

PATHOPHYSIOLOGY COURSE - ENDOCRINE MODULE
Pathophysiology of Mineral Metabolism (Ca, P, Mg) and
Skeletal Homeostasis

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Sources:

Basic and Clinical Endocrinology, Greenspan and Forsham, editors, 2nd Edition, 1986.

Basic Medical Endocrinology, HM Goodman, Raven Press, New York, 1988.

Hunter Heath, III, M.D., *The Mineral Endocrine System: Calcium Phosphorus and Skeletal Material*, prepared for the freshman endocrine course, Mayo Foundation for Medical Education and Research. The authors wish to thank Dr. Heath for allowing us to utilize part of his material in the preparation of this chapter.

Objectives:

1. Briefly outline physiologic principles and concepts of metabolism of calcium, phosphorus, magnesium and their regulations by parathyroid hormone, calcitonin and vitamin D. Discuss basic regulations of bone metabolism.
2. Describe the mechanisms capable of causing hypercalcemia and hypocalcemia and some of the disease processes associated with these biochemical variations.
3. Describe the mechanisms causing hyperphosphatemia and hypophosphatemia and their effects.
4. Describe the mechanisms causing hypermagnesemia and hypomagnesemia and their effects.

REVIEW OF PHYSIOLOGY OF MINERAL METABOLISM

Calcium, phosphorus, magnesium and bone metabolism. Actions of the more important "regulators": parathyroid hormone, calcitonin and vitamin D.

I. Calcium (Ca)

A. Distribution

1. The total body calcium in an adult approximates 1000 gm – 1700 gm (depending on information sourced). About 99% of this is in bone, primarily as hydroxyapatite crystals $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$. About 4-6 gm of the total body Ca is exchangeable or in rapid dynamic equilibrium with Ca elsewhere in the body. This labile or exchangeable pool of Ca is 20x greater than the total amount of Ca in the plasma. The remainder of body Ca exchanges at a very slow rate.
2. Extracellular fluid (ECF) contains about 1 gm of Ca. The concentration is 10^{-3}M .
3. Intracellular Calcium (Ca) concentration is 10,000x lower than ECF (10^{-7}M). There is an active calcium pumping mechanism to prevent the flooding of extracellular calcium into the cells. The maintenance of both extracellular and intracellular calcium ions at appropriate levels is of immediate, critical importance to life, and there are redundant, interacting mechanisms for control of these concentrations.

B. Transport of Calcium in Plasma

Plasma has about 2/3 organic phosphorus, and Pi comprises 1/3. This Pi is mostly in the form of ions of orthophosphoric acid Ca, Mg, Na complexes. About 50% is ionized and the remainder is complexed.

Plasma Pi varies more than Ca. Normal levels vary with age (highest in infants, lower in children and lowest in adults). Meal ingestion may lower plasma Pi, because insulin promotes cellular phosphate uptake. Normal fasting serum Pi in adults is 2.5-4.5 mg/dl.

C. Functions

1. The concentration of Ca ion in extracellular fluids critically affects numerous biological processes, including (among many):

- a. Nerve and muscle cell activity: Ca deficit causes hyper-excitability of these cells. It has been proposed that low extracellular Ca increases the shift of sodium (Na) to the intracellular space, which in turn mobilizes Ca from intracellular stores such as the sarcoplasmic reticulum. This high Ca concentration in the cytosol results in increased contractility.
 - b. Endocrine function: Ca is essential for normal secretion of many hormones.
 - c. Blood coagulation: Ca is an essential factor.
2. Cell: The concentration of Ca ion in the cytosol regulates many processes, including:
 - a. Actin-myosin interaction.
 - b. Enzyme activity.
 - c. Differentiation, growth, and division of cells. Very high calcium in the cytosol may cause cell damage and death by activation of Ca-sensitive neutral proteases.
 3. Bone: Ca is the fifth most abundant element in the body, and is in crystalline form, with phosphorus, and a proteinaceous matrix form, the major structural support of the body (bone and skeleton).

D. Overall Aspects of Ca Metabolism

The dietary intake of Ca varies markedly among individuals but usually ranges from 500-1500 mg/dl in the United States, mostly from milk and dairy products. The recommended dietary allowance for calcium in adults is 1000-1500 mg/d. An 8-ounce cup of pasteurized whole cow's milk contains about 290 mg calcium.

1. Intestinal Ca absorption: Although the highest rate of absorption occurs in the duodenum, the ingested calcium spends more time in the longer ileum and the jejunum and probably the greatest part of calcium absorption takes place there. Colonic Ca exchange is minor. Calcium is absorbed by an active process which requires metabolic energy and a metabolite of vitamin D, 1,25 dihydroxycholecalciferol [1,25 (OH)₂D₃]. There is also a passive absorption that occurs at very high levels of calcium intake and requires no metabolic energy. The net calcium absorption of these two processes is dependent on intake, but generally is less than 20% of the ingested calcium. In other words, only approximately 150 mg will be absorbed in an individual with a dietary Ca intake of 1000 mg a day.

