Physiology of PTH and Vitamin D/Ca and P --1 and 2
Linda Costanzo, Ph.D.

OBJECTIVES:

After studying this lecture, the student should understand:

1. The forms of calcium in plasma.
2. The effect of acid-base disorders on ionized calcium concentration.
3. The components of overall calcium balance.
4. The regulation of PTH secretion.
5. The actions and mechanisms of action of PTH on bone, kidney, and intestine.
6. Calcium handling along the nephron and the effects of parathyroid hormone, loop diuretics, and thiazide diuretics.
7. The pathophysiology of primary hyperparathyroidism, secondary hyperparathyroidism, hypoparathyroidism, and pseudohypoparathyroidism.
8. Vitamin D metabolism and the regulation of 1α-hydroxylase.
9. The actions and mechanisms of 1,25 dihydroxycholecalciferol on intestine, bone, and kidney.
10. The pathophysiology renal osteodystrophy.

OPTIONAL READING:


1. OVERVIEW OF Ca HOMEOSTASIS

Virtually every physiological function is affected by changes in extracellular or intracellular calcium concentration. Consider its familiar role in excitation-contraction coupling, neurotransmission, excitation-secretion coupling (exocrine and endocrine) and blood clotting.

The concentration of calcium in extracellular fluid is tightly controlled by the complicated interplay of three hormonal systems: parathyroid hormone (PTH), calcitonin, and vitamin D.

A. Forms of Ca in plasma

The total Ca in plasma comes in three forms: (1) bound to plasma proteins, (2) complexed to anions, and (3) ionized.
40% of total calcium is protein-bound, mainly to plasma albumin. 10% is complexed to anions in plasma, primarily HCO₃⁻, phosphate and citrate. 50% is free, ionized Ca²⁺. **Free, ionized Ca²⁺ is the biologically active form.**

**Changes in plasma protein concentration** may alter total Ca concentration without altering the ionized [Ca²⁺]. On the other hand, **changes in the plasma concentration of a complexing anion** like phosphate or citrate may have a profound effect on ionized [Ca²⁺] with serious physiologic consequences; e.g. increasing plasma phosphate will lower ionized [Ca²⁺]. **Acid-base disturbances** may influence the fraction of total Ca which is protein-bound. In acidemia, H⁺ will displace Ca²⁺ on plasma proteins, increasing the free ionized Ca²⁺; alkalemia will decrease the free ionized Ca²⁺. Thus, measurements of total Ca may not give an accurate reflection of ionized [Ca²⁺].

An elevation of plasma ionized Ca²⁺ is hypercalcemia. Symptoms of hypercalcemia are neurologic (lethargy, coma, weakness, hyporeflexia), gastrointestinal (constipation) and renal (polyuria and polydipsia due to ADH resistance).

A decrease in plasma ionized Ca²⁺ is hypocalcemia. Symptoms of hypocalcemia are dramatic and include spontaneous muscle cramps in mild hypocalcemia to tetany and clonic seizures in severe hypocalcemia. Classically, tapping with a finger over the supramandibular portion of the parotid gland causes spasm in the muscles innervated by the facial nerve (twitches in upper lip)—**Chvostek's sign**. More specific is the **Trousseau sign** where inflation of a blood pressure cuff around the upper arm evokes carpopedal spasm.

**Intracellular ionized Ca²⁺ is very low**, about 10⁻⁷ M, maintained by a cell membrane Ca-pump and Ca-Na exchange, and uptake and release of Ca from intracellular organelles.

### B. Overall Ca homeostasis

To maintain perfect Ca²⁺ balance, the amount of Ca entering the body must equal the amount of Ca leaving the body. Consider the next diagram which shows typical daily Ca balance in an adult human being.
The daily American diet includes about 1000 mg of elemental Ca, the amount in one quart of milk or in 5 regular strength Tums. At this intake level, 35% or 350 mg is absorbed from the gastrointestinal tract. About 150 mg is secreted back into the intestinal lumen, so net Ca absorption is 200 mg. Therefore 800 mg is excreted in the feces. To maintain perfect Ca balance, net excretion of Ca in urine must equal net absorption from the gastrointestinal tract. The daily filtered Ca load is the product of ultrafilterable [Ca] x GFR. Ultrafilterable [Ca] is the non-protein bound moiety, or 6 mg/dL; GFR is 125 ml/min. Thus filtered Ca load = 6mg/dL x 125 ml/min x 1440 min/day or 10,800 mg/day. Of this, 10,600 mg/day, or 98% of the filtered load, are reabsorbed by the renal tubules, leaving 200 mg/day to be excreted in the urine.

