Ca PTH
Zinc Copper
Mg Li
Chromium

CALCIUM, PHOSPHORUS, MAGNESIUM AND TRACE METALS

Unit 3-Lecture #5
Lecture Goal(s): To introduce the physiologic significance of select minerals and trace metals to develop an understanding of why laboratory testing may be required and to correlate results with disease. Laboratory analysis of minerals and trace metals will also be considered.

Lecture Objectives: Upon completion of this class material each student will be able to do the following:

1. Cog/I Tell the distribution of magnesium in the body and note the physiologically active form of magnesium.
2. Cog/II Describe the regulatory controls on magnesium levels in the body and explain the effects of aldosterone on these control mechanisms.
3. Cog/I List the normal range for total serum magnesium. List causes for increases and decreases in magnesium levels in the body.
4. Cog/II Discuss the physiologic effects of magnesium. Compare and contrast the effects of low and high serum magnesium levels on cardiac and skeletal muscle function.
5. Cog/III Evaluate the Mg^{+2}/Ca^{+2} ratio during open heart surgery.
6. Cog/I List methods of analysis for magnesium and explain the purpose for EGTA (ethylene glycol-bis(βaminoethyl ether)-N,N-tetraacetic acid) in colorimetric assays.
7. Cog/I List normal levels and panic values for calcium and phosphate in the blood stream. Describe the different forms in which these two ions may be found in the body.
8. Cog/I Tell the distribution of calcium within the body.
9. Cog/II Describe the formation of the physiologically active form of vitamin D.
10. Cog/II Describe calcium regulation with emphasis on $1,25(OH)_2D_3$, 1-hydroxylase, parathyroid hormone, and calcitonin. Note factors that may increase or decrease the level/activity of these four components of calcium regulation.
11. Cog/III Evaluate the following parameters in cases of hyperparathyroidism, Vitamin D intoxication, Paget's disease, and osteoporosis.
    a. calcium
    b. phosphate
    c. alkaline phosphatase
    d. parathyroid hormone
    e. $1,25(OH)_2D_3$
    f. urine calcium
    g. urine phosphate
12. Cog/I List the methods for measuring calcium and explain the purpose for 8-hydroxyquinoline in colorimetric assays.
13. Cog/I List the method of method for measuring phosphate levels in the blood stream.

14. Cog/II Discuss the complexities associated with the measurement of parathyroid hormone. Note the current technique that appears to standardize parathyroid hormone measurements.
15. Cog/I Explain the primary reason for lithium analyses in the clinical laboratory and note the most common method of analysis.
16. Cog/I List the therapeutic range, toxic level, and lethal level for lithium in the body.
17. Cog/I Explain the function of copper in the body and note the most common method of analysis.
18. Cog/I Explain copper absorption and the formation of ceruloplasmin. List normal ceruloplasmin levels in the blood stream.
19. Cog/II Correlate serum ceruloplasmin and copper levels with Wilson's disease. Explain the symptoms associated with Wilson's disease resulting from copper entering tissues.
20. Cog/I List the known physiologic effects of zinc in the body and note the method of zinc analysis.
22. Cog/I List the physiologic importance of chromium in the body.

Suggested Reading: Chapter 28 in Kaplan

This lecture will consider the major ions in the body other than the electrolytes. These other ions are generally classified as either minerals or trace metals. These two classifications differ based on the amount of the individual ion found in the body. Concentrations of minerals in biological tissues are found in the gram per kilogram range. Trace elements are found in the body in the milligram per kilogram range.

The major minerals considered are magnesium, calcium, and phosphorus. Physiologically, phosphorus is exists as phosphate. The concentration of these three minerals in plasma are dependent on the net effect of bone mineral deposition and resorption, intestinal absorption, and renal excretion. Parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3 are the principal hormones regulating these processes.