2. Calcium excretion: Most of the Ca is excreted via the urine and feces. Unless there is excessive perspiration, the dermal losses do not exceed 50 mg/d. The normal daily (24 hour) urinary excretion in adults is less than 250 mg for women and less than 300 mg for men on normal calcium diets.

The renal handling of Ca can be summarized as follows: ultrafiltrable Ca is freely filtered through the glomerulus. 40% is reabsorbed at the level of the proximal tubule; another 50% is reabsorbed at the loop of Henle and about 9% is reabsorbed at the distal tubule. This results in a urinary excretion of approximately 1% of the filtered load. Of great importance is the amount reabsorbed at the distal tubule because it is regulated by parathyroid hormone (PTH) which increases the reabsorption of calcium at that level. Diuretics also affect calcium excretion: furosemide enhances calcium excretion by blocking reabsorption at the thick ascending limb of the loop of Henle and thiazides suppress calcium excretion by enhancing reabsorption at the distal tubule.

The urinary excretion of calcium is increased by:

Increased plasma Ca
Deprivation of phosphate
Excessive vitamin D
Increased urinary excretion of sodium
Immobilization
Corticosteroid administration
Increased dietary Ca
Metabolic acidosis
Hyperthyroidism
“idiopathic”

Urinary excretion of Ca is decreased by:

Decreased ultrafiltrable plasma Ca
Decreased glomerular filtration rate
Parathyroid hormone
Decreased dietary Ca
Increased dietary phosphate (increased Ca utilization in growth, pregnancy and lactation)

3. Role of the Skeleton in Ca metabolism: Bone is the major reservoir of calcium in the body. After drinking a glass of milk, a fraction of the absorbed calcium is incorporated into bone in order to be released later to the circulation during fasting. Thus, plasma Ca remains constant (less than 5% variation).

II. Phosphorus (P)

A. Distribution

1. Total body phosphorus is approximately 500-800g, 85-90% of which is in the skeleton, leaving approximately 100g in soft tissues. There are multiple pools of P having different turnover rates; bones and teeth have the lowest rates. A major portion of P is incorporated into organic phosphorus compounds (phospholipids of cell membranes, nucleic acids etc.). Here we consider mainly inorganic phosphorus (Pi).

Phosphorus is not as finely regulated as plasma calcium but is under some hormonal control via PTH and renal production of $1,25(\text{OH})_2\text{D}_3$.

B. Transport of Pi in Plasma

1. Total plasma phosphorus is surprisingly high, about 12 mg/dl, about 2/3 organic phosphorus, and Pi comprises 1/3. This Pi is mostly in the form of ions of orthophosphoric acid, Ca, Mg, Na complexes. About 50% is ionized and the remainder is complexed.

Plasma Pi varies more than Ca. Normal levels vary with age (highest in infants, lower in children and lowest in adults). Meal ingestion may lower plasma Pi, because insulin promotes cellular phosphate uptake. Normal fasting serum Pi in adults is 2.5-4.5 mg/dl.

C. Functions

1. Phosphorus (P) is an element of crucial importance to virtually all systems.

Example:

- a). Energy Metabolism: High-energy phosphate bonds are essential to life, in the form of ATP and others, which store free energy available from oxidative reactions.
- b). Hormone action: Adenosine 3',5'-cyclic monophosphate (cyclic AMP or cAMP) is a high-energy phosphate compound which acts as an intracellular "second messenger" mediating the action of many hormones on target cells.
- c). Red cells 2,3 - diphosphoglycerate deficiency leads to increased O_2 affinity for hemoglobin, and thus to decreased tissue delivery of O_2 .

D. **Phosphorus Metabolism**

The normal phosphorus intake varies widely. High-P foods include milk and dairy products, meat and cereal grains. An 8 oz. (240 g) cup of pasteurized whole milk contains approximately 227 mg P. American adults ingest 800-1500 mg P/day. Contrary to calcium, which is absorbed in a lower proportion, about 70-80% of dietary phosphorus is absorbed by the intestine and a similar amount is daily excreted in urine (600- 1000 mg/d).

The renal phosphate handling is complex. About 85-90% of the Pi filtered by the glomerulus is reabsorbed by the tubules. The proximal tubule is responsible for most P reabsorption. This active transport process is powerfully inhibited by PTH. Therefore, increased PTH inhibits phosphate reabsorption and increases the net urinary P excretion. If persistent, this can lead to decreased serum Pi.

