

Etiology of hypocalcemia in adults

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INTRODUCTION — The major factors that influence the serum calcium concentration are parathyroid hormone (PTH), vitamin D, the calcium ion itself [1], and phosphate. Low serum calcium concentrations are most often caused by disorders of parathyroid hormone (PTH) or vitamin D. Other causes of hypocalcemia include disorders that result in a decrease in serum ionized calcium concentration by binding of calcium within the vascular space or by its deposition in tissues, as can occur with hyperphosphatemia.

The causes of hypocalcemia in adults will be reviewed here. The etiology of hypocalcemia in neonates and children and the clinical manifestations, evaluation, and treatment of hypocalcemia in adults are discussed elsewhere. (See "[Etiology of hypocalcemia in infants and children](#)" and "[Clinical manifestations of hypocalcemia](#)" and "[Diagnostic approach to hypocalcemia](#)" and "[Treatment of hypocalcemia](#)".)

CALCIUM HOMEOSTASIS — Serum calcium concentrations are normally maintained within the very narrow range that is required for the optimal activity of the many extracellular and intracellular processes calcium regulates. Calcium in the blood is transported partly bound to plasma proteins (about 45 percent), notably albumin, partly bound to small anions such as phosphate and citrate (about 15 percent), and partly in the free or ionized state (about 40 percent). (See "[Relation between total and ionized serum calcium concentrations](#)".)

Although only the ionized calcium is metabolically active (ie, subject to transport into cells) most laboratories report total serum calcium concentrations. Concentrations of total calcium in normal serum generally range between 8.5 and 10.5 mg/dL (2.12 to 2.62 mmol/L) and levels below this are considered to be consistent with hypocalcemia. The normal range of ionized calcium is 4.65 to 5.25 mg/dL (1.16 to 1.31 mmol/L).

Hypoalbuminemia — When protein concentrations (particularly albumin) fluctuate substantially, total calcium levels may vary, whereas the ionized calcium, whose level is hormonally regulated, remains relatively stable. Thus, total serum calcium concentrations may not accurately reflect the physiologically important ionized (or free) calcium concentration. As an example, in volume overload, chronic illness, and malnutrition or nephrotic syndrome (where serum protein can be reduced), total plasma calcium is low but the ionized calcium is normal. This phenomenon is called pseudohypocalcemia.

The serum total calcium concentration falls approximately 0.8 mg/dL for every 1 g/dL reduction in the serum albumin concentration. Thus, in patients with hypoalbuminemia, the measured serum calcium concentration should be corrected for the abnormality in albumin ([calculator 1](#)), or for standard units ([calculator 2](#)). If a laboratory known to measure ionized calcium reliably is available, some authorities prefer to measure the serum ionized calcium in this situation. (See "[Relation between total and ionized serum calcium concentrations](#)".)

Acid-base disturbances — Even in the presence of a normal serum albumin, changes in blood pH can alter the equilibrium constant of the albumin-calcium complex, with acidosis reducing the binding and alkalosis enhancing it. Thus, in critically ill or post-surgical patients, correcting total calcium for albumin is not necessarily accurate because of changes in pH and affinity of calcium binding [2]. In one study, for example, the use of the formula that corrected the calcium concentration based upon albumin level had a sensitivity of only 5 percent [2]. Consequently, when major shifts in pH are present, it is most prudent to directly measure the ionized calcium level in order to determine the presence of hypocalcemia.

Hormone regulation — The major hormones that regulate serum calcium are parathyroid hormone (PTH) and vitamin

D via effects on bone, kidney, and the gastrointestinal tract. Calcium itself acts to regulate its own blood levels by acting via a calcium sensing receptor (CaSR) in the parathyroid gland to inhibit PTH secretion and on a CaSR in the loop of Henle to stimulate renal calcium excretion [1].

PTH is secreted almost instantaneously in response to very small reductions in serum ionized calcium, which are sensed by the CaSR. The increase in PTH release raises the serum calcium concentration toward normal via three actions:

- Decreased urinary calcium excretion due to stimulation of calcium reabsorption in the distal tubule
- Increased intestinal calcium absorption mediated by increased renal production of 1,25-dihydroxyvitamin D (calcitriol), the most active form of vitamin D
- Increased bone resorption

Hypocalcemia may occur when PTH secretion is insufficient to act on kidney, bone, and intestine to normalize serum calcium (hypoparathyroidism). When parathyroid gland and PTH are functioning normally, then other causes of hypocalcemia, such as vitamin D deficiency, are characterized by high PTH (secondary hyperparathyroidism). Thus, it is useful to characterize hypocalcemia broadly as associated with low PTH or high PTH ([table 1](#)) [3].

