproPTH) by parathyroid chief cells. The “pre” or signal sequence targets it for translocation to the lumen of the endoplasmic reticulum, where it is cleaved off, and eventual exocytosis. The “pro” piece is removed during the biogenesis of secretory granules, generating biologically active PTH(1-84). The biosynthesis and secretion of PTH as well as parathyroid cellular proliferation are stimulated by hypo- and inhibited by hypercalcemia, and intracellular degradation of PTH increases with high Ca\(^{2+}\). A variety of other factors modulate PTH secretion, but \(1,25(OH)_2D\) and probably the extracellular phosphate concentration are the only other currently known, physiologically relevant regulators of parathyroid function, inhibiting and stimulating, respectively, PTH secretion, PTH gene expression and parathyroid cellular proliferation. PTH acts on its target tissues via a specific, high affinity receptor, PTHR-1, which, like the CaSR, is a GPCR. Additional PTH receptors encoded by different genes have been identified, but their biological functions remain to be fully elucidated. PTHR-1 couples to activation of both adenylate cyclase and phospholipase C. It also mediates many of the actions of parathyroid hormone-related protein (PTHrP), a key paracrine regulator of bone growth and other developmental processes. It will be discussed in detail in other lectures. The principal target tissues for PTH are bone and kidney.

In bone, PTH acts on osteoblasts, inhibiting their function and activating osteoclasts through the RANK-RANKL system as described in Dr. Strewler’s lecture on the regulation of bone cell function, thereby leading to net release of
Ca$^{2+}$ and phosphate from bone. Sustained elevations in PTH eventually increase the number of osteoclasts by stimulating the process of osteoclastogenesis, with a secondary increase in osteoblasts through the “coupling” of resorption to formation. In contrast to the resorptive effects of sustained PTH elevations, the hormone has anabolic actions on bone when administered intermittently. In the kidney, PTH (1) enhances proximal tubular synthesis of 1,25(OH)$_2$D$_3$, which acts synergistically with PTH to promote bone resorption and also increases GI absorption of Ca$^{2+}$ and phosphate, (2) induces phosphaturia in the proximal and distal tubules and (3) increases renal tubular Ca$^{2+}$ reabsorption in the thick ascending limb (TAL) and distal convoluted tubule (DCT).

(2) Calcitonin: CT is synthesized in the parafollicular (C) cells of the thyroid by alternative splicing of a gene which also encodes calcitonin gene-related peptide (CGRP), a neurotransmitter and vasodilator not involved in Ca$^{2+}$ homeostasis. CT is secreted in response to hypercalcemia. CT inhibits bone resorption and increases urinary calcium excretion thereby reducing Ca$^{2+}_o$. Although these actions are physiologically relevant in some mammals, such as rodents, CT has only a limited, if any, role in mineral ion metabolism in normal adult humans.

(3) 1,25(OH)$_2$D$_3$: 1,25(OH)$_2$D$_3$ is formed from vitamin D$_3$ by the sequential 25-hydroxylation of the latter in the liver and 1-hydroxylation in the proximal tubule. Vitamin D$_3$ arises from (a) photoconversion of 7-dehydrocholesterol to previtamin D$_3$ in the skin, which is then activated by light in the UVB spectrum (295-300 nm), followed by spontaneous conversion to vitamin D$_3$ or (b) absorption from the diet—a process requiring bile salts and an intact small bowel mucosa. The conversion of vitamin D$_3$ to 25(OH)D$_3$ by a mitochondrial, mixed function oxidase is loosely regulated (determined largely by substrate concentration), while the 1-hydroxylation of 25(OH) D$_3$ is stimulated by PTH and inhibited by elevated extracellular concentrations of Ca$^{2+}_o$ and/or 1,25(OH)$_2$D$_3$, and by several cytokines (e.g., IL-1, TNF-α). The responses of the 1-hydroxylase to elevated concentrations of calcium and phosphate make good homeostatic sense, because they reduce the movement of both ions into the ECF from intestine and bone (see below).