Urinary Pi excretion is increased by:

- PTH
- Increased plasma Pi
- Calcitonin
- Renal Tubular disease
- Volume expansion

Urinary Pi excretion is decreased by:

- Chronic renal failure
- PTH deficiency (hypoparathyroidism)
- Low plasma Pi
- Growth Hormone
- 1,25 (OH)₂D₃

III. **Magnesium (Mg)**

Total body Mg approximates 25g; it is the fourth most abundant cation extracellularly, and the second most abundant cation intracellularly. Bone contains about 60% of total body Mg. The normal serum Mg is 1.7-2.1 mg/dl. Serum Mg is quite constant but the mechanism of its regulation is not well known. The kidney is the major organ controlling Mg excretion. Renal excretion is quite sensitive to Mg depletion and ranges from 2- 10% of the filtered load. Magnesium deficiency can cause neuromuscular hyperexcitability. Chronic Mg depletion is accompanied by hypocalcemia due to partial inhibition of PTH secretion and a blunted skeletal response to PTH.

REGULATORS OF MINERAL METABOLISM

I. Parathyroid Hormone

Parathyroid hormone is a polypeptide comprising a linear sequence of eighty-four amino acids, M.W. 9,500. All known biologic effects of PTH are present in the N-terminal which is the first thirty-four amino acids (PTH [1-34]). The COOH-terminal region of the molecule has a prolonged half life and is easily detected by antibodies in radioimmunoassays. It has no biological activity. This "C-terminal" is degraded by the kidney. Thus, in the presence of mild or severe renal insufficiency, significant amounts of C-terminal fragments are present in the circulation obscuring the "real" biologically active PTH concentration. Assays for "intact" PTH that do not detect PTH fragments have become available and have enhanced clinical value over former assays that also detected fragments of PTH.

A. Secretion of PTH: The primary control of PTH secretion is the plasma-ionized calcium (Ca_2^+). Low plasma Ca stimulates and high Ca inhibits PTH secretion in an inverse sigmoidal relationship. There are other potential regulators of PTH secretion which include $1,25(\text{OH})_2\text{D}_3$. Parathyroid hormone secretion by individual parathyroid cells is the product of the amount of PTH secreted by each cell and the total amount of parathyroid tissue. There is a basal secretion of PTH by each individual cell that is not inhibited by calcium. Therefore, increased amount of parathyroid tissue as in the case of hyperplasia or adenoma can result in increased PTH secretion (hyperparathyroidism).

B. Actions of PTH:

1. Bone: The effects of PTH in bone are complex; it activates osteoblasts and osteocytes. The PTH-stimulated osteoblasts send chemical messengers that stimulate osteoclasts. Sustained chronic high levels of PTH result, therefore, in increased bone turnover with high activity of all bone cells: osteoblasts, osteocytes and osteoclasts. However, the action on osteoclasts predominates and the net result is increased bone resorption. The PTH-stimulated osteocytes are responsible for mobilization of calcium through osteocytic-osteolysis. In addition, the effect of PTH in osteoblasts is acute and short lasting. In simple terms, chronic hyperparathyroidism (increased secretion of PTH) results in bone mobilization and osteopenia (thin bones).
2. Kidney: The second major target of PTH is the kidney. In the kidney PTH increases distal tubular reabsorption of Ca and therefore decreases urinary calcium excretion. It decreases or inhibits renal tubular reabsorption of phosphate in the proximal tubule. This action is mediated by an increased production of cAMP and elevation of cytosolic calcium which are intracellular messengers of PTH action. It increases renal 1α -hydroxylation of 25 hydroxyvitamin D,

increasing the production of 1,25 dihydroxycholecalciferol [1,25 (OH)₂D₃] which in turn increases intestinal calcium absorption. It decreases renal tubular bicarbonate reabsorption, resulting in bicarbonaturia, and in excess may cause mild metabolic acidosis.

The primary effect of parathyroid hormone (PTH) at the cellular level is translocation of calcium into the cytosol which results in a stimulation of cellular activity. The increased cytosolic calcium caused by excessive PTH may be deleterious in tissues, not only on primary targets of the hormone such as bone and kidney but also in non primary target tissues such as muscle and nerve.

In summary, the combined effects of PTH in bone and kidney result in:

- a. Elevation of plasma calcium due to i) bone resorption ii) increased distal tubular reabsorption iii) and increased production of 1,25 (OH)₂D₃.
- b. Low serum phosphorus due to inhibition of phosphorus reabsorption at the level of the proximal tubule of the kidney.

II. Vitamin D

Although vitamin D has been known for approximately 80 years, the discovery of the most potent and fast acting metabolite of vitamin D, 1,25 dihydroxycholecalciferol was accomplished less than 25 years ago. Vitamin D is synthesized in the skin by the action of ultra-violet light on 7 - Dehydrocholesterol. Vitamin D₃ (cholecalciferol), and is transported by a carrier protein in the plasma to the liver where it undergoes hydroxylation of the 25-carbon position of the side chain to produce 25 hydroxycholecalciferol (25 OH D₃) This is transported by carrier proteins in the plasma to the kidney where it undergoes a variety of metabolically controlled hydroxylations. The major product is 1,25 dihydroxycholecalciferol [1,25 (OH)₂D₃] which is the most potent and rapid acting metabolite now known. There is no tight control for the production of D₃ and 25 hydroxyvitamin. However, 1,25 (OH)₂D₃ is tightly controlled by the concentration of serum calcium, phosphorus and PTH. Low calcium, low phosphorus and high PTH stimulate the production of 1,25 (OH)₂D₃ and vice versa, high calcium, high phosphorus and low PTH reduce its synthesis.

