Misconceptions in Evaluation and Treatment of Calcium Abnormalities and Parathyroid Disorders

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KEYWORDS

• Calcium • Hypercalcemia • Hypocalcemia • Parathyroid • Hyperparathyroidism • Hypoparathyroidism • Adenoma

KEY POINTS

- The treatment goal for hypocalcemia secondary to hypoparathyroidism is low-normal to marginally low serum calcium with normal 24-hour urine calcium.
- Normal intact parathyroid hormone in the presence of hypercalcemia is not physiologic and does not rule out primary hyperparathyroidism (PHPT).
- Localization (imaging) studies are used to aid preoperative mapping for parathyroidectomy rather than required to make the diagnosis of PHTP.
- Parathyroidectomy is the recommended intervention for PHPT in patients who meet surgical criteria.

EPIDEMIOLOGY

Eucalcemia is essential for multiple physiologic processes, including nerve conduction, muscle contraction, and bone strength. Even mild abnormalities in serum calcium levels may be pathologic and should be investigated. Primary hyperparathyroidism (PHPT) is most often the cause of outpatient hypercalcemia and is present in about 1% of the adult population.[1] PHPT is 2 to 3 times more common in women and is most often caused by a single parathyroid adenoma.[1] Conversely, hypocalcemia secondary to hypoparathyroidism is the most common complication after thyroidectomy after inadvertent removal or damage to one or more of the parathyroid glands.[2,3] However, the actual incidence of postoperative hypoparathyroidism is not well determined due to a discordance of criteria to define these cases.[2] This review explores the manifestation, pathophysiology, causes, evaluation, and treatment of calcium disorders.

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In particular, this review delineates common misconceptions in the evaluation and treatment of calcium disorders and describes the appropriate alternatives.

CALCIUM METABOLISM

Calcium balance is maintained by a harmony between gut absorption, renal reabsorption, and bone matrix turnover.[4] In response to decreased serum calcium, parathyroid hormone (PTH) is released, which stimulates both renal tubular reabsorption and bone calcium resorption.[4] In addition, PTH promotes hydroxylation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (the most active form of vitamin D) from the kidney, which allows for increased intestinal calcium absorption and bone resorption.[4] Finally, 1,25-dihydroxyvitamin D provides negative feedback to the parathyroid glands to decrease PTH secretion.[4]

Conversely, elevated serum calcium levels suppress PTH release; this limits renal tubular reabsorption, bone calcium resorption, and 1,25-dihydroxyvitamin D production. Lower 1,25-dihydroxyvitamin D further decreases bone resorption as well as intestinal calcium absorption. This confluence of events results in a net decrease in serum calcium in an effort to reinstate normocalcemia.

HYPOCALCEMIA

Whether hypocalcemia is found incidentally on comprehensive or basic metabolic panel or during a diagnostic evaluation, an investigation for clinical manifestations is prudent. Patients may be asymptomatic or may report muscle cramping or tingling to the perioral region, hands, or feet.[2] On examination, there may be no clinical manifestations. However, in severe hypocalcemia, positive Chvostek and Trousseau signs may be present[2]: positive Chvostek sign is a provoked twitching or spasm in the ipsilateral facial muscle by stimulating the facial nerve (tapping the masseter muscle anterior to the jaw angle); positive Trousseau sign is observing carpopedal spasm on inflation of sphygmomanometer on the ipsilateral arm for 3 minutes (**Figs. 1** and **2**).

Although Chvostek and Trousseau signs are pathognomonic for hypocalcemia, hyperesthesias may be attributed to other conditions, including but not limited to, neuropathy, multiple sclerosis, and anxiety. Clinical judgment should be used when interpreting the relevancy of the symptoms. If the symptoms seem out of proportion to the level of hypocalcemia or persist after correction, other causes should be investigated.

Diagnostic Approach

Once hypocalcemia is detected, the first step is to confirm the abnormal finding and is done by assessing serum calcium levels in the context of albumin[3] using the equation corrected calcium = serum calcium + 0.8 $\times$ (4 $-$ serum albumin). Ionized calcium, or the measurement of biochemically active calcium, is useful if hypocalcemia is suspected based on history and symptoms, but total serum calcium is within normal limits (and vice versa). After confirming hypocalcemia, the next studies should be targeted at assessing for the most common cause: parathyroid disease. This assessment is done using measures of intact PTH (iPTH) as well as assessing levels that can affect the interpretation of iPTH with 25-hydroxyvitamin D level, renal functions, phosphorus, and magnesium.[3] Assessment for underlying hypomagnesemia should be considered and corrected because low magnesium levels will limit calcium absorption because of PTH resistance.[2]