143 | Serum Calcium

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Definition

Calcium is the most abundant mineral element in the body. About 98% of the 1200 g of calcium in the adult is in the form of hydroxyapatite in the skeleton. Hydroxyapatite is a lattice-like crystal composed of calcium, phosphorus, and hydroxide. The remaining calcium is in the extracellular fluid (50%) and in various tissues, especially skeletal muscle. Calcium is maintained within a fairly narrow range from 8.5 to 10.5 mg/dl (4.3 to 5.3 mEq/L or 2.2 to 2.7 mmol/L). Normal values and reference ranges may vary among laboratories as much as 0.5 mg/dl.

Technique

The measurement of serum calcium is fraught with possible errors. Several means of contamination might lead to false elevations of serum calcium concentration. Falsely low levels are less common, so if several measurements are obtained, the lowest is usually the most accurate. The precision of the SMAC analysis, an automated colorimetric technique, is usually equal or superior to that of manual analysis. Nevertheless, falsely high or low values may be obtained in patients with liver or renal failure or in patients with lipemic or hemolyzed specimens. Venous occlusion of the arm during venipuncture may increase the total concentration of serum calcium by up to 0.3 mmol/L. This results from an increase in plasma protein concentration caused by hemodynamic changes. Another source of error is posture. If the patient stands up from a supine position, there may be an increase of 0.05 to 0.20 mmol/L in serum calcium. Still another possible source of error is hemolysis. Some methods of measuring calcium are affected by high levels of hemoglobin, and red cells may take up calcium after prolonged contact. If an error is suspected and the measurement is to be redone, the blood should be drawn following an overnight fast because the daily intake of calcium may contribute to the serum calcium concentration as much as 0.15 mmol/L.

Still other variations in the level of serum calcium need to be mentioned. Exercise just before venipuncture tends to increase serum calcium, so the patient should be rested for at least 15 minutes prior to sampling. Men tend to have a higher serum calcium by 0.02 to 0.04 mmol/L during summer versus winter. Postmenopausal women, however, have higher levels of calcium in winter as compared to summer. Men 15 to 45 years of age tend to have serum calcium levels 0.02 to 0.05 mmol/L higher than similarly aged women. While these values generally fall for both sexes during this 30-year period, this trend reverses for women after the age of 45 until they reach 75 when serum calcium levels again tend to fall.

Basic Science

Although all calcium in the body is technically *ionized*, the term usually only applies to the free ionic fraction that is physiologically active in blood (Table 143.1). The portion of total calcium that forms ion couplets with anions such as bicarbonate and/or citrate is known as *complexed calcium.* Together, the ionized and complexed calcium constitute the diffusible fraction of calcium. This portion may also be called the *ultrafilterable calcium,* since it passes through biologic membranes. This is unlike protein-bound calcium, which is not diffusible. About 90% of the protein-bound calcium is linked to albumin with the remaining 10% bound to a variety of globulins. There are 12 binding sites on each albumin molecule and only about 10 to 15% are utilized under normal conditions. Therefore, when an excess of calcium in the blood occurs, each of the three calcium fractions (i.e., ionized, complexed, protein-bound) increases in the same ratio, resulting in a constant proportion of ultrafilterable calcium.

The ability of protein to bind calcium acts as a buffer that alters the effect of an acute load of calcium on the concentration of ionized calcium by about 50%. Still another consequence of the large number of unfilled binding sites for calcium is that competition by magnesium does not have a significant effect on ionized calcium concentration. The most vital parameter affecting protein binding of calcium is the pH. An alkalemic pH leads to an increase in binding and hence a decrease in the fraction of ionized calcium. The reason for this is twofold: (1) competition between H^+ and Ca^{++} for binding sites; and (2) alteration in configuration of the albumin molecule.

The plasma level of complexed calcium is usually estimated by the difference between ionized and ultrafilterable calcium. As alluded to above, complexed calcium consists of ionic couplets with anions such as HCO_3 and HPO_4 and with organic ions such as lactate and citrate. The most abundant form seems to be $CaHCO_3^+$. As a consequence there is still another mechanism whereby pH alters the ionized calcium concentration. A rise in pH leads to an increase of

Table 143.1
Values of Serum Calcium Fractions

Fraction	Milligrams per deciliter (mg/dl)	Percent (%)
Ionized (free ions)	4.40	44
Total diffusible	5.60	56
Protein-bound	4.60	46
Complexed	1.00	10
Total	10.00	100

HCO_3, which then forms more complexed $CaHCO_3^+$, and therefore a fall in ionized calcium.

A departure of 1.0 g/dl from the normal albumin concentration will account for an alteration of the protein-bound calcium fraction and, hence, the total calcium level of about 0.8 mg/dl.