The major trace elements considered are lithium, copper, zinc, and chromium. Trace elements play an important role in the function of the body. Some of these functions include: participation in electron transport system, cofactors for a wide variety of enzyme systems, and are vital components of several metalloproteins. Trace element deficiencies most commonly are acquired and occur as a result of nutritional deficiencies, insufficient intestinal absorption, or increased loss or utilization.

Magnesium

Magnesium is one of the most abundant cations in the body and it is essential to many physiochemical processes. The body of an adult contains 20 to 30 grams of magnesium, about 50 to 60 percent of which is present in bones. Most of the rest is in soft tissue such as muscle. Approximately one percent of the magnesium that is present in the body is in the blood.

Magnesium serves as an activator for a large number of enzymes (more than 300). Also, magnesium is essential for the preservation of the macromolecular structure of DNA, RNA, and ribosomes.

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19. Cog/II Correlate serum ceruloplasmin and copper levels with Wilson's disease. Explain the symptoms associated with Wilson's disease resulting from copper entering tissues.

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22. Cog/I List the physiologic importance of chromium in the body.

Magnesium also influences calcium movement in the body.

Approximately one third of the average daily dietary intake of magnesium is absorbed primarily in the small intestine. This absorption process is poorly controlled and homeostasis is maintained largely by renal excretion and renal tubular reabsorption. The exact control mechanism is not fully known, but aldosterone may play a role. It is believed that aldosterone promotes the secretion of magnesium and the reabsorption of sodium.

The physiologic role of magnesium has been confusing, but is now becoming more clear. The ionized form of magnesium is the physiologically active form. It appears that ionized magnesium acts as a calcium channel blocker in the heart.

↑ mg ≠ Ca
Addisons
↓ Ald
↑ in Epsom

Increased magnesium appears to block calcium entry into cardiac smooth muscle leading to bradycardia and paralysis. These increased levels are most often found in patients with renal disease and in patients on magnesium therapy. Increased levels are also found in Addison's disease (associated with a decreased aldosterone) and with ingestion of Epson salts (which contain magnesium) for constipation.

Decreased magnesium levels would allow more calcium to enter cardiac smooth muscle, which can be associated with dysrhythmias, hypertension, stroke, and heart failure.

Decreased magnesium levels may be seen in the following:

1. Gastrointestinal disorders such as malabsorption or prolonged diarrhea
2. Acute alcoholism
3. Cushing's syndrome (increased aldosterone)
4. Post surgery (open heart)

It is interesting that both calcium and magnesium are found low following surgery. Perhaps these two deficiencies balance each other to prevent cardiac dysrhythmias.

Tetany, which is commonly associated with low calcium levels, may also be caused by a low serum concentration of magnesium. Usually this "magnesium deficiency tetany" only shows a low serum magnesium and the calcium level is normal. Also, as with calcium, tetany reflects a deficiency in ionized magnesium and not total magnesium.

When considering measurement of magnesium, one should keep in mind that it is the second most abundant cation inside the cell. Therefore, a hemolyzed sample cannot be used for analysis.

Ionized magnesium can only be measured using an ion selective electrode. Whole blood normally maintains a narrow range for ionized magnesium at 0.5 - 0.67 mmol/L.

The availability of both ionized magnesium and calcium ISE allows the monitoring of these minerals during and after open heart surgery. It is believed that acute hypotension encountered from time to time in open heart surgery is associated with drops in the magnesium^{+2}/Ca^{+2} ratio.

Several colorimetric methods are available to measure total magnesium. The main point to know about these methods is that the first step involves the removal of calcium, which would otherwise interfere with the test. (For calcium colorimetric procedures, magnesium must be removed.) EGTA, ethylene glycol-bis-(β-aminoethylether)-N,N-tetraacetic acid is used to remove calcium prior to analysis.

In terms of accuracy, speed, and convenience, the determination of total magnesium by atomic absorption spectrophotometry is the method of choice. Normal serum levels for total magnesium using atomic absorption is 1.3 - 2.1 mEq/L or 0.7 - 1.1 mmol/L. (Note that the valence of Magnesium is 2.)