The Ca in extracellular fluid is in equilibrium with a readily exchangeable Ca pool on the surface of bone. Daily, as much as 500 mg of Ca leaves bone and enters ECF by bone resorption and 500 mg leaves ECF and is deposited in newly formed bone; this process is bone remodeling.

The above figures describe the adult in perfect Ca balance. Naturally, the growing child is in a state of positive Ca balance, whereby more Ca is absorbed from intestine than is excreted in the urine, the difference being deposited in growing bone. Conversely, a lactating female may be in
**negative Ca balance** if intestinal Ca absorption is less than the sum of Ca lost in urine and in breast milk (350 mg Ca/Liter); in this case, net Ca is lost from maternal bone to make up the difference.

II. **PARATHYROID HORMONE**

*The plasma Ca$^{+2}$ concentration is primarily regulated by the actions of parathyroid hormone.* PTH increases the plasma Ca concentration by coordinated actions on bone and kidney and an indirect action on intestine.

A. **Synthesis and secretion of PTH**

PTH is an 84-amino acid single chain protein with molecular weight of 9000 daltons.

![Figure 2.](image)

It is synthesized as follows:

```
pre-pro-PTH   (115 amino acids)  
\downarrow
pro-PTH       (90 amino acids)  
\downarrow
PTH           (84 amino acids)  
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The peptide chain for pre-pro-PTH is synthesized on the ribosome where 25 amino acids are cleaved from the N-terminus, leaving pro-PTH. Pro-PTH is transported to the Golgi apparatus where another 6 amino acids are cleaved to form PTH. The PTH is stored in secretory granules for eventual release by exocytosis. Some of the PTH synthesized is degraded in the parathyroid glands rather than being stored in exocytic vesicles.

The most important regulator of PTH secretion is the plasma Ca\(^{+2}\) concentration. Low plasma Ca\(^{+2}\) stimulates PTH secretion; high plasma Ca\(^{+2}\) inhibits secretion. Maximal secretory rates are achieved when total plasma [Ca] falls below 7 mg/dL; as plasma [Ca] rises, PTH secretion falls. Above plasma concentrations of 11 mg/dL there is a basal rate of PTH secretion which cannot be suppressed by further increases in plasma Ca.

![Figure 3. Alterations in PTH secretion in response to changes in plasma Ca](image)

Alterations in PTH secretion in response to changes in plasma Ca occur within minutes. Parathyroid cell membranes contain Ca\(^{2+}\)-sensing receptors linked to phospholipase C via a Gq protein. When extracellular (plasma) Ca\(^{2+}\) is increased, Ca\(^{2+}\) binds to the receptor, activates phospholipase C, increases intracellular IP3/Ca\(^{2+}\), and inhibits PTH secretion. Conversely, when extracellular (plasma) Ca\(^{2+}\) is decreased, less Ca\(^{2+}\) binds to the receptor, which inhibits phospholipase C, decreases IP3/Ca\(^{2+}\) and stimulates PTH secretion.

Plasma Ca\(^{+2}\) levels also regulate PTH synthesis and degradation. Long-term hypocalcemia stimulates transcriptional events, increases PTH stores and eventually causes parathyroid hyperplasia. Prolonged hypercalcemia inhibits transcriptional events and reduces glandular PTH stores.
Changes in plasma Mg$^{2+}$ mimic the effects of Ca. Low Mg$^{2+}$ stimulates PTH secretion; high Mg$^{2+}$ inhibits. Paradoxically, severe prolonged hypomagnesemia inhibits PTH secretion.

B. PTH Actions

The actions of PTH are detectable within minutes to hours and are coordinated to increase plasma calcium concentration and decrease plasma phosphate concentration. They are:

**Bone:** ▲ bone resorption

**Kidney:** ▲ tubular phosphate reabsorption (phosphaturia)

▲ tubular Ca reabsorption (hypocalciuria)

**Intestine:** ▲ Ca absorption (indirect; via activation of vitamin D)

1. **PTH actions on bone.** PTH has both direct and indirect actions on bone. PTH receptors are located on osteoblasts, not on osteoclasts. (1) Initially and transiently, PTH acts directly on osteoblasts to cause an increase in bone formation. (This short-lived action is the basis for using intermittent PTH injections to treat osteoporosis.) (2) In a second, indirect action, PTH causes a long-lasting increase in bone resorption. In this second action, PTH binds to its receptors on the osteoblasts, cytokines are released from osteoblasts, which stimulate bone resorption in osteoclasts via a paracrine action.