A. Actions of Vitamin D

In man, most of the biologic effects of vitamin D are currently attributed to 1,25 (OH)₂D₃, the most active metabolite. The major target organs of vitamin D are the intestine, skeleton, kidney and muscle. In addition, recent developments appear to indicate that 1,25 (OH)₂D₃ is an important immunoregulatory hormone and it has been shown that this vitamin may have anti-tumor properties.

1. Intestine: Vitamin D increases calcium/phosphate transport from the gut lumen into the blood. The action of vitamin D in calcium absorption is complex and involves the stimulation of the synthesis of a calcium binding protein which is in charge of the transport of calcium from the lumen of the intestine to the serosal side.
2. Bone: Vitamin D stimulates osteoblasts (bone formation) and osteoclasts (bone resorption), as well as cell differentiation. Moreover, historically the most important action of vitamin D in bone is the promotion of mineralization of osteoid (the collagen matrix of bone). Thus, vitamin D deficiency results in a soft, rubber-like bone with a tendency for fractures and deformities such as bowing of long bones in children with rickets.
3. Kidney: Vitamin D affects calcium and phosphorus handling by the renal tubule. The effects though are complex and involve the interaction between vitamin D and PTH and the plasma levels of calcium and phosphorus.
4. Muscle: Patients with osteomalacia (adults) or rickets (children) frequently have profound muscle weakness which is rapidly and specifically reversed by vitamin D. The mechanisms of the actions of vitamin D in muscle are not known.

III. CALCITONIN

This is a 32 amino acid hormone secreted by the parafollicular C-cells of the thyroid. The secretion of calcitonin is stimulated by hypercalcemia and its release is inhibited by hypocalcemia (just the opposite of the effects of plasma calcium on PTH). In spite of these effects, clearly demonstrated in animals and humans, there is no clear cut delineation of the role of calcitonin in bone and calcium homeostasis in humans under normal circumstances. Malignant tumors of the C-cells of the thyroid occur both sporadically and as a part of the multiple endocrine neoplasia syndrome, type 2. This tumor, called medullary thyroid carcinoma, almost always secretes an excess of calcitonin so the measurement of this hormone in plasma can be used in the diagnosis, and also in the evaluation of recurrence or progression of this tumor.

The major action of calcitonin is the inhibition of osteoclasts. Thus, this agent can markedly reduce bone resorption in a matter of hours.

The "butterfly" model developed by C.D. Arnaud gives a pictorial demonstration of the rather complex regulation of calcium and phosphorus homeostasis and it allows a rapid visualization of potential pathogenic mechanisms that can be applied to many disease states (Figure 1).

