## BACKGROUND

Calcium is the most abundant mineral in the body. Calcium is involved in many critical metabolic functions including vascular contraction and vasodilation, muscle function, nerve transmission, intracellular signaling and hormonal secretion.\(^1\),\(^2\) Less than 1% of total body calcium is used to support these metabolic functions and the remaining calcium supply supports the structure and function in the bones and teeth.\(^1\),\(^2\)

As calcium is important for many cellular activities (e.g., electrical conduction, contractility, enzyme and hormone activity), reduced calcium levels have been suggested to cause decreased cellular and organ performance, particularly cardiovascular dysfunction. Therefore, serum calcium is very tightly regulated and does not fluctuate with dietary intake changes.\(^1\),\(^2\) The body uses bone tissue as a source of calcium to maintain constant concentrations of calcium in blood, muscle, and intercellular fluids.\(^1\),\(^2\)
Total calcium level includes the ionized calcium and bound calcium (with albumin). The amount of total calcium varies with the level of serum albumin, a protein to which calcium is bound. The biologic effect of calcium is determined by the amount of ionized calcium, rather than the total calcium. Ionized calcium circulates freely in the bloodstream and comprises 46-50% of all circulating calcium. Ionized calcium can be used by the body in such vital processes as muscular contraction, cardiac function, transmission of nerve impulses, hormone secretion, glycogen metabolism, cell division and membrane integrity, and blood clotting.

**Total Versus Ionized Calcium Testing**

Total serum calcium is most often satisfactory and sufficient for patient management for the evaluation of calcium metabolism. In most cases, it is a good reflection of the amount of free calcium present in the blood since the balance between free and bound is usually stable and predictable. However, in some people, the balance between bound and free calcium is disturbed and total calcium is not a good reflection of calcium status. In these circumstances, the measurement of ionized calcium may be necessary. Ionized calcium testing is useful to evaluate non-bound calcium, a measure of the physiologically active calcium fraction. Some conditions where ionized calcium should be the test of choice include: critically ill patients who are receiving blood transfusions or intravenous fluids, patients undergoing major surgery, and patients with blood protein abnormalities like low albumin.

**Calcium Disturbances**

Higher-than-normal levels of calcium is called hypercalcemia and can be described with symptoms including nausea and vomiting, prominent skeletal muscle weakness, anorexia, polyuria/nocturia/polydipsia, constipation, stupor, abdominal pain, coma, dehydration, ECG changes/prolongation of QT interval, lethargy, confusion, and flank pain due to renal calculi.

A total serum calcium test may be necessary for hypercalcemia associated with the following conditions: hyperparathyroidism, malignancies, adrenal insufficiency, acromegaly, hypervitaminosis D, and certain drugs. Similarly, hypercalcemia of ionized calcium may be due to: 3

- Decreased levels of calcium in the urine from an unknown cause
- Hyperparathyroidism
- Lack of mobility
- Milk-alkali syndrome
- Multiple myeloma
- Paget’s disease
- Sarcoidosis
- Thiazide diuretics
- Tumors
- Vitamin D excess

Lower-than-normal levels of calcium is called hypocalcemia and can be described with symptoms including muscle twitching, ECG changes/shortened QT interval, Chvostek’s sign (facial muscle spasm), arrhythmias, Trousseau’s sign (carpopedal spasm), bronchospasm, tetany, dysphagia, muscle cramping, diplopia and photophobia, seizure activity, anxiety, malaise, unexplained dementia/depression/psychosis, and numbness/tingling.
A total serum calcium test may be necessary for hypocalcemia associated with the following conditions: hypoparathyroidism, hypoalbuminemia, renal failure, pancreatitis, vitamin D deficiency, severe malnutrition and malabsorption, septic shock, and certain drugs. Likewise, hypocalcemia of ionized calcium may be due to:

- Hypoparathyroidism
- Malabsorption
- Osteomalacia
- Pancreatitis
- Renal failure
- Rickets
- Vitamin D deficiency

Calcium disturbances can be seen in a number of conditions. The association of decreased serum total calcium and ionized calcium levels with critical illness is well documented. In critically ill surgical patients, low ionized calcium and elevated parathormone are early predictors of mortality. Reports suggest that ionized calcium is superior in identifying calcium disturbances in patients receiving transfusions with citrated blood; in critically ill patients; and in patients with the late stages of chronic kidney disease (CKD), hyperparathyroidism, and hypercalcemia of malignancy. Ionized calcium may also have greater diagnostic accuracy in hyperparathyroidism, hypercalcemia of malignancy, and neonatal hypocalcemia. Even though ionized calcium is often studied in patients with critical illnesses in the inpatient setting, direct measurement of ionized calcium is now suggested in several ambulatory conditions, including patients in the later stages of CKD as well as in patients with suspected hyperparathyroidism and MEN1.

**Parathyroid Disease**

Parathyroid glands are little glands in the neck that secrete parathyroid hormone (PTH) which is the main regulator of calcium homeostasis in the body. In response to low serum ionized calcium levels, PTH production and secretion are upregulated. PTH normalizes calcium by enhancing calcium reabsorption in distal renal tubular cells, stimulating osteoclast-mediated bone resorption and catalyzing the conversion of vitamin D, which in turn enhances calcium reabsorption from the GI tract.