The calcium homeostatic system depends on several important factors: parathyroid hormone (PTH), vitamin D, phosphate, and magnesium. PTH serves as a receptor arm to correct alterations in the steady-state level of serum calcium. A small fall in ionized calcium will quickly lead to a rise in PTH secretion. The result of this increase in PTH is a rapid release of calcium from bone. This release requires the active form of vitamin D, 1,25-dihydroxycholecalciferol (1,25-DHCC), but is not dependent on bone turnover or an increase in the number of osteoclasts. This effect of PTH most probably is mediated via the transport of calcium from the bone extracellular fluid (ECF). Only if the requirement for calcium is sufficient and prolonged does PTH affect osteoclast proliferation and increase bone turnover.

PTH also acts to maintain the steady-state level of serum calcium by its action on the kidney. It increases the tubular reabsorption of calcium and magnesium and decreases the tubular reabsorption of phosphate, sodium, bicarbonate, potassium, and amino acids. PTH activates the adenylate cyclase system by binding with receptor sites in the renal cortex. It thus leads to an increase in cyclic adenoside monophosphate.

Vitamin D increases the concentration of serum calcium by several mechanisms. As mentioned above, it potentiates the effect of PTH on the bone. Vitamin D also increases the intestinal absorption of calcium, as well as bone resorption and the tubular reabsorption of calcium. The effects on intestinal reabsorption of calcium and bone resorption seem to be due primarily to the active metabolite 1,25-DHCC, but other metabolites may contribute to some of the other effects on serum calcium.

The serum phosphorus level also plays a role in the maintenance of a steady-state concentration of serum calcium. While there is no exact solubility product for calcium and phosphorus, a rise in serum phosphate usually leads to a fall in serum calcium. Some of this decrement may be caused by enhanced formation of $CaHPO_4$ complexes in the serum. A fall in the level of serum phosphate will conversely lead to an increase in the serum ionized and bone ECF calcium. Some of the mechanisms that contribute to the drop of calcium include hypercalciuria and hypoparathyroidism induced by phosphate depletion.

Alterations of serum magnesium within the normal range (1.5 to 2.5 mEq/L) do not appear to affect the concentration of serum calcium. But hypermagnesemia tends to suppress PTH secretion and may lead to mild hypocalcemia. Conversely, a moderate decrement in serum magnesium may stimulate PTH secretion. With a fall in serum magnesium below a concentration of 1.0 mEq/L, PTH secretion is suppressed and resistance to the action of PTH on target organs develops.

Table 143.2
Causes of Hypocalcemia

PTH deficiency
  Genetic
  Acquired (e.g., surgical, irradiation, neoplastic invasion)
  Transient (e.g., hypomagnesemia)

Vitamin D deficiency
  Cholecalciferol deficiency (e.g., sunlight deprivation, dietary insufficiency, gut malabsorption)
  25-Hydroxycholecalciferol deficiency (e.g., impaired hepatic hydroxylation, hepatobiliary disease, nephrotic syndrome, anticonvulsant therapy)
  1,25-Dihydroxycholecalciferol deficiency (e.g., renal failure, hyperphosphatemia)

Transient hypocalcemia
  Intravascular redistribution (e.g., massive transfusion with acid blood)
  Sudden increase in net deposition in bone
    Decreased bone resorption (e.g., mithramycin, calcitonin)
    Increased mineralization (e.g., treatment of rickets)
    Increased bone formation (e.g., osteoblastic metastasis)
  Failure to increase bone resorption in response to calcium depletion (e.g., medullary carcinoma of thyroid)
    Increased soft tissue deposition (e.g., rhabdomyolysis, pancreatitis, hyperphosphatemia)

Source: Modified from Parfitt and Kleerekoper, 1980.

Table 143.3
Causes of Hypercalcemia

Hyperparathyroidism
Metastatic disease of bone
Humoral hypercalcemia
  Ectopic production of PTH-like substance
  Prostagladin induced
  WDHA
Vitamin A/D excess
Milk-alkali syndrome
Sarcoidosis
Immobilization (in setting of posttrauma or osteoporosis)
Hyperthyroidism
Thiazide diuretics
Childhood hypercalcemia
  Idiopathic infantile hypercalcemia
  Hypothyroidism
  Blue-diaper syndrome
  Hypophosphatasia
Proliferative disorders
  Lymphoma
  Sarcoma
  Leukemia
Miscellaneous
  Acromegaly
  Familial hypocalciuric hypercalcemia
  Pheochromocytoma
  Berylliosis
  Tuberculosis
  Rhabdomyolysis with acute renal failure

Source: Modified from Parfitt and Kleerekoper, 1980.