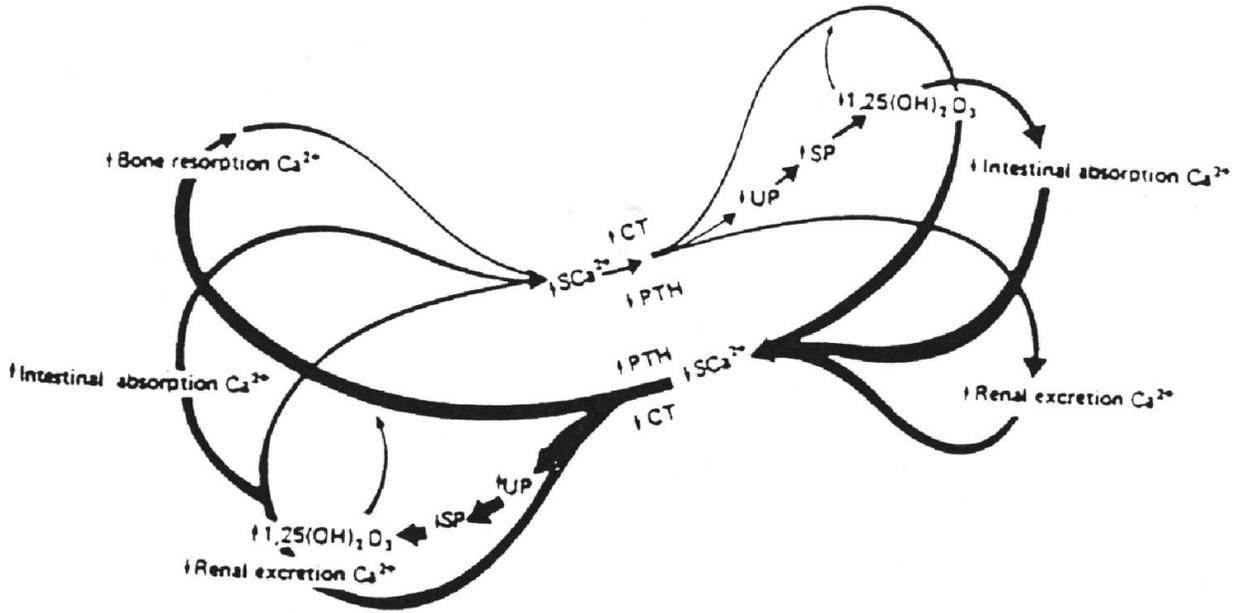


Figure 1

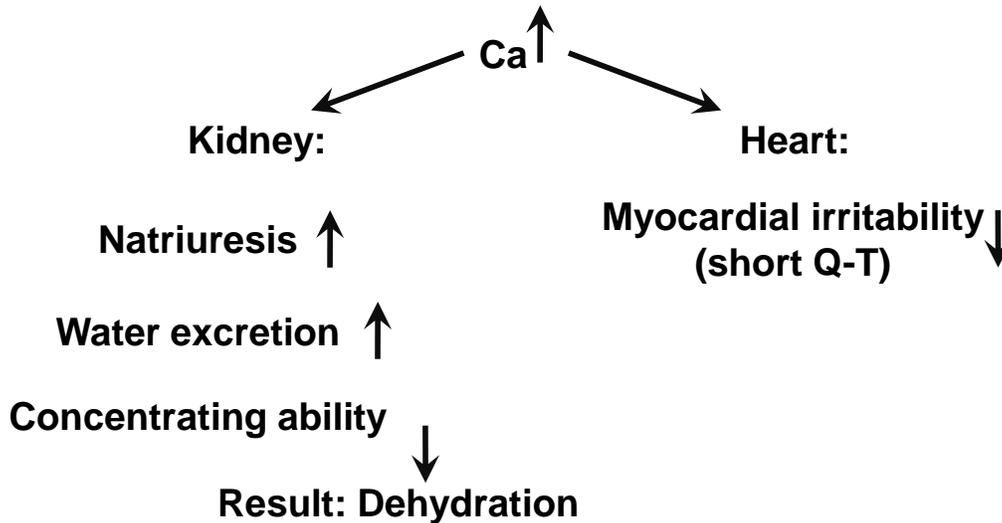
Arnaud's "Butterfly" Model of Calcium Homeostasis.

Regulation of calcium homeostasis. Three overlapping control loops interlock and relate to one another through the level of blood concentrations of ionic calcium, PTH, and CT. Each loop involves a calciotropic hormone target organ (bone, intestine, kidney). The limbs on the left depict physiologic events that increase the blood concentration of calcium (SCa^{2+}), and limbs on the right, events that decrease this concentration. UP=urine phosphorus, SP=serum phosphorus. (Reproduced with permission of the author and publishers).

MAJOR DISORDERS OF MINERAL METABOLISM

After reading the preceding pages, it will be relatively easy to understand the pathophysiology of major disorders involving mineral metabolism.

- I. Hypercalcemia (high serum total Ca^+ with normal albumin or high ionized Ca^{2+}). This is a common disorder that could affect almost every tissue of the body. Independent of the cause, hypercalcemia affects most organs. The major effects can be seen in kidneys and heart. The following diagram summarizes the effects of the elevation of plasma calcium on the kidneys, causing natriuresis and increased water excretion by reducing the concentrating ability of the distal and collecting tubules. This action is mediated by the inhibition of the action of ADH (anti-diuretic hormone) by high plasma Ca^+ , resulting in dehydration. At the same time, hypercalcemia affects the central nervous system causing lethargy and coma.



Hypercalcemia also affects the heart, reducing myocardial irritability and shortening the Q-T interval. If hypercalcemia is prolonged, such as in primary hyperparathyroidism, it is not unusual to observe the following symptoms and signs: polyuria, polydipsia, kidney stones, neurological changes and muscle weakness. As a matter of fact, weakness and fatigability are probably the most common symptoms in hyperparathyroidism.