   The overall effect of PTH is to promote bone resorption, delivering Ca$^{2+}$ and phosphate from mineralized bone into extracellular fluid. As bone is resorbed, hydroxyproline is released from bone matrix and excreted in the urine.

2. **PTH actions on kidney.** Two segments of the nephron have PTH-sensitive adenylate cyclase: PTH increases cAMP production in proximal tubules and distal tubules. One of the earliest detectable effects of PTH is increased (nephrogenous) urinary cyclic AMP.
Phosphate is freely filtered at the glomerulus. 75% of the filtered phosphate is reabsorbed in the proximal tubule, 15% is reabsorbed in the loop of Henle, none in the distal tubule or collecting duct. In proximal tubule, phosphate is one of several substances co-transported with Na across the luminal membrane. The Na gradient across the luminal membrane is maintained by the Na-K pump at the basolateral membrane. PTH, as shown below, via activation of adenylate cyclase at the basolateral membrane and elevation of intracellular cAMP inhibits the Na-phosphate cotransporter. Because little phosphate is reabsorbed after the proximal tubule, phosphaturia results. PTH also inhibits Na, Ca, HCO-3 and fluid absorption in proximal tubule.

**The cellular actions of PTH** are initiated by binding of hormone to the **basolateral cell membrane receptors** which are coupled to
adenylate cyclase by a guanine nucleotide-dependent regulatory protein (Gs). Activation of adenylate cyclase causes elevation of intracellular cyclic AMP, followed by activation of a protein kinase which phosphorylates a luminal membrane protein, inhibiting the Na-phosphate cotransporter. The cyclic AMP generated as a second messenger is transporter across the luminal membrane and excreted in the urine (urinary cyclic AMP).
60% of total plasma Ca is ultrafilterable, the ionized and the complexed. Of the Ca filtered, 67% is **reabsorbed in proximal tubule**. Proximal Ca reabsorption is tightly coupled to Na and fluid reabsorption and is mostly passive. Paradoxically, PTH inhibits proximal Ca reabsorption because it inhibits Na and fluid reabsorption. The **loop of Henle reabsorbs 25% of the filtered Ca**, again by a passive mechanism linked to Na reabsorption. In contrast, the **distal tubule actively reabsorbs 8% of the filtered Ca** load. Quantitatively this amount may seem insignificant. However, the distal tubule is the last nephron segment to reabsorb Ca so it determines exactly how much Ca will be excreted in the urine. **Distal tubule Ca reabsorption is increased by PTH.** (This regulatory action of PTH on terminal nephron Ca reabsorption is analogous to the regulation of Na reabsorption by aldosterone and of water reabsorption by ADH in the terminal portions of the nephron.)
**Diuretics** have important effects on nephron Ca reabsorption.

1. **Loop diuretics (furosemide)** cause calciuresis. They inhibit Ca reabsorption because Ca is reabsorbed passively along with Na in the Loop; when Na reabsorption is inhibited, by furosemide, so is Ca reabsorption. This important action of loop diuretics forms the basis for their usefulness in treating severe, life-threatening hypercalcemia.

2. **Distal diuretics (either thiazides or K-sparing)** are totally different from loop diuretics. They produce hypocalciuria, or lowering of urinary Ca excretion. They do so by increasing distal tubule Ca reabsorption while simultaneously inhibiting distal Na reabsorption. The hypocalciuric action of thiazides makes them useful in the medical management of hypercalciuric stone-formers.

3. **PTH action on intestine.** PTH increases intestinal Ca absorption indirectly by activating the 1α-hydroxylase enzyme in kidney to produce more 1,25(OH)$_2$ vitamin D$_3$. (See below for details).

4. **Summary of PTH actions.**

![Diagram of PTH actions](image-url)

Figure 7.