Calcium and Phosphate

Calcium and phosphate are very closely related and will therefore be considered together.

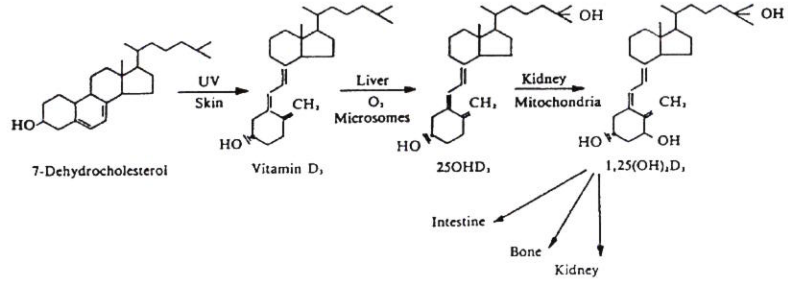
Normal serum calcium levels are 9.0 - 11.0 mg/dL.

Panic values for calcium are: ≤ 7.0 mg/dL (tetany may develop)
≥ 13.5 mg/dL (patient may enter into a coma)

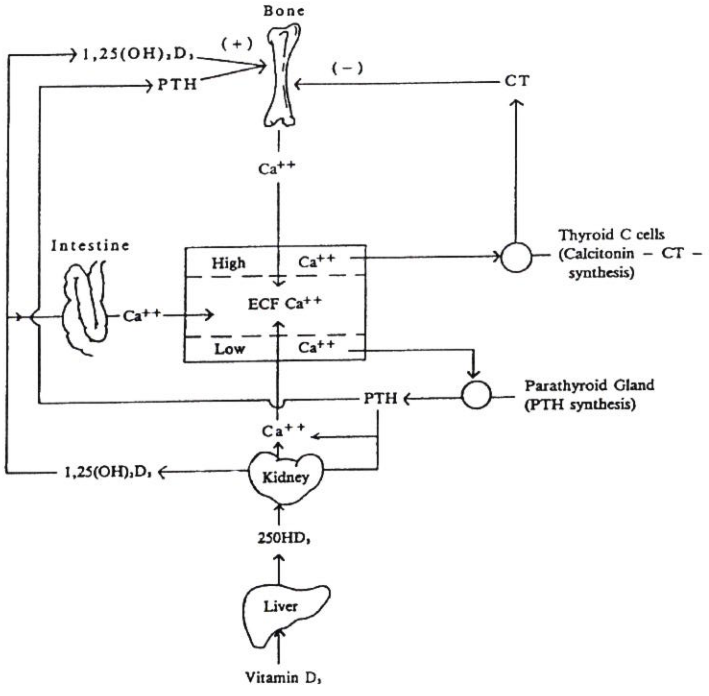
This lower level of calcium is dependant somewhat on pH and protein concentration because both of these factors affect the amount of calcium that is exists in the ionized form (i.e. the physiologically active form).

Normal phosphate levels are 3.0 - 4.5 mg/dL. Most of the phosphate in extracellular fluid is inorganic. It is primarily found as HPO_4^{-2} (dibasic) and $H_2PO_4^-$ (monobasic). At pH 7.4, the dibasic HPO_4^{-2} makes up 80 percent of the inorganic phosphate, while monobasic $H_2PO_4^-$ makes up 20 percent. Approximately 90 percent of phosphate in the blood stream is filtered at the glomerulus. Of the filtered phosphate, 85 - 95 percent of this will be reabsorbed in the PCT under the influence of hormones.