A. Causes of Hypercalcemia

1. Primary hyperparathyroidism: This occurs when the parathyroid glands do not respond to $+\text{Ca}$ with inhibition of PTH secretion. The glands

become autonomous and therefore, the normal calcium-PTH feedback mechanism is not operating. The most frequent causes of primary hyperparathyroidism are adenoma of one of the parathyroid glands and less frequently idiopathic hyperplasia of multiple glands. When the actions of PTH, described in the preceding pages, are exaggerated, hypercalcemia occurs for the following reasons:

PTH - ↑ renal Ca reabsorption (distal tubule)

PTH - ↑ renal synthesis of $1,25(\text{OH})_2\text{D}_3$, which in turn increases
Intestinal calcium absorption

PTH - decreased renal P reabsorption (proximal tubule), resulting in
decreased serum P

PTH - ↑ bone resorption

Secondary hyperparathyroidism is not a cause of hypercalcemia: The plasma ionized Ca is low because of high P_i , as occurs in renal failure. The low CA^{2+} stimulates PTH secretion. Low serum Ca also occurs in malabsorption syndromes (chronic diarrhea, pancreatic insufficiency, etc) and in vitamin D deficiency. In these cases, quite often the serum phosphorus is also low, in part due to malabsorption but also in part due to the secondary elevation of parathyroid hormone secretion which reduces phosphate reabsorption by the kidney.

Recently nephrologists and endocrinologists are focusing on documenting secondary hyperparathyroidism in chronic kidney disease (CKD). At stage 3 and 4, CKD may start as early as a GFR of 60 ml/min. The importance of this earlier detection is to prevent renal osteodystrophy and perhaps other metabolic disturbance that may have cardiovascular implications.

Tertiary Hyperparathyroidism: This condition may occur after successful renal transplantation because of severe and chronic renal failure. The sequence of events is as follows: A patient with chronic renal failure has elevated serum phosphate which in turn reduces the ionized calcium resulting in high PTH (secondary hyperparathyroidism). With a successful renal transplantation, it is expected that all the alterations caused by the chronic renal failure would be corrected. Unfortunately, this is not always the case. The parathyroid glands may have become so large that the correction of renal insufficiency is unable to reduce the size and function of the hypertrophic parathyroid glands. They continue to secrete an excessive amount of PTH and this results in a clinical picture very similar to primary hyperparathyroidism, i.e., high calcium, low phosphorus.

B. Malignancy

Malignancy and primary hyperparathyroidism are together responsible for more than 95% of the cases of hypercalcemia. Cancer of the breast, lungs, etc., can metastasize to bone causing bone destruction with mobilization of large

amounts of Ca. More importantly, cancers can produce humoral factors, such as interleukin-1, which are potent stimulators of osteoclasts. Cancers can also produce "PTH-related peptide" which mimics most of the actions of PTH but is not readily detected by standard radioimmunoassays because of a slightly different amino acid composition. Although all malignant tumors are theoretically capable of producing PTH-related peptide, this is more frequently observed in squamous cell cancer of the lung. Interleukin-1, on the other hand, is often responsible for hypercalcemia in multiple myeloma.

C. Sarcoidosis

Sarcoidosis (and other granulomatous diseases such as tuberculosis) can produce hypercalcemia by increasing the synthesis of 1,25 dihydrocholecalciferol or 1,25 (OH)₂ by the granuloma.

D. Vitamin D intoxication - Intestinal calcium absorption.

E. Thyrotoxicosis - Bone resorption (excessive thyroid hormone stimulates osteoclasts).

F. Immobilization - Bone resorption.

II. Hypocalcemia (low serum total Ca + normal albumin or low Ca²⁺)

A. Causes

1. Hypoparathyroidism (surgical or idiopathic)

- ↓ Renal Ca reabsorption.
- ↓ Renal synthesis of 1,25 (OH)₂D₃.
- ↑ Renal P reabsorption, resulting in increased serum P.
- ↓ Bone resorption (osteoporosis is uncommon).

2. Pseudohypoparathyroidism

Type I

PTH is present but receptor cells are unable to make cAMP (hormone messenger).

Type II

PTH - cAMP systems work but there is no Phosphate response in the kidney.

3. Low Mg (functional hypoparathyroidism)

- ↓ PTH action on receptor tissues
- ↓ PTH secretion

4. Other causes

Intestinal malabsorption
Vitamin D deficiency (osteomalacia)
High P in renal failure
"hungry bone syndrome" (after successful treatment of hyperparathyroidism or malignancy).

B. Major Clinical Manifestation

Neuromuscular hyperexcitability (decreased threshold of excitation) Tetany and/or Convulsions.

Pathophysiology of tetany and convulsions: Low plasma Ca^{2+} causes \uparrow deformity and \uparrow permeability of axonal and other plasma membranes for other ions, i.e. Na^+ . Na^+ \uparrow in the cells = \uparrow release of Ca^{2+} from intracellular stores (sarcoplasmic reticulum in muscle) = \downarrow ed threshold for excitation = tetany or convulsion.

C. Other Manifestations

Basal ganglia calcification
Papilledema and increased intracranial pressure
Psychiatric disorders
Skin, hair, and fingernail abnormalities
Candida infections
Inhibition of normal dental development
Lenticular cataracts
Intestinal malabsorption
Prolongation of the QT and ST intervals in the electrocardiogram

III. Hyperphosphatemia

Hyperphosphatemia most frequently occurs in renal insufficiency because of the decreased phosphate excretion. This in turn reduces the ionized calcium resulting in an elevation of PTH secretion. High serum phosphorus in adults occurs in acromegaly (excessive secretion of growth hormone). It must be remembered that during infancy and childhood there is a physiological elevation of serum phosphorus in comparison to the adult levels because of high growth rate. In addition to renal failure and acromegaly, high serum phosphorus is observed in hypoparathyroidism. Since PTH inhibits phosphate reabsorption, its absence results in an exaggerated reabsorption of phosphate causing hyperphosphatemia.