1,25(OH)$_2$D$_3$ stimulates the gastrointestinal absorption of both Ca$^{2+}$ and phosphate by independent transport mechanisms and also stimulates bone resorption, both by increasing the formation of osteoclasts from their mononuclear precursors and by activating existing osteoclasts through indirect actions mediated by osteoblasts (e.g., via RANKL). Calcium is absorbed in the GI tract, in the proximal small bowel, especially the duodenum, and cecum, by influx through an apical calcium-permeable ion channel, TRPV6, diffusion across the cell via the calcium-binding protein, calbindin-D9k, and pumping across the basolateral membrane via the Ca$^{2+}$-ATPase and sodium-calcium exchanger. Phosphate is absorbed via the type II sodium-phosphate cotransporter, NaPi-2b. Because both calcium and phosphate ions are released from bone during bone resorption, the direct action of 1,25(OH)$_2$D$_3$ on bone, similar to its effects on the intestine, will increase both serum calcium and phosphate concentrations. 1,25(OH)$_2$D$_3$ exerts its actions by interacting with an intracellular receptor, the vitamin D receptor (VDR), which is a transcription factor. 1,25(OH)$_2$D$_3$
participates in bone formation both during growth of the skeleton and thereafter, although the bones form and grow normally in mice with “knockout” of the VDR as long as blood levels of calcium and phosphate are maintained close to normal. Thus a key action of 1,25(OH)\textsubscript{2}D\textsubscript{3} is to contribute to the maintenance of normal circulating concentrations of both calcium and phosphate.

(4) \text{Ca}^{2+}\subscript{o}: \text{Ca}^{2+}\subscript{o} not only regulates the secretion of other calciotropic hormones but also itself acts as a “hormone” via its own cell surface receptor to regulate target tissues. For example, elevated \text{Ca}^{2+}\subscript{o} directly inhibits PTH-stimulated \text{Ca}^{2+}\ subscripts{reabsorption} in the TAL, thereby promoting calciuria. Thus while 1,25(OH)\textsubscript{2}D\textsubscript{3} and PTH are the body’s principal \text{Ca}^{2+}\subscript{o}-elevating hormones, \text{Ca}^{2+}\subscript{o} can be viewed as its major \text{Ca}^{2+}\subscript{o}-lowering “hormone”. It does so via the CaSR both indirectly by inhibiting the secretion and/or production of PTH and 1,25(OH)\textsubscript{2}D\textsubscript{3} and by stimulating CT secretion, and directly by its calciuric action in the kidney. \text{Ca}^{2+} also enhances bone formation and reduces bone resorption, in part via the CaSR.

d. Integrated control of calcium homeostasis

(1) Defense against hypocalcemia (see Figure 2). A reduction in \text{Ca}^{2+}\ subscripts{o} stimulates PTH secretion, thereby enhancing renal \text{Ca}^{2+}\ subscripts{reabsorption} and skeletal \text{Ca}^{2+}\ release, which will generally restore normocalcemia. Persistent hypocalemia stimulates the 1-hydroxylation of 25(OH)D\textsubscript{3} within several hours via the decrease in \text{Ca}^{2+}\subscript{o} per se as well as the resultant elevation in PTH levels. 1,25(OH)\textsubscript{2}D\textsubscript{3} acts synergistically with PTH to promote the further release of skeletal \text{Ca}^{2+} and also directly enhances GI \text{Ca}^{2+}\ absorption. If hypocalcemia still is not corrected, secondary parathyroid hyperplasia ensues over weeks or longer, and there is also stimulation of osteoclast formation from their mononuclear precursors by PTH and 1,25(OH)\textsubscript{2}D\textsubscript{3}. If bone loss persists unchecked, however, it can eventually compromise the structural integrity of bone, leading to bone pain and fractures.

(2) Defense against hypercalcemia. The homeostatic responses to a \text{Ca}^{2+}\ load are the converse of those seen with hypocalcemia. Increased \text{Ca}^{2+}\subscript{o} influx into the extracellular fluid (usually from bone or intestine) that is sufficient to raise \text{Ca}^{2+}\subscript{o} inhibits PTH secretion, thereby reducing renal \text{Ca}^{2+}\ subscripts{reabsorption} and inhibiting skeletal \text{Ca}^{2+}\ release. As noted previously, elevating \text{Ca}^{2+}\subscript{o} also directly promotes calciuria. If hypercalcemia persists, 1,25(OH)\textsubscript{2}D\textsubscript{3} levels fall, thereby diminishing skeletal \text{Ca}^{2+}\ release further and reducing GI \text{Ca}^{2+}\ absorption.