High calcium levels are often caused by parathyroid disease. Primary hyperparathyroidism (PHPT) occurs in 1% of population and most common cause of hypercalcemia in an outpatient population. Therefore testing ionized calcium is reasonable to evaluate patients with clinical signs and symptoms of:

- hyperparathyroidism such as weakness, fatigue, bone pain, confusion, depression, nausea, vomiting, polyuria, in which parathyroid disease is suspected;

- hypoparathyroidism such as Chvostek’s sign, Trousseau’s sign, dysphagia, tetany, increased deep tendon reflexes, etc. in which parathyroid disease is suspected;

- ectopic parathyroid hormone producing neoplasms;

- previously diagnosed hyper or hypoparathyroidism; or

- pseudohypoparathyroidism
Even patients with “mild” disease and moderate hypercalcemia can have lipoprotein abnormalities, hypertension, glucose intolerance, and increased morbidity and mortality from cardiovascular disease. Additionally, there is the risk of low bone mineral density and increased fractures.

Many guidelines and criteria for biochemical diagnosis of PHPT relies on total serum calcium levels, however it has been suggested that analyzing ionized calcium can improve the diagnosis of mild PHPT from healthy subjects. In a study to investigate the accuracy of biochemical diagnosis of PHPT, 436 patients had total and ionized calcium analyzed. The results of this study demonstrated that ionized calcium together with total calcium is superior to total calcium and ionized calcium alone. If total and ionized calcium are not used in the diagnostic workup of PHPT, some 4% of patients will be overlooked.

Cancer

There are many different types of cancer in humans and of those; there are at least 5 that are known to be associated with high calcium levels in the blood. These cancers include multiple myeloma, lung cancer (mostly squamous cell cancer of the lung), breast cancer (advanced disease), kidney cancer, and squamous cell cancer of the head and neck. About 10% to 15% of people with one of these types of cancer will have a high calcium level at one time or another. Very high blood calcium is the most common life-threatening emergency associated with these cancers, and is typically seen at the end-stage of the cancer.

Cancer causes hypercalcemia in several ways. When the metastatic cancer spreads to the bones it grows there and slowly erodes the center of the bone, releasing calcium into the blood. Some tumors increase blood calcium by secreting hormones and proteins that circulate and cause the bones to release calcium.

Multiple Myeloma

Multiple myeloma is a cancer and the most common cancer cause of high calcium. Nearly half of all people with myeloma have hypercalcemia at some stage during their disease. Multiple myeloma is a cancer of the plasma cells (a type of white blood cell) that are found in the bone marrow. Plasma cells develop from B lymphocytes (a different type of white blood cell) and they produce antibodies that help the body fight infection (bacteria and viruses). When a plasma cell becomes malignant it will divide many times and produce many copies of itself that form tumors in the bone marrow. Over a period of years these tumor erode the inside of the bone, producing holes in the bones (called "lytic" lesions).

Other Conditions

Monitoring of ionized calcium is also important in several other conditions including hypo or hyperthyroidism, celiac disease, sprue, pancreatitis, malabsorption, coma, extreme vitamin D deficiency, shock, respiratory failure or sepsis that may need monitoring of ionized calcium.

Premature infants with hypoproteinemia and acidosis also may be monitored for ionized calcium while as an inpatient. Heart, lung, and liver transplant patients would also likely be monitored with ionized calcium. Intraoperative monitoring of ionized calcium is also warranted in cases where homeostasis is impaired, such as liver transplantation, and also during blood product transfusion, where substantial loads of citrate calcium chelator can be delivered at a rate exceeding the liver’s metabolic capacity.
Ionized calcium is also necessary to monitor in patients with renal disease, chronic renal failure, renal transplantation, or on hemodialysis. Additionally, hypocalcemia can occur in severe attacks of acute pancreatitis. In a study of 17 patients with acute pancreatitis, Croton et al, demonstrated that directly measured ionized calcium was a better indicator of early stage hypocalcemia than calculated ionized calcium. In a study by Burman, et al, the researchers speculated that ionized calcium levels may be a more sensitive indicator of altered calcium metabolism than total calcium in hyperthyroid patients. In 45 patients with hyperthyroidism, the frequency of elevations of total and ionized serum calcium levels was 27% and 47%, respectively. Moreover, all patients with elevated total calcium had elevated ionized calcium levels, and there were 9 subjects with normal total but elevated ionized calcium concentrations.

Sarcoidosis is a rare autoimmune disease for which the cause remains unknown. Sarcoidosis can often go many years before being detected, and is often found by accident when a chest x-ray is obtained for some other reason. Other patients may be symptomatic with a cough or shortness of breath and the disease is then treated with steroids. Sarcoidosis causes high calcium, however the reason why is unclear.

**POLICY**

For the CPT code(s) in the attached files, the patient should have the corresponding (ICD-10-CM) code(s).

**ICD-10 Diagnosis Codes (Proven)**

CMP-048 Calcium Studies ICD10 v1.0
REFERENCES


POLICY HISTORY/REVISION HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
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<tr>
<td>01/21/2017</td>
<td>Updated ICD10 codes as per CMS recommendations. Removed ICD9 code file.</td>
</tr>
<tr>
<td>10/01/2015</td>
<td>Removed ICD9 table. Embedded ICD9/ICD10 PDF files.</td>
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