IV. Hypophosphatemia

Low serum phosphorus is observed in hyperparathyroidism, (see above) in conditions characterized by intestinal malabsorption and in vitamin D deficiency, but also can be related to a defect of the kidney in reabsorbing phosphate. There is an entity named "familial hypophosphatemia", characterized by a renal defect in reabsorption of

phosphate, inappropriate synthesis of $1,25 \text{ (OH)}_2$ Vitamin D by the kidney and apparently by a defect in the osteoblasts.

V. Hypermagnesemia

Hypermagnesemia occurs in renal insufficiency. The intake of high quantities of Mg, particularly Mg salts present in antacids, in patients with low glomerular function, results in a chronic accumulation of magnesium which may reach critical levels. Hypermagnesemia causes reduction in neuromuscular excitability and may result in lethargy and coma.

SELF-TEST QUESTIONS

These questions will help you to judge your fundamental knowledge on the material covered in this chapter. I hope you will learn even more than this.

What are the fractions of Ca in plasma, and their approximate concentration?

Name at least 3 physiological functions of Ca ion.

Extracellular Ca concentration is _____ M and intracellular is _____ M.

Normal adult dietary Ca intake approximates _____ to _____ mg/d; mostly from which foods?

Describe the renal handling of Ca and its hormonal control.

Describe several essential roles of phosphorus.

Normal serum inorganic phosphate concentrations in adults are _____ to _____ mg/d. In children are lower or higher?

Most dietary P comes from which foods.

Describe the renal handling of phosphate ion and its hormonal regulation. Specially, know the role of PTH.

What are the organic and inorganic structural elements of normal, mature bone?

Describe and give the functions of osteoblasts, osteoclasts and osteocytes.

Outline the processes of bone formation, and remodeling.

What factor(s) control(s) PTH secretion?

Define the major effects of PTH on bone, kidney, and gut.

What is the major effect of PTH on vitamin D metabolism?

Draw the currently accepted scheme of vitamin D synthesis and activation, from skin to target organ.

What metabolite is most potent?

Which factors control $1,25(\text{OH})_2\text{D}_3$ production?

Outline the processes of bone formation and resorption.

Compare and differentiate osteoporosis and osteomalacia.

What is 'coupling' in bone metabolism?

Does hypercalcemia cause increased free water clearance?

Mechanisms of hypercalcemia in primary hyperparathyroidism:

In malignancy:

Which disease causes low serum Ca and high Pi?

Chronic low Mg causes hypocalcemia, Why?

Mechanisms of hypocalcemia - induced tetany:

Why is P elevated in chronic renal failure?

Why is P elevated in acromegaly?

Name 3 factors that enhance bone mineralization.

Why may Dilantin cause osteomalacia?

In Paget's disease, are resorption and formation reduced or elevated?

Is "coupling" present?

Case Presentation

Mr. John Doe is a 45-year-old man, who presented because of weakness and tiredness.

History of Present Illness: Mr. Doe had noticed that during the last 5 years his endurance to play tennis had decreased considerably. Occasionally, he had aches and pains in the extremities and a certain degree of stiffness in the early morning hours. He had lost 5 lbs. in the last year for no apparent reason. He had noticed polyuria (excretion of large volumes of urine) accompanied by nocturia (he gets up 3x during the night to urinate). He is a very athletic individual and he had always been walking up stairs at work. However, during the last year he noticed that he could hardly go up two flights and had decided to use the elevator.

Past History: Appendectomy age 18. He had been in good health most of his life and had served two years in the Navy.

Review of systems: Occasional headaches. The patient denied cough, chest pain, palpitations, and severe sweating. He had noticed frequent heartburn that he controlled with tablets of Tums, no more than 6 a week. He denied a history of kidney stones, hematuria (blood in urine), burning or urgency in urination or flank pain. The urine was recently checked during an application for insurance and found to be normal (negative glucose). At the time, the blood pressure was reported to be within normal limits. He passed the medical examination and the insurance was granted.

Social History: Mr. Doe works in a financial institution. He has had a bright career with frequent promotions until approximately three years ago when he started to notice decreased concentration in his work. As a matter of fact, he says, "I have to work much harder to accomplish the same amount of work that I used to accomplish easily in the past". He is married and has two children and a good family relationship, although he had noticed that he had become more irritable and rough with the children in the last couple of years. Occasionally, he has outbursts of rage with his wife that he thinks are unjustified. This had created a certain degree of tension in his family life. He does not smoke and he drinks a glass of wine when dining out with his wife approximately once a week. He was an enthusiastic tennis player and performed exceedingly well until 4 or 5 years ago.