Tietz notes that "*Phosphate is often referred to as phosphorus, a practice that is inaccurate and misleading because only phosphate circulates in blood and is measured, not elemental phosphorus. This practice originated because phosphate is often calculated and reported as milligrams per deciliter of phosphorus rather than phosphate. It would be more correct to report these values as phosphate reported as milligrams per decililter of phosphorus. A far more satisfactory approach would be to adopt SI units (millimoles per liter). This would allow results to be reported as phosphate, eliminating the need to specify whether results are expressed as phosphate or phosphorus.*"



The diagram below illustrates calcium homeostatic mechanisms. Hypocalcemia induces PTH secretion that functions in kidney and bone. PTH secretion stimulates kidney synthesis of $1,25(OH)_2D_3$ and promotes renal reabsorption of calcium. $1,25(OH)_2D_3$ enhances intestinal calcium absorption and together with PTH promotes Ca^{+2} mobilization from bone. Hypercalcemia may induce calcitonin secretion which inhibits bone resorption. (Note, ECF in the diagram below refers to extracellular fluid.)



Inhibition of the kidney 1-hydroxylase enzyme occurs when serum phosphate levels are high. This is an important mechanism in the etiology of renal osteodystrophy, a secondary bone disease that often accompanies chronic renal failure, especially in patients on long term dialysis. In renal failure, phosphate is retained, inhibiting the 1-hydroxylase so less $1,25(OH)_2D_3$ is synthesized. In addition, the activity of the kidney 1-hydroxylase is reduced as a result of the loss of functional renal tissue. Low levels of $1,25(OH)_2D_3$ causes a decreased absorption of calcium from the gut, and the resulting low serum ionized calcium leads to increased secretion of PTH. In the early stages of renal failure, serum calcium is often kept near normal levels, but at the expense of bone which is resorbed by the action of PTH. It is this action of PTH that leads to the secondary pathologic changes in bone. Other inhibitors of the kidney 1-hydroxylase enzyme include glucocorticoids, certain drugs such as phenobarbital and phenytoin, and the end product of the enzymatic reaction, $1,25(OH)_2D_3$.

A second modulator of calcium homeostasis is PTH, a hormone secreted by the parathyroid gland. When ionized Ca^{+2} is low, PTH secretion from the parathyroid gland is increased, and vice versa. PTH increases plasma calcium by its action on three organs; bone, kidney, and intestine. Together with $1,25(OH)_2D_3$ it effects a transfer of calcium from bone to extracellular fluid and plasma. In the distal tubule, PTH increases reabsorption of calcium but depresses the reabsorption of phosphate. Additionally, it inhibits tubular reabsorption of HCO_3^- and diminishes the secretion of H^+. Hypersecretion of PTH can therefore result in a metabolic acidosis.

Finally, PTH can indirectly enhance the absorption of calcium from the small intestine through the regulation of vitamin D_3 metabolism. As previously mentioned, PTH stimulates the 1-hydroxylase enzyme in the kidney that is responsible for synthesis of $1,25(OH)_2D_3$, the active form of vitamin D. The $1,25(OH)_2D_3$ promotes absorption of both calcium and phosphate from the small intestine. However, since PTH increases the urinary excretion of phosphate, serum phosphate levels are maintained near normal, while serum calcium is selectively increased.

A third mechanism for regulation of serum calcium is thought to involve calcitonin, a hormone produced by the C cells of the thyroid gland. High plasma calcium concentrations stimulate calcitonin release, and low plasma calcium levels inhibit its release. Calcitonin is capable of decreasing plasma calcium by directly inhibiting resorption of bone. Calcitonin has been reported to increase the renal excretion of calcium, but its effect on the kidney and GI tract have not been well studied. Calcitonin excess (associated with medullary carcinoma of the thyroid) and calcitonin deficiency (associated with surgical removal of the thyroid) do not usually disturb calcium homeostasis. Further studies of this hormone are needed before its true physiological role in man is understood. The regulation of serum-ionized calcium by $1,25(OH)_2D_3$, PTH , and calcitonin is summarized in the diagram above.