To summarize PTH actions, increased bone resorption provides Ca and phosphate to extracellular fluid. Alone, the bone effect would not elevate plasma Ca\(^{+2}\), because of complexation of Ca\(^{+2}\) with phosphate. Importantly, the coordinated action of PTH on kidney to inhibit phosphate reabsorption, causing phosphaturia and elimination of the phosphate resorbed from bone, a consequent fall in plasma phosphate, allows plasma Ca\(^{+2}\) to rise. Also, PTH increases renal tubular Ca\(^{+2}\) reabsorption providing more Ca to the extracellular fluid and contributing to the rise in plasma Ca\(^{+2}\) concentration.

C. PTH - Pathophysiology

1. Hyperparathyroidism is characterized by high circulating levels of PTH, hypercalcemia and hypophosphatemia. The high blood Ca\(^{+2}\) results from increased rates of bone resorption and increased renal reabsorption of Ca\(^{+2}\). The low blood phosphate results from decreased renal reabsorption of phosphate (phosphaturia). 1\(^{\circ}\) hyperparathyroidism may be caused by parathyroid adenomas. 2\(^{\circ}\) hyperparathyroidism results from vitamin D deficiency or chronic renal failure.

2. Hypoparathyroidism is associated with low circulating PTH, hypocalcemia and hyperphosphatemia. Causes are congenital or surgical.

3. Pseudohypoparathyroidism Type Ia (Albright's hereditary osteodystrophy) is a genetically transmitted disorder (autosomal dominant) associated with hypocalcemia and hyperphosphatemia but, paradoxically, high circulating levels of PTH. The kidneys and bone are resistant to PTH. The characteristic appearance is of short stature, round face, short neck and short metacarpals and metatarsals. Typically, PTH infusion does not increase plasma Ca, urinary phosphate or urinary cyclic AMP, as it would in a patient with hypoparathyroidism. The biochemical defect in the end organs has been identified in pseudohypoparathyroidism; patients are deficient in the guanine nucleotide regulatory protein (Gs) which couples the PTH receptor to adenyylate cyclase; thus cyclic AMP production and the subsequent physiologic actions of PTH on kidney and bone are blocked. Actually, patients often have multiple hormone resistance due to defective Gs coupling protein in several hormone systems.

Pseudohypoparathyroidism Types Ib, Ic and II. Sub-populations have variants of the disease as follows: Type Ib (hypocalcemia, hyperphosphatemia, no Albright's, normal G\(_s\), PTH receptor defect);
**Type Ic** (hypocalcemia, hyperphosphatemia, with Albright's, normal Gs, defect is in catalytic unit of adenyl cyclase; **Type II** (hypocalcemia, hyperphosphatemia, normal Gs, normal urinary cAMP, no phosphaturic response to PTH, defect is distal to cAMP.

**Pseudopseudohypoparathyroidism** occurs in a sub-population with Albright's osteodystrophy but normal serum Ca and P and no identifiable biochemical defects. These findings suggest that the manifestations of Albright's do not result from hypocalcemia, hyperphosphatemia or Gs deficiency, but are a separate, related genetic disorder.

### III. VITAMIN D

In children, deficiency of vitamin D causes [rickets](https://en.wikipedia.org/wiki/Rickets) where bone mineralization at the epiphyseal plates is compromised, producing characteristic growth failure and deformities. In adults, vitamin D deficiency causes [osteomalacia](https://en.wikipedia.org/wiki/Osteomalacia), with softening and bending of long bones. Our advances in understanding the metabolism and actions of vitamin D have provided one of the most dramatic examples of basic science applied to clinical treatment.

**A. Vitamin D metabolism**

There are two sources of vitamin D in humans: (1) vitamin D$_3$ in the skin from UV irradiation of 7-dehydrocholesterol and (2) vitamin D$_2$ (differing only by the addition of a double bond between C-21 and C-22) from ergosterol in the diet. If human beings are exposed to the ultraviolet rays of the sun, then dietary ultraviolet rays of the sun, then dietary vitamin D is unnecessary. I shall consider only vitamin D$_3$ or cholecalciferol.