Family History: The mother had a thyroid operation. The father and a younger sister have had several episodes of nephrolithiasis (kidney stones).

Physical Examination: Vital signs: Weight - 176 lbs., Respiration - 24, Height - 5'11", Temperature 97°, Pulse 72, Blood pressure 140/90. 45-year-old Caucasian man in no acute distress. The skin is normal in turgor, color and temperature. Examination of the head, ears, nose and throat are unremarkable. Examination of the neck is essentially negative. The thyroid is not palpable. No palpable lymph nodes. Cardiovascular examination is unremarkable. The peripheral pulses are present and equal in the four extremities. The abdomen was soft and unremarkable.

The deep tendon reflexes are normal. There is no deficit in sensorium and there is no obvious reduction in muscle strength. Examination of the skeleton and extremities is essentially negative.

There is no bone tenderness on palpation of dorsal and lumbar spine, pelvic bones or long bones.

Laboratory:

- Red cell count 4,500,000
- Hematocrit 45%
- White blood cell count 9,000
- Normal differential
- Platelets normal
- Erythrocyte Sedimentation rate 8 (normal)

Urinalysis:

- Specific gravity 1.005
- pH 6.5
- No blood, glucose or protein
- Normal Sediment

<u>Serum Chemistries</u>	<u>Patient Values</u>	<u>Normal Range</u>
Sodium	140	135-146 mEq/L
Potassium	4.6	3.6-5.3 mEq/L
Chloride	106	95-110 mEq/L
Carbon Dioxide	28	22-32 mEq/L
Urea Nitrogen	13	6-24 mg/dl
Creatinine	1.2	0.5-1.4 mg/dl
Glucose	87	60-110 mg/dl
Uric Acid	9.4	3.3-9.0 mg/dl
Cholesterol	210	120-200 mg/dl
Calcium	11.6 H	8.6-10.6 mg/dl
Phosphorus	2.0 L	2.5-4.5 mg/dl
Total protein	7.4	6.0-8.3 g/dl
Albumin	4.2	3.5-5.2 g/dl
Lactate Dehydrog. (LD)	99	100-225 U/L
Creatine Kinase (CK)	90	0-175 U/L
SGOT (AST)	39	0-40 U/L
SGPT(ALT)	16	0-40 U/L
GGT	24	2-30 U/L
Alkaline Phosphatase	100	30-115 U/L
Total Bilirubin	0.7	0.1 - 1.0 mg/dl
Direct Bilirubin	0.1	0.0-0.4 mg/dl
Triglycerides	127	42-250 Age Dependent
Iron	72	40-150 mg/dl
BUN/Creat Ratio	11	10-24
Globulin	3.2	2.0-4.4 g/dl
ALB/GLOB Ratio	1	1.0-2.2
Indirect Bilirubin	0.6	0.1-1.0 mg/dl
Ionized Ca	6.1 H	4.3-5.3 mg/dl

Thyroid function tests: within normal limits

Serum intact PTH: 87 and 99 in 2 determinations (normal 20-65 pg/ml)

Chest x-ray: normal

Dual photon bone densitometry: Close to 2 SD below the mean.

Bone Scan: within normal limits.

Ultrasound of the neck: No thyroid or parathyroid enlargement was observed.

The diagnosis of hyperparathyroidism was made but the patient requested the opinion of an endocrinologist. However, he postponed the consultation for 8 months. By then, the weakness was more severe and he felt "very nervous". The endocrinologist confirmed the elevated Ca # (12 mg/dl) and PTH-I (110 pg/ml). With the diagnosis of primary hyperparathyroidism, a surgical neck exploration was carried out.

The four parathyroid glands were individualized. The right superior was found to be enlarged and according to the surgeon was compatible with a parathyroid adenoma. This gland was removed and was found to weigh 200 mg. (The normal combined weight of four parathyroid glands is approximately 120 mg). The histological diagnosis was parathyroid adenoma. Biopsies were obtained on the three remaining glands and were reported to be normal.

Following surgery the patient developed hypocalcemia and hypomagnesemia 48 hours later that were promptly corrected with intravenous administration of calcium and intramuscular injections of magnesium. Calcium supplementation was added to the diet and six days after surgery the serum Ca, P and Mg were normal, without requiring intravenous calcium or parental magnesium. The patient was discharged and in one week, he returned to this normal occupation. It was recommended that the patient's father and sister obtain serum Ca determinations.

During the next three months, serial serum Ca, Mg and Pi were reported to be within normal limits. He noticed a progressive increase in muscle strength. One year after surgery the patient was feeling extremely well. His endurance had increased considerably and he felt more relaxed and content. The serum Ca, P and Mg were normal.