The most common causes of hypercalcemia are primary hyperparathyroidism and malignancy. Primary hyperparathyroidism, characterized by increased secretion of PTH, is usually caused by parathyroid adenoma or hyperplasia of the gland. In neoplasia, direct infiltration of bone by malignant tissue can cause hypercalcemia. In other carcinomas, hypercalcemia is not associated with bony metastases, and it is postulated that tumor might release humoral factors that mimic the action of PTH. Hypercalcemia of malignancy is most often associated with breast cancer and multiple myeloma. Other causes of hypercalcemia are excessive ingestion of milk or sodium bicarbonate (milk-alkali syndrome) and excessive ingestion of vitamin D. Immobilization of part or all of the body results in a relative increase in bone resorption and can lead to hypercalcemia (observed in early space flights).

The most common causes of hypocalcemia include hypoparathyroidism, renal osteodystrophy, and conditions that result in deficiencies of vitamin D_3 and magnesium. Hypoparathyroidism can be caused

by surgical damage to the parathyroid glands during thyroidectomy or by autoimmune destruction. Renal osteodystrophy, described previously, is a secondary metabolic bone disease associated with chronic renal failure. (It should be noted that in end stage renal failure, an increase in serum calcium, along with other end products of metabolism, may occur because the glomerulus can no longer effectively filter the blood.) Deficiency of vitamin D_3 or its malabsorption from the gut leads to osteomalacia. As in renal osteodystrophy, this disorder is characterized by hypocalcemia associated with increased levels of PTH. Such conditions are termed secondary hyperparathyroidism. In osteomalacia, there is decreased mineralization of bone. This differs from osteoporosis, in which the bone mass itself is reduced. Osteoporosis commonly affects the elderly and is characterized by normal laboratory values for calcium, phosphate, and PTH. Hypocalcemia can also be caused by decreased magnesium levels, which impair the secretion of PTH.

Hyperphosphatemia may be seen in cell lysis syndromes such as hemolyis, leukemia, and tumor lysis (from chemotherapy). In these cases, phosphate moves from intracellular fluid to extracellular fluid. Plasma phosphate is not as tightly controlled as calcium. Renal excretions is the primary mechanism for regulating phosphate levels. Decreased renal excretion may result in elevated phosphate levels. This may be seen in cases where glomerular filtration is decreased, such as in renal failure and hypovolemia. Also, hyperphosphatemia may be seen in hypoparathyroidism (where reduced PTH permits phosphate reabsorption) and pseudohypoparathyroidism (where the kidney does not respond to PTH permitting phosphate reabsorption).

Hypophosphatemia may be seen in situations where phosphate distributes from extracellular fluid to intracellular fluid. This is typically seen in association with the excessive movement of glucose into the cell, such as in the case of diabetic ketoacidosis treated with insulin. Hypophosphatemia may also be seen in situations of decreased intestinal absorption associated with a vitamin D deficiency, starvation, and malabsorption. Also, hypophosphatemia may be seen in association with increased renal excretion of phosphate, such as in hyperparathyroidism (where increased PTH increases phosphate excretion).

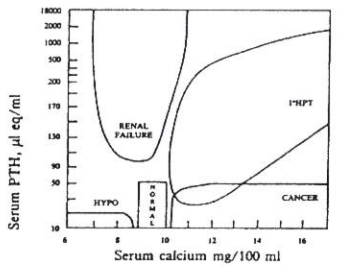
Laboratory investigation of suspected calcium disorders includes determinations of serum and urinary calcium and phosphate. In primary hyperparathyroidism, serum calcium is increased as a result of the increased PTH, while urinary calcium can be either normal or increased. Tubular reabsorption of calcium is increased by PTH, but persistently high serum levels eventually exceed the tubular maximum so that more calcium appears in the urine. Serum phosphate tends to be either normal or slightly low in primary hyperparathyroidism as the effects of PTH on urinary phosphate excretion balance the increased intestinal absorption of phosphate. Determination of ionized calcium can be helpful, especially in assessing patients with borderline hyperparathyroidism when the total calcium is normal or only slightly elevated. Serum levels of alkaline phosphatase, an enzyme produced by osteoblast bone cells, are elevated when there is accelerated turnover of bone. Serum alkaline phosphatase levels are also elevated in liver disease, but differentiation of bone and liver disease generally is not a diagnostic problem. Alkaline phosphatase levels may be normal or increased in primary hyperparathyroidism. It is markedly increased in Paget's disease, a disorder of unknown etiology characterized by excessive resorption and formation of bone.