Vitamin D$_3$ circulates to the liver where it is hydroxylated to 25 (OH)-cholecalciferol. The hydroxylation occurs in the endoplasmic reticulum, requires NADPH, O$_2$ and Mg$^{2+}$, but not cytochrome P450. **25 (OH)-cholecalciferol is the principal circulating form of vitamin D** bound to an a-globulin carrier protein.

In nephrectomized animals, neither vitamin D$_3$ nor 25 (OH)-cholecalciferol is active. This observation led DeLuca and others in the early 1970's to the significant finding that the **active metabolite of vitamin D3 is produced in the kidney.** 25 (OH)-cholecalciferol circulates to the kidney and is hydroxylated in **proximal tubule** cells.

**1,25 (OH)$_2$-cholecalciferol is the active form of vitamin D.** Hydroxylation at C-1 occurs in renal mitochondria, catalyzed by a 1 $\alpha$-hydroxylase enzyme requiring NADPH, O$_2$, Mg$^{2+}$ and cytochrome P450. **When inadequate amounts of Ca are being absorbed from the GI tract, 1,25 (OH)$_2$-cholecalciferol is the preferred route of metabolism.**

**24,25 (OH)$_2$-cholecalciferol is the inactive metabolite. This is the preferred route of metabolism when adequate amounts of Ca are being absorbed from the GI tract,** i.e. when there is vitamin D sufficiency.

Hydroxylation of 25 (OH)-cholecalciferol at C-1 or C-24 is reciprocally related. When Ca conservation is necessary, 1-hydroxylation predominates; when Ca is sufficient, then 24-hydroxylation predominates.
**B. Regulation of vitamin D metabolism**

Control of vitamin D metabolism is exerted in the kidney at the level of the 1α-hydroxylase enzyme. As already shown, when plasma Ca\(^{+2}\) is low and there is a Ca deficit, 1α-hydroxylation is stimulated; conversely, when plasma Ca\(^{+2}\) is normal or high, then 1α-hydroxylation is suppressed.

Regulation occurs by three potential mechanisms. The three mechanisms are related to one another and may represent a single mechanism:

1. ↓ Plasma [Ca\(^{+2}\)] increases 1α-hydroxylase, stimulating production of 1,25 (OH)\(_2\)-cholecalciferol. 1,25 (OH)\(_2\)-cholecalciferol will, in turn, increase intestinal Ca\(^{+2}\) absorption to help restore plasma [Ca\(^{+2}\)] back to normal. When plasma [Ca\(^{+2}\)] is normal or too high, 1α-hydroxylase is inhibited and the inactive metabolite is produced instead.

2. ↑ PTH levels increase 1α-hydroxylase. When plasma [Ca\(^{+2}\)] is low (see above) then circulating levels of PTH rise. Increased PTH levels stimulate 1α-hydroxylase and production of the active metabolite. It is probable that lowering plasma [Ca\(^{+2}\)] does not directly stimulate 1α-hydroxylase but that the effect is mediated via increases in circulating PTH.

3. ↓ plasma [phosphate] increases 1α-hydroxylase. Experimentally, in the absence of the parathyroid glands and when plasma [Ca\(^{+2}\)] is normal, lowering plasma [phosphate] stimulates 1α-hydroxylase directly. It is possible that the effect of PTH (above) is not a direct one, but is secondary to the ↓ in plasma [phosphate] which PTH produces by its phosphaturic action. In addition, because PTH inhibits phosphate reabsorption in proximal tubule cells (the same cells that make 1,25 (OH)\(_2\)-cholecalciferol) one would expect that PTH decreases [phosphate] inside the proximal cell, stimulating the 1α-hydroxylase enzyme.

4. Prolactin and growth hormone may increase 1α-hydroxylase activity to provide more Ca during growth or lactation; direct evidence in humans is lacking.

**C. Actions of 1,25 (OH)\(_2\)-cholecalciferol**

The actions of 1,25 (OH)\(_2\)-cholecalciferol are coordinated to increase plasma Ca and phosphate concentrations to promote bone mineralization. They are:
The cellular actions of 1,25 (OH)$_2$-cholecalciferol are detectable after a minimum time lag of 12 hours. (Contrast to minutes for PTH actions.) 1,25 (OH)$_2$-cholecalciferol acts on its target cells through mechanisms common to steroid hormones. 1,25 (OH)$_2$-cholecalciferol combines with a cytosolic receptor and the hormone-receptor complex enters the nucleus where it stimulates transcription of mRNA which is translated into a new protein. In intestinal mucosa and renal distal tubule this is the cytosolic 10,000 dalton vitamin D-dependent calcium binding protein (CaBP), or calbindin D-28K.

1. **1,25 (OH)$_2$-cholecalciferol action on intestine**