(1) Changes in phosphate metabolism resulting from \text{Ca}^{2+}\ subscripts{homeostatic responses}. An elegant features of the \text{Ca}^{2+}\ subscripts{homeostatic system} is that it also contributes to maintaining a normal extracellular phosphate level. For instance, during hypocalemia serum phosphate could potentially increase because the PTH-induced rise in 1,25(OH)\textsubscript{2}D\textsubscript{3} stimulates GI absorption and skeletal release of both \text{Ca}^{2+} and phosphate. Any increase in phosphate concentration, however, is mitigated by the phosphaturic action of PTH. Conversely, during hypercalcemia there is reduced availability of phosphate from both intestine and bone owing to reduced levels of PTH and 1,25(OH)\textsubscript{2}D\textsubscript{3}, but the decrease in circulating PTH prevents hypophosphatemia by reducing renal phosphate excretion.
Recent data indicate that fibroblast growth factor 23 (FGF23) is the phosphaturic agent causing hypophosphatemia in tumor-induced hypophosphatemic osteomalacia (oncogenic osteomalacia) as well as in a form of autosomal dominant hypophosphatemic rickets (ADHR). FGF23 regulates phosphate metabolism under normal circumstances, as documented by the marked hyperphosphatemia in mice with knockout of the FGF23 gene. FGF23 is produced principally by osteocytes, and it acts through one or more FGF receptors and a co-receptor, called klotho, to inhibit sodium-dependent phosphate absorption in the kidney and reduce the synthesis of 1,25(OH)_2D_3. Calcitriol, in contrast, increases the production of FGF23. These latter two feedback loops may serve to reduce serum phosphate when it is high (e.g., by stimulating FGF23 and reducing 1,25(OH)_2D_3) and to limit 1,25(OH)_2D_3-induced increases in serum phosphate [i.e., by stimulating FGF23, which can then promote phosphaturia and reduce 1,25(OH)_2D_3 synthesis], respectively. FGF23 secretion is also stimulated by hyperphosphatemia and inhibited by hypophosphatemia, thereby enabling it to serve as a key regulator of extracellular phosphate homeostasis. Additional phosphatoninns that may participate in phosphate homeostasis include frizzle-related protein-4 (FRP-4), FGF- and matrix extracellular phosphoglycoprotein. Further studies are needed to understand the full range of tissues in which FGF23 and these other putative phosphatoninns are expressed as well as the factors controlling their secretion. Further details in this exciting and fast-moving area of research can be found in the Suggested Reading at the beginning of this syllabus. Note that although two of the three elements needed for phosphate homeostasis have been identified [i.e., (1) phosphate transporters and (2) hormones regulating them], the third element, a phosphate-sensing mechanism(s), remains mysterious.

The discovery of FGF23 and, more recently, increasing appreciation of the protean roles of α-klotho, have highlighted the complex interrelationships between the systems regulating calcium and phosphate homeostasis. Ultimately, the two can’t be studied in isolation, but must be understood in terms of the rich, somewhat convoluted manner in which they interact. This is readily apparent from the cross-talk mediated by PTH, 1,25(OH)_2D_3 and FGF23, for example, in the fluxes of both calcium and phosphate through intestine, kidney and bone.

A. Pathophysiological principles underlying hyper- and hypocalcemic disorders

What follows is a brief discussion of a conceptual framework that I have found useful in understanding and diagnosing hyper- and hypocalcemic disorders. Examples, but not comprehensive lists, of various classes of disorders are given below. The recommended reading given at the beginning of the syllabus provides several helpful sources for additional reading—particularly the “Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism”. During the course of my lecture I will also described the principal clinical manifestations of hyper- and hypocalcemia as they relate to the most common causes of these disorders of mineral ion homeostasis.