PTH secretion is increased in hyperparathyroidism and osteomalacia but is decreased in hypoparathyroidism and in cases of excess vitamin D_3 ingestion. Plasma PTH levels are normal in malignancy unless the tumor is producing an ectopic PTH-like hormone. The measurement of PTH by radioimmunoassay is complex because of the heterogenous nature of circulating PTH. Various hormonal fragments, along with intact PTH, are secreted by the parathyroid gland, and PTH fragments are also produced by peripheral metabolism of the intact hormone. The biologic activity of PTH is localized in the amino (N)-terminal portion of the molecule. However, the half-life of intact PTH and (N)-terminal fragments is very short. For this reason, antibodies directed toward the longer-lived middle and/or carboxy (C)-terminal regions of PTH have currently proven more useful in the discrimination between normal and abnormal states of parathyroid function. This will be considered in greater detail below.

Levels of $1,25(OH)_2D_3$, are elevated only in hyperparathyroidism and are normal or low in most other disorders. However, the serum concentration of $1,25(OH)_2D_3$ is in the ng/L range, and assays of the compound are not yet routinely performed. Serum protein electrophoresis and X-rays of axial skeleton, hands, and skull can also aid in the diagnosis. The biochemical findings in disorders of calcium metabolism are summarized in the table on the following page.

As you review the table below, focus on the following four diseases.

1. Osteoporosis
2. Hyperparathyroidism
3. Vitamin D intoxication
4. Paget's disease (osteitis deformans)



	Plasma					Urine	
Disease	**Ca**	**P**	**Alk Phos**	**PTH**	**1,25(OH)$_2$D$_3$**	**Ca**	**P**
Hyperparathyroidism	⇑	⇓⇒	⇑⇒	⇑	⇑	⇑⇒	⇑
Hypoparathyroidism	⇓	⇑	⇒	⇓	⇓	⇓	⇓
Vit D intoxication	⇑	⇑⇓	⇒	⇓	⇒⇓	⇑	⇑
Osteomalacia	⇓	⇓	⇑	⇑	⇓	⇓	⇓
Paget's Disease	⇑⇒	⇒	⇑	⇒	⇒?	⇑	⇒
Renal osteodystrophy	⇓⇒	⇑	⇑	⇑	⇓	⇓	⇓
Osteoporosis	⇒	⇒	⇒	⇒	⇒	⇒⇑	⇒
Cancer with bone metastasis	⇑⇒	⇒	⇒⇑	⇒	⇒⇓	⇑	⇒
Cancer without bone metastasis	⇑⇒	⇓⇒	⇒⇑	⇒⇑	⇒⇓	⇑	⇑⇒

⇑ - increase ⇓ - decrease ⇒ - no change

Methods Used to Measure Calcium and Phosphate

For calcium analysis, serum or heparinized plasma is used. Blood in oxalate or EDTA is not suitable because these bind Ca^{+2} to prevent clotting.

Total calcium can be determined using atomic absorption spectrophotometry.

A colorimetric method is more commonly used in the clinical laboratory to measure total calcium in which calcium is complexed with a high colored chromophore. One of the most widely used chromophores is **o-cresolphthalein complexone** in an alkaline solution. The addition of a small amount of 8-hydroxyquinoline to the reagent prevents interference from magnesium. In this test the absorbance of the colored complex is measured at 580 nm and the absorbance is proportional to the total calcium concentration.

Ionized (or free) calcium is measured by ion selective electrodes. In the past, ionized calcium has been very difficult to measure. Factors such as the blood sample having to be treated anaerobically and tested immediately after collection have been important factors. These measurements are temperature and pH sensitive. Electrode technology has steadily improved over the years and now very accurate measurements of ionized calcium can be obtained. Many instruments measured ionized calcium and pH simultaneously in order to calculate ionized calcium corrected to a pH of 7.4.