HYPOCALCEMIA WITH LOW PTH (HYPOPARATHYROIDISM) — Hypocalcemia with low PTH occurs when there is decreased secretion of PTH due to destruction of the parathyroid glands (autoimmune, post-surgical), abnormal parathyroid gland development, or altered regulation of parathyroid hormone production and secretion. The most common cause of hypoparathyroidism is surgical.

Destruction of the parathyroid glands

Surgical — Surgical hypoparathyroidism can occur after thyroid, parathyroid, or radical neck surgery for head and neck cancer [3,4]. It may be transient, with recovery in days, weeks or months; permanent; or even intermittent. Transient hypoparathyroidism may be due to manipulation of the blood supply to or removal of one or more parathyroid glands during surgery, whereas intermittent hypoparathyroidism is due to decreased parathyroid reserve.

Transient hypoparathyroidism occurs in up to 20 percent of patients after surgery for thyroid cancer and permanent hypoparathyroidism occurs in 0.8 to 3.0 percent of patients after total thyroidectomy, particularly when the goiter is extensive and anatomic landmarks are displaced and obscured. (See "[Differentiated thyroid cancer: Surgical treatment](#)", section on 'Hypoparathyroidism'.)

Hypoparathyroidism after parathyroidectomy also may be transient, resulting from suppression of the remaining parathyroid tissue by prior hypercalcemia, or it may be severe and prolonged, accompanied by hypophosphatemia, as in the hungry bone syndrome. Hypocalcemia due to hungry bone syndrome may persist despite recovery of PTH secretion from the remaining normal glands. Thus, serum PTH concentrations may be low, normal, or even elevated. (See "[Hungry bone syndrome following parathyroidectomy](#)".)

Autoimmune — Acquired hypoparathyroidism not related to surgery is most often an autoimmune disease [3,5,6]. Permanent hypoparathyroidism can result from immune-mediated destruction of the parathyroid glands [3]. Alternatively, hypoparathyroidism may result from activating antibodies to the calcium sensing receptor that decrease PTH secretion. The antibodies are not destructive and may remit spontaneously. Activating antibodies to the calcium sensing receptor have been reported in patients with isolated acquired hypoparathyroidism and in patients with hypoparathyroidism associated with polyglandular autoimmune syndromes. (See "[Disorders of the calcium-sensing receptor: Familial hypocalciuric hypercalcemia and autosomal dominant hypocalcemia](#)", section on 'Acquired disorders of the calcium-sensing receptor'.)

Autoimmune hypoparathyroidism is a common feature of polyglandular autoimmune syndrome type I, which is a familial disorder (the most common other features are chronic mucocutaneous candidiasis and adrenal insufficiency). This syndrome typically presents in childhood with candidiasis, followed several years later by hypoparathyroidism, and then adrenal insufficiency during adolescence. (See "[Causes of primary adrenal insufficiency \(Addison's disease\)](#)", section on

['Polyglandular autoimmune syndrome type I.'](#))

Other — Other causes of hypoparathyroidism due to parathyroid gland destruction, all very rare, include irradiation and storage or infiltrative diseases of the parathyroid glands (hemochromatosis, Wilson's disease, granulomas, or metastatic cancer) [7-10]. Symptomatic hypoparathyroidism has also been described in association with HIV infection. (See ["Bone and calcium disorders in HIV-infected patients", section on 'Alterations in bone and calcium metabolism'](#).)

Abnormal parathyroid gland development — Genetic defects may result in X-linked or in autosomal recessive hypoparathyroidism due to abnormal parathyroid gland development. The latter has been associated with mutations in the transcription factor glial-cell missing B (GCMB). In addition, hypoparathyroidism may be associated with complex congenital syndromes (eg, DiGeorge syndrome). (See ["Etiology of hypocalcemia in infants and children", section on 'Genetic'](#).)

Altered regulation of PTH — Autosomal dominant or autosomal recessive hypoparathyroidism may be due to mutations in the signal peptide sequence of preproPTH, which impair the normal processing of preproPTH to PTH. (See ["Etiology of hypocalcemia in infants and children", section on 'Genetic'](#).)

Activating mutations of the calcium-sensing receptor (CaSR) that decrease the set point of CaSR, so that PTH is not released at serum calcium concentrations that normally trigger PTH release, may also give rise to familial or autosomal dominant hypoparathyroidism or to sporadic disease. In contrast to other causes of hypocalcemia, urinary calcium excretion is normal or high, presumably due to increased activation of the CaSR in the kidney. (See ["Disorders of the calcium-sensing receptor: Familial hypocalciuric hypercalcemia and autosomal dominant hypocalcemia", section on 'Hypoparathyroidism'](#) and ["Disorders of the calcium-sensing receptor: Familial hypocalciuric hypercalcemia and autosomal dominant hypocalcemia", section on 'Acquired disorders of the calcium-sensing receptor'](#).)