1. Hypercalcemic disorders
There are three general categories of hypercalcemic disorders, which are listed below, with a few illustrative examples of individual disorders of each class and the various pathophysiological mechanisms involved. Some lump b. and c. together into a broad class of PTH-independent forms of hypercalcemia. In addition to the general principles delineated below, further details will be provided in the lecture accompanying this syllabus.

a. Reset “calciostat” leading to PTH-dependent hypercalcemia
1. Examples: FHH, NSHPT, primary hyperparathyroidism.
2. Pathophysiology: Resetting upward of the “calciostat” in parathyroid (and--in the cases of FHH and NSHPT--the kidney) resets the homeostatic system so that it maintains a higher than normal level of Ca\(^{2+}\)—doing so using the same renal, intestinal and skeletal mechanisms utilized in the defense against hypocalcemia.
3. Key clinical sequellae: Renal (impaired renal function, stones, nephrocalcinosis), CNS (lethargy, depressed mental status), GI (nausea, anorexia, etc.).

b. Excess influx of calcium from intestine into the ECF inadequately compensated by enhanced renal calcium excretion (“absorptive hypercalcemia”)
1. Example: excess oral intake of calcium.
2. Pathophysiology: Increased calcium absorption initiates the defense against hypercalcemia, including (1) decreased PTH secretion, which then causes (2) reduced synthesis of 1,25(OH)\(_2\)D\(_3\), (3) decreased release of skeletal calcium, and (4) increased renal calcium excretion.
3. Key clinical sequellae: Same as for other forms of hypercalcemia.

c. Excess calcium influx from bone inadequately compensated by renal calcium excretion (“resorptive hypercalcemia”)
1. Example: hypercalcemia of malignancy, immobilization-induced hypercalcemia.
2. Pathophysiology: Increased, unregulated release of skeletal calcium produces (1) decreased PTH secretion, thereby leading to (2) reduced synthesis of 1,25(OH)\(_2\)D\(_3\), (3) decreased release of skeletal Ca\(^{2+}\), and (4) increased renal Ca\(^{2+}\) excretion, as in absorptive hypercalcemia. Note that excess vitamin D intake or production will cause increases in both intestinal Ca\(^{2+}\) absorption and bone resorption, through direct actions of vitamin D, thereby causing a combination of absorptive and resorptive hypercalcemia.
3. Key clinical sequellae: Same as for other forms of hypercalcemia.

1. Hypocalcemic disorders

While transient hypocalcemia can occasionally result from causes such as deposition of calcium in soft tissues or the binding of calcium to anions such as citrate, almost all cases of chronic hypocalcemia are caused by one of the three following mechanisms:

a. Reset calciostat
1. Example: Autosomal dominant hypocalcemia due to activating CaSR mutations.
2. **Pathophysiology**: Resetting downward of the “calciostat” in parathyroid and kidney resets the homeostatic system so that it maintains hypocalcemia.

3. **Key clinical sequellae**: Neuromuscular irritability (seizures, cramps, paresthesias), enamel hypoplasia, basal ganglia calcification, anxiety, depression.

**b. Defective production or action of PTH**

1. **Example**: parathyroid agenesis, post-surgical or autoimmune hypoparathyroidism, pseudohypoparathyroidism (decreased end organ response to PTH).

2. **Pathophysiology**: Diminished PTH production/action causes (1) reduced $1,25(OH)_2D_3$ synthesis, (2) decreased intestinal Ca$^{2+}$ absorption, (3) reduced renal Ca$^{2+}$ reabsorption and increased renal phosphate reabsorption, and (4) reduced release of skeletal Ca$^{2+}$, thereby leading to hypocalcemia and hyperphosphatemia.

   **Key clinical sequellae**: Same as in 1.a.

**c. Defective production or action of vitamin D**

1. **Examples**: Reduced sun exposure or vitamin D intake, malabsorption, chronic renal insufficiency (thereby decreasing 1-hydroxylation), hereditary defect in renal 1-hydroxylase, defective vitamin D receptor.

2. **Pathophysiology**: Diminished production/action of $1,25(OH)_2D_3$ (1) reduces GI calcium absorption, (2) decreases release of skeletal calcium, and (3) induces 2° hyperparathyroidism, which promotes renal calcium retention and phosphate wasting, leading to mild hypocalcemia and more marked hypophosphatemia.

3. **Key clinical sequellae**: Same as in 1.a. if hypocalcemia is marked, more commonly sequellae are 2° to reduced Ca x P product (e.g., rickets, osteomalacia), or hypophosphatemia per se (e.g., hemolytic anemia, CNS dysfunction, skeletal, cardiac muscle weakness).

**Attributions of figures:**

**Figure 2**: Reprinted from Brown EM. Mechanisms underlying the regulation of PTH secretion in vivo and in vitro. Current Opinions in Nephrology and Hypertension 1993;2:541-551.