The primary test used to measure serum phosphate involves an ammonium phosphomolybdate complex. In this test, protein is precipitated by trichloracetic acid. Phosphate is then converted to an ammonium

phosphomolybdate complex by the addition of ammonium molybdate. The absorbance of the solution is read at 700 nm and is proportional to the serum phosphate concentration.

Parathyroid Hormone

It has previously been noted that "*Various hormonal fragments, along with intact PTH, are secreted by the parathyroid gland, and PTH fragments are also produced by peripheral metabolism of the intact hormone.*"

The parathyroid hormone is a string of amino acids which resembles insulin in many ways. It begins with the synthesis of pre-proparathyroid hormone (115 amino acids) in the chief cells of the parathyroid gland. This is rapidly converted to proparathyroid hormone (90 amino acids) by proteolysis. This is followed by a second proteolytic step to give intact parathyroid hormone (84 amino acids). This intact form of the hormone is stored in chief cells and is the primary form secreted into the blood stream.

Once in the blood stream, parathyroid hormone is quickly cleaved or metabolized primarily in the liver and kidney. The half life of PTH is approximately 15 - 30 minutes. The metabolites include:

1. Amino-terminal (N–terminal) fragment of at least 34 amino acids (very short half life)
2. Several carboxy-terminal (C-terminal) fragments (half life of approximately 2 - 4 hours)
3. Mid -molecule fragments (half life of approximately 2 - 4 hours)

Examples of the mid-molecule fragments include:

1. Amino acids 53 - 84
2. Amino acids 44 - 68
3. Amino acids 35 - 64

The biological activity of parathyroid hormone appears to reside in the first 30 amino acids of the N–terminal portion of the molecule. The C-terminal and mid-molecule fragments are biologically inert and are removed by renal excretion.

Measurement of Parathyroid Hormone

Radioimmunoassay (RIA) methods are the only widely available procedures for measuring parathyroid hormone at this point. However, the measurement by RIA is complicated by several factors. Plasma not only contains intact parathyroid hormone, but it also contains N-terminal, C-terminal, and mid-molecule fragments. Also, the relative concentrations of these vary from condition to condition and from patient to patient. On top of this, RIA methods differ in their ability to detect the various fragments. Therefore, one RIA method may be useful in differentiating a euparathyroid (i.e., normal) individual from a hypoparathyroid individual, but totally ineffective in differentiating primary hyperparathyroidism from hypercalcemia of malignancy.

To address this problem, Tietz makes the following recommendation. "*With the advent of sensitive and specific two-site immunometric methods for measuring intact PTH, there seems to be little reason for clinical laboratories to use any other assays for PTH. Unfortunately, although these two-site immunometric immunoassays for intact PTH have been available for more than 10 years, laboratories continue to receive and analyze specimens with the less specific and less sensitive competitive RIAs (e.g., C-terminal, N-terminal, mid-fragment).*

As we complete the portion of the lecture on minerals, consider the following situation.

A 33-year-old woman, with a history of recurrent renal calculi, was hospitalized with an acute episode of

renal colic. Chemical analysis of the renal stone showed that it contained calcium phosphate. X-rays revealed evidence of bone resorption in the phalanges and distal clavicle. The patient had no hepatosplenomegaly, palpable lymph nodes, or breast or abdominal masses. She was taking no medication, and her family history was negative. The following laboratory data were obtained.

Test	Result
Serum calcium	12.8 mg/dL (8.4-10.2)
Albumin	4.0 mg/dL (3.5-5.0)
Serum phosphate	2.0 mg/dL (2.7-4.5)
Alkaline phosphatase	100 U/L (20-70)
Urine calcium	400 mg/24 hrs (50-250)
Urine phosphorus	1.5 g/24 hrs (0.4-1.3)
Serum PTH	170 µLeq/mL (20-70)

Questions to consider:

1. What is the most probable laboratory diagnosis for the patient?
2. Would the patient's vitamin D_3 ($1,25(OH)_2D_3$) be expected to be increased or decreased?