In addition, functional hypoparathyroidism can be caused by both hypomagnesemia and by acute severe hypermagnesemia. (See ["Disorders of magnesium metabolism"](#) below.)

HYPOCALCEMIA WITH HIGH PTH — Other disorders that cause hypocalcemia are associated with a high PTH. In these cases, PTH is increased in response to low serum calcium concentrations, in an attempt to mobilize calcium from kidney and bone and to increase 1,25-dihydroxyvitamin D production. Chronic hypocalcemia occurs when these actions are inadequate to restore the serum calcium to normal.

Vitamin D deficiency or resistance — Decreased production or action of vitamin D may cause hypocalcemia with a high PTH. Causes of vitamin D deficiency include poor intake or malabsorption coupled with reduced exposure to ultraviolet light, decreased 25-hydroxylation of vitamin D to form calcidiol (25-hydroxyvitamin D) in the liver, increased metabolism to inactive metabolites, decreased 1-hydroxylation of calcidiol to calcitriol (1,25-dihydroxyvitamin D) in the kidney, and decreased calcitriol action. (See ["Causes of vitamin D deficiency and resistance"](#).)

Chronic kidney disease — The most common cause of an acquired decrease in renal production of 1,25-dihydroxyvitamin D is chronic kidney disease (CKD). In contrast to other forms of hypocalcemia associated with vitamin D deficiency, hypocalcemia in CKD is also due to the occurrence of hyperphosphatemia (due to reduction in the filtered phosphate load and a reduction in the fractional excretion of phosphorus) [11]. Hypocalcemia typically does not occur until end stage CKD (G5, eGFR <15 mL/min or treatment by dialysis). (See ["Hyperphosphatemia"](#) below and ["Management of secondary hyperparathyroidism and mineral metabolism abnormalities in dialysis patients"](#).)

PTH resistance (impaired PTH action) — Pseudohypoparathyroidism, which presents in childhood, refers to a group of heterogeneous disorders defined by target organ (kidney and bone) unresponsiveness to PTH. It is characterized by hypocalcemia, hyperphosphatemia and, in contrast to hypoparathyroidism, elevated rather than reduced PTH concentrations. This disorder is discussed elsewhere. (See ["Etiology of hypocalcemia in infants and children", section on 'End-organ resistance/pseudohypoparathyroidism'](#).)

Extravascular deposition — Ionized calcium can be lost from the extracellular fluid either by deposition in tissues or by binding within the vascular space.

Hyperphosphatemia — In patients with impaired renal excretion or in acute renal failure, increased phosphate intake (overzealous oral administration or phosphate enemas) or excess tissue breakdown (rhabdomyolysis, tumor lysis) can cause acute hypocalcemia. (See "[Overview of the causes and treatment of hyperphosphatemia](#)" and "[Tumor lysis syndrome: Definition, pathogenesis, clinical manifestations, etiology and risk factors](#)".)

In hyperphosphatemia, calcium is deposited mostly in bone, but also in extraskeletal tissue. Chronic hyperphosphatemia is almost always due to reduced phosphate clearance in chronic kidney disease where primary impairment of calcitriol synthesis in renal failure (leading to decreased intestinal calcium absorption) further aggravates the hypocalcemia. (See "[Overview of chronic kidney disease-mineral bone disease \(CKD-MBD\)](#)", section on '[Hypocalcemia and calcium-sensing receptor](#)' and "[Overview of chronic kidney disease-mineral bone disease \(CKD-MBD\)](#)", section on '[Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism](#)'.)

Osteoblastic metastases — Occasional patients with widespread osteoblastic metastases, particularly those with breast or prostate cancer, have hypocalcemia. The presumed cause is deposition of calcium in the newly formed bone around the tumor [12,13]. In a study of 131 men with advanced prostate cancer, 34 percent had elevated serum PTH concentrations, and of these, 56 percent had a low serum ionized calcium [13]. Hypocalcemia and secondary hyperparathyroidism was most common in those with progressive disease and bone metastases.

Acute pancreatitis — Hypocalcemia is also a frequent finding in patients with acute pancreatitis, where it is associated with precipitation of calcium soaps in the abdominal cavity [14]. The actual mechanism remains unclear. Although PTH concentrations are variable, they are typically elevated in response to hypocalcemia [15].