   ![Diagram](image)

   Figure 10.

   1,25 (OH)$_2$-cholecalciferol stimulates Ca absorption by production of vitamin D-dependent CaBP. Intestinal CaBP is absent in vitamin D-deficiency. CaBP probably acts as an intracellular Ca chelator or buffer, keeping intracellular Ca$^{2+}$ concentration low and thereby maintaining the favorable electrochemical gradient for Ca diffusion across the brush border membrane into the cell interior. CaBP may also facilitate the diffusion of Ca through the cell to the basolateral membrane where it is actively transported into blood via Ca-dependent ATPase. 1,25 (OH)$_2$-cholecalciferol also stimulates the intestinal Ca-ATPase.

   **On a low Ca diet**, the intestine adapts to increase the fraction of ingested Ca absorbed. This adaptation occurs via vitamin D, whereby low Ca diet
decreases plasma Ca → increases PTH → increases production of 1,25... → increases intestinal Ca absorption.

1,25 (OH)₂-cholecalciferol increases active phosphate absorption, but little is known about the mechanism.

2. 1,25 (OH)₂-cholecalciferol actions on kidney. The hormone stimulates reabsorption of filtered Ca and phosphate. Quantitatively, these actions are much less important than the parallel actions on intestine. In kidney, as in intestine, vitamin D-dependent CaBP is only present in vitamin D-sufficiency. The CaBP has been localized to the distal tubule, suggesting is the site where 1,25 (OH)₂-cholecalciferol stimulates Ca reabsorption.

3. 1,25 (OH)₂-cholecalciferol actions on bone. 1,25 (OH)₂-cholecalciferol stimulates bone resorption, an effect requiring new protein synthesis. This effect of 1,25 (OH)₂-cholecalciferol is synergistic (cooperative) with the bone-resorbing action of PTH.

To summarize the actions of vitamin D, increased intestinal absorption and increased renal reabsorption of Ca and phosphate and increased bone resorption all work to provide more Ca and phosphate to extracellular fluid. Adequate Ca and phosphate in extracellular fluid is necessary for normal bone mineralization to proceed. Conversely, normal bone mineralization cannot proceed when there is a deficit of Ca and phosphate due to 1,25 (OH)₂-cholecalciferol deficiency (rickets or osteomalacia).

IV. CALCITONIN
A. Synthesis and secretion.

Calcitonin is a 32 amino acid peptide synthesized and secreted by C (parafollicular) cells of the thyroid. Its synthesis proceeds through a pre-pro to a pro hormone to calcitonin.

The stimuli for secretion of calcitonin are:
1. Elevation of plasma [Ca⁺²]. Increases in plasma Ca cause circulating calcitonin levels to rise 2 to 10 fold. Likewise, decreases in plasma calcium cause a fall. Ca modulates calcitonin secretion via a cAMP-dependent mechanism in the C cell.

2. Ingestion of food, via gastrin, causes elevation of circulating calcitonin levels.

B. Calcitonin actions

Calcitonin's major action is to inhibit bone resorption bringing plasma [Ca⁺²] down towards normal. The physiologic or
pathophysiologic relevance of calcitonin's effect on bone or role in Ca homeostasis is debatable because: (1) the inhibition of bone resorption is only transitory, (2) plasma [Ca] is normal after total thyroidectomy and (3) high circulating levels of calcitonin, such as occurs in medullary carcinoma of the thyroid do not lower plasma Ca or affect bone density.

V. CASE STUDY OF RENAL OSTEODYSTROPHY

A 30-y.o. female with advanced renal failure was receiving peritoneal dialysis while awaiting transplantation. She was admitted to the hospital for evaluation because in the preceding month she had experienced severe bone pain and pruritus (itching). Upon admission, blood values were as follows (compared to normal):

<table>
<thead>
<tr>
<th>Substance</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate</td>
<td>↑ (hyperphosphatemia)</td>
</tr>
<tr>
<td>Ca(^{2+})</td>
<td>↓ (hypocalcemia)</td>
</tr>
<tr>
<td>PTH</td>
<td>↑</td>
</tr>
<tr>
<td>1,25(OH)(_2)-cholecalciferol</td>
<td>↓</td>
</tr>
</tbody>
</table>

Radiologic examination revealed increased bone resorption, osteomalacia and soft-tissue calcification.