The answers to these questions are at the end of this lecture.

TRACE METALS

Lithium

Under normal circumstances, there is very little lithium in the body. Lithium ions in the form of lithium carbonate (Li_2CO_3) are of value in treating manic-depressive psychoses. It has a calming effect upon the manic stage and it is frequently given as a therapeutic measure to forestall possible attacks.

Maintenance levels of individuals on lithium are usually kept between 0.5 and 1.0 mmol/L. A serum lithium level of 2 mmol/L or greater is toxic to most individuals. Therefore, patients receiving this drug are usually monitored frequently during the early phase of treatment. A serum concentration of 5 mmol/L has been shown to be lethal. Since lithium has a valence of one, results in mmol/L equal results in mEq/L.

The analytical method of choice for lithium is the atomic absorption spectrophotometer.

Copper

Copper is an essential trace element in the body and its total quantity in the body is approximately 100 mg. It is required for hemoglobin synthesis and is an important constituent of many enzyme systems in the body. It is found primarily in the enzyme superoxide dismutase which functions to protect cells in the body from the toxic free radical superoxide ion O_2 which is generated during aerobic metabolism.

Normal serum levels for copper are 70 - 150 µg/dL.

Most of the copper that is ingested is lost through the stool. A small portion of that ingested is absorbed by the upper small intestine. When copper enters the blood stream it is first loosely bound to albumin. This is for transport to the liver. In the liver this copper is incorporated into the alpha-2 globulin ceruloplasmin. This serves as the copper transport protein in the body. Normal ceruloplasmin levels are usually between 25 - 45 mg/dL.

Wilson's
↑ Cu
↓ ceruloplasmin

The most important abnormality in copper metabolism is in association with Wilson's Disease. This is an inherited disease characterized by degenerative changes in the liver and basal ganglia of the brain due to the excessive deposition of copper in these areas. The most common clinical symptoms in Wilson's Disease are in association with the central nervous system, such as tremor, incoordination, etc.

The biochemical defect in Wilson's disease has not been totally agreed upon at this point, but, the ceruloplasmin level associated with this disease is ordinarily decreased (usually less than 20 mg/dL). At the same time, the plasma copper level is increased. Also, it has been determined that copper levels in the CSF are elevated.

Treatment for Wilson's disease usually involves D-penicillamine which promotes copper excretion in the urine following chelation. penicillin?

The method of choice for measuring copper is atomic absorption spectrophotometry.

Zinc

Zinc is an essential element in the body and it is also an important component of many enzyme systems.

An observation relating to zinc has been made in patients who develop decreased taste and olfactory acuity without any apparent cause. These patients have shown improvement following zinc supplementation.

There has also been some response to zinc therapy by patients with bed sores. In addition, improvement in healing of extensive burns or wounds has been observed following zinc sulfate administration to patients with zinc depletion.

Normal serum levels for zinc are 60 - 115 µg/dL.

Chromium

Chromium has only recently been recognized as an essential trace element. It is a component of a few enzyme systems and its major physiologic role is related to its action on insulin. Chromium is required as a cofactor for the initiation of the action of insulin on peripheral tissues.

Normal serum levels for chromium are <50 ng/dL.

Answer to questions:

In this exercise, total serum calcium concentration was greatly increased while the serum albumin was in the normal range, indicating a true hypercalcemic state. Alkaline phosphatase level was increased, consistent with accelerated turnover of bone. The serum phosphate concentration was low, while urinary excretion was increased. This correlates with the increased serum levels of PTH. There was no evidence of malignancy or peptic ulcer (excludes milk-alkali syndrome) so the most probable diagnosis is primary hyperparathyroidism. The level of $1,25(OH)_2D_3$ would be elevated here due to activation of the kidney hydroxylase enzyme by PTH.