Clinical Significance

The importance of normal serum calcium concentration can best be appreciated by a review of the clinical manifestations of hypocalcemia (Table 143.2) and hypercalcemia (Table 143.3). The former most often leads to tetany, convulsive seizures, and cardiovascular, psychiatric, and a variety of ectodermal effects. Hypercalcemia is usually associated with soft tissue calcification, tubulointerstitial nephropathy, anorexia, nausea, electrocardiographic disturbances, and a spectrum of neurologic changes from headache to coma.

Increased neural excitability is a fairly common manifestation of hypocalcemia. The patient usually describes tingling of the tips of the fingers and around the mouth. If

unabated, these symptoms progress in severity and extend to the limbs and face. The patient may also describe numbness over these areas that may be accompanied by pain and carpal spasm. Most of these patients will have a positive Chvostek's and/or Trousseau's sign.

Hypocalcemia may increase central, as well as peripheral, neural excitability, and two types of convulsive seizures may result. First, the patient may suffer from a seizure disorder similar to a patient without hypocalcemia, such as petit mal, jacksonian, or grand mal. Second, systemic tetany may progress to prolonged tonic spasms, which are also referred to as *cerebral tetany*.

The most common cardiovascular manifestations of hypocalcemia involve disturbances of the electrical rhythm. A fall in serum calcium will delay ventricular repolarization and thus increase the Q-T interval and ST segment. This may progress and produce 2:1 heart block. Chronic hypocalcemia may also lead to less than adequate cardiac performance associated with a reduction in blood pressure.

A variety of psychiatric manifestations may accompany hypocalcemia. These include psychoneurosis, psychosis, and an organic brain syndrome. Following parathyroid surgery and the development of hypocalcemia and hypomagnesemia, an acute psychosis may develop characterized by hallucinations and paranoia. These are reversible on correction of the electrolyte disturbances.

Several defects of the ectoderm are often seen in patients with chronic hypocalcemia. Cataracts are the most common feature. This results from alteration of the local sodium pump with eventual lens degeneration and the development of dystrophic calcifications. Defects in the development of the enamel of teeth may occur if the hypocalcemia precedes the maturation of the respective tooth. Hair and nails may also be affected by chronic hypocalcemia. Both may become dry and brittle; their growth may even be stunted.

Still more unusual effects of hypocalcemia may rarely occur. These include disturbances of blood coagulation, intestinal malabsorption, defective bone mineralization (when associated with vitamin D deficiency), secondary hyperparathyroidism in the neonate of a hypocalcemic mother, slight papilledema, and calcification of the basal ganglion.

The manifestations, and hence the clinical significance, of hypercalcemia consist of five effects: soft tissue calcification, tubulointerstitial renal disease, anorexia and nausea, Q-T prolongation of the electrocardiogram, and an acute brain syndrome.

Three sites of soft tissue calcification occur with hypercalcemia even in the absence of serum phosphate elevations. These are corneal and/or conjunctival calcification, chondrocalcinosis, and renal calcification. While corneal calcifications are usually asymptomatic, conjunctival calcifications often are quite irritating. Band keratopathy is a distinct entity caused by dystrophic calcification often in the setting of hypercalcemia, but less common than either of the other forms of calcification. Calcium pyrophosphate arthritis (i.e., chondrocalcinosis) has an increased incidence in the hypercalcemia of hyperparathyroidism (HPTH), but not in other forms of hypercalcemia.

The clinical characteristics of hypercalcemic renal disease include a mild to moderate fall in creatinine clearance, mild to moderate elevation of blood pressure, mild proteinuria, and impaired concentrating ability associated with polyuria and nocturia. Pathologic changes usually consist of interstitial fibrosis and medullary calcifications which, if severe, appear as calcinosis by x-ray. A variety of tubular dysfunctions may rarely occur in addition to those mentioned. These include glycosuria, phosphaturia, impaired potassium reabsorption, and enhanced hydrogen ion secretion.

The most common gastrointestinal effects of hypercalcemia include anorexia, nausea, and constipation. The constipation is likely the result of dehydration and decreased appetite, while the nausea seems to be a central effect. The incidence of ulcer disease in HPTH remains controversial, whereas the frequency of acute pancreatitis seems to be increased in patients with HPTH.

Even though steady-state levels of serum calcium are important to myocardial function, cardiovascular abnormalities associated with hypercalcemia are limited to shortening of the Q-T interval, rare episodes of heart block, and a tendency to arrhythmias in the presence of digitalis treatment. Hypertension is a fairly common effect of hypercalcemia and may be caused by increased peripheral resistance and/or positive cardiac inotropism.

An acute brain syndrome may be the most common side effect of moderate to severe hypercalcemia. Symptoms such as depression, chronic recurrent headache, and memory impairment are often associated with chronic hypercalcemia of a mild to moderate degree. More pronounced elevations of serum calcium usually lead to a spectrum of symptoms ranging from mental confusion or delirium to stupor and coma. The EEG often shows diffuse slowing consistent with a metabolic encephalopathy.

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