**COMMENTS.** Her chronic renal disease with decreased renal mass caused hyperphosphatemia due to decreased GFR, decreased phosphate filtered and phosphate retention. The decreased renal mass also cause decreased production of 1,25 (OH)\(_2\)-cholecalciferol. (The hyperphosphatemia would also contribute by inhibiting production of 1,25 in whatever renal tissue is left.) Thus, circulating levels of active vitamin D are decreased which decreases intestinal Ca absorption, causing hypocalcemia. (The hyperphosphatemia also decreases Ca\(^{2+}\) by complexing ionized Ca\(^{2+}\)). Hypocalcemia causes secondary hyperparathyroidism; other factors contributing to the secondary hyperparathyroidism are skeletal resistance to PTH and decreased renal degradation of PTH (kidney is major site of PTH catabolism).

Thus, the chronic renal disease caused phosphate retention and decreased 1,25 production. Hyperphosphatemia and decreased 1,25 caused hypocalcemia. Hypocalcemia, decreased renal degradation of PTH and skeletal resistance to PTH caused secondary hyperparathyroidism.

The bone pain was caused by increased bone resorption due to excess PTH and by osteomalacia due to decreased 1,25. Calcification and pruritus was due to deposition of Ca-P salts in skin and soft tissues.

Appropriate treatment should include restriction of dietary phosphate and intestinal phosphate binders (Al gels) to offset hyperphosphatemia; Ca supplementation to correct negative Ca balance; treatment with 1,25 (OH)\(_2\)-
cholecalciferol to bypass renal defect in its synthesis. These measures should reduce secondary hyperparathyroidism; if not, parathyroidectomy may be necessary.

VI. **SAMPLE QUESTIONS AND ANSWERS FOR PTH-VITAMIN D**

1. Circulating PTH levels will be elevated:
   A. in primary hyperparathyroidism.
   B. if serum Ca\(^{2+}\) is lowered by a Ca-chelating agent.
   C. in chronic renal failure.
   D. in vitamin D intoxication.

   Ans. = A

   A. Right. The primary problem is over-secretion of PTH.
   B. Right. The major stimulus for PTH secretion is decreased serum Ca\(^{2+}\).
   C. Right. Chronic renal failure causes hyperphosphatemia, causing hypocalcemia, causing increased PTH. Renal failure also decreases production of 1,25 which causes hypocalcemia and increased PTH.
   D. Wrong. Increased vitamin D leads to increased gut Ca absorption; the increased plasma Ca shuts off PTH secretion.

2. On a low Ca diet, which of the following will be increased?
   A. calcitonin levels
   B. fraction of the ingested Ca absorbed
   C. 24,25 (OH)\(_2\)-cholecalciferol levels
   D. 1,25 (OH)\(_2\)-cholecalciferol levels

   Ans. = C

   A. Wrong. If anything, serum Ca would be lowered, shutting off calcitonin.
   B. Right. See #3 and 4. ↑ 1,25 levels will ↑ the fraction of Ca absorbed from gut.
C. Wrong. Serum Ca will be lowered, so turns off synthesis of 24,25; turn on synthesis of 1,25.
D. Right. See #3.

3. A patient presents with the following:

↑ bone resorption
↑ serum Ca\textsuperscript{2+}
↓ serum phosphate
↑ urinary cyclic AMP

Which of the following is the likely diagnosis?
A. Primary hyperparathyroidism.
B. Congenital hypoparathyroidism
C. Vitamin D intoxication
D. Pseudohypoparathyroidism
E. Chronic renal failure

Ans. = A

A. Right. ↑ PTH levels will ↑ bone resorption, increasing serum Ca. Serum phosphate decreases because PTH inhibits renal phosphate reabsorption. Urinary cyclic AMP increases because PTH stimulates the renal adenyl cyclase.
B. Wrong. Hypoparathyroidism would have the inverse of A, due to lack of PTH.
C. Wrong. Vitamin D intoxication would cause increased gut Ca absorption and increased bone resorption, increasing both serum Ca and P. PTH secretion would be turned off, so urinary cyclic AMP would decrease.
D. Wrong. Bone and kidney would be resistant to PTH. So hypocalcemia and hyperphosphatemia. Urinary cyclic AMP low because PTH doesn't activate renal adenyl cyclase (no Gs protein).
E. Wrong. Does cause hyperphosphatemia, but hypocalcemia results from high phosphate and ↓ 1,25 production. Would see ↑ bone resorption. Not sure about urinary cyclic AMP; high PTH should increase it, but renal tissue is diseased, so might not. Distinction here is the hypocalcemia.