Sepsis or severe illness — The incidence of hypocalcemia in critically ill or postsurgical patients approaches 80 to 90 percent [16]. Sepsis and severe burns can also be associated with clinically important hypocalcemia. The cause appears to be a combination of impaired secretion of PTH coupled with reduced calcitriol production [17,18] and end-organ resistance to the action of PTH; the probable underlying mechanisms include hypomagnesemia and actions of inflammatory cytokines on the parathyroid glands, kidneys, and bone.

Hypocalcemia is common in the toxic-shock syndrome [19]. In addition to the above mechanisms, high serum calcitonin concentrations (which inhibit bone resorption) have been found in some patients.

Surgery — Hypocalcemia can occur during and soon after surgery, most often in patients who received large volumes of blood, because the citrate used as an anticoagulant chelates calcium. In these cases, total calcium is normal while ionized calcium is reduced as a result of citrate binding. It can also occur during and after major surgery in patients who do not receive transfusions [20]. Most of the reduction in serum calcium is due to volume expansion and hypoalbuminemia and does not affect the ionized calcium concentration. However, some patients have ionized hypocalcemia with a compensatory increase in serum PTH concentrations. These changes, which are proportional to the severity of the surgery/anesthesia procedure, subside within hours after the operation.

DISORDERS OF MAGNESIUM METABOLISM — As noted above, magnesium depletion can cause hypocalcemia by producing PTH resistance, which occurs when serum magnesium concentrations fall below 0.8 mEq/L (1 mg/dL or 0.4 mmol/L) or by decreasing PTH secretion, which occurs in patients with more severe hypomagnesemia (see "[Clinical manifestations of magnesium depletion](#)", section on '[Calcium metabolism](#)'). The hypocalcemia cannot be corrected with calcium; the patients must be given magnesium. (See "[Treatment of hypocalcemia](#)", section on '[Concurrent hypomagnesemia](#)'.)

Malabsorption, chronic alcoholism, and [cisplatin](#) therapy are the most common causes of hypomagnesemia; others include prolonged parenteral fluid administration, diuretic therapy, and the administration of aminoglycosides (see "[Causes of hypomagnesemia](#)"). Despite PTH resistance or PTH deficiency, most patients with hypomagnesemia have normal or low serum phosphate concentrations, probably because of poor intake.

Although magnesium depletion is typically suspected from the presence of hypomagnesemia, a few patients with magnesium-responsive hypocalcemia but **normal** serum magnesium concentrations have been described. (See "[Clinical manifestations of magnesium depletion](#)", section on '[Normomagnesemic magnesium depletion](#)'.)

Severe hypermagnesemia, a very rare disorder, can also cause hypocalcemia, by suppressing the secretion of PTH [21]. This requires a serum magnesium concentration above 5 mEq/L (6 mg/dL or 2.5 mmol/L), a concentration encountered only when magnesium is given to women with eclampsia. Symptomatic hypocalcemia is rare in these patients, most likely due to its short duration and the antagonistic neuromuscular effects of hypermagnesemia. Similarly, asymptomatic hypocalcemia has been reported during magnesium treatment in aneurysmal subarachnoid hemorrhage [22]. (See "[Symptoms of hypermagnesemia](#)", [section on 'Hypocalcemia'](#) and "[Causes and treatment of hypermagnesemia](#)".)

DRUGS

Calcium chelators — Substances such as citrate (used to inhibit coagulation in banked blood or plasma), lactate, [foscarnet](#), and sodium EDTA chelate calcium in serum, thereby reducing serum ionized calcium concentrations but not serum total calcium concentrations. Acute respiratory alkalosis, which increases calcium binding to albumin in serum, also reduces serum ionized calcium concentrations. (See "[Relation between total and ionized serum calcium concentrations](#)".)

Symptomatic hypocalcemia during transfusion of citrated blood or plasma is rare [23], because normal subjects rapidly metabolize citrate in the liver and kidney. However, a clinically important fall in serum ionized calcium concentration can occur if citrate metabolism is impaired due to hepatic or renal failure or if large quantities of citrate are given rapidly, for example during plasma exchange, leukapheresis, or massive blood transfusion [24]. (See "[Therapeutic apheresis \(plasma exchange or cytapheresis\): Complications](#)" and "[Massive blood transfusion](#)" and "[Blood donor screening: Procedures and processes to enhance safety for the blood recipient and the blood donor](#)", [section on 'Citrate toxicity'](#).)

A similar effect can occur in patients with lactic acidosis due to shock or sepsis [25]. For this reason, serum ionized calcium should be measured periodically in patients with these disorders.

Bisphosphonates — Hypocalcemia may result from the treatment of hypercalcemia, skeletal metastases, Paget disease of bone, or osteoporosis with bisphosphonates, which act to reduce osteoclastic bone resorption. Hypocalcemia is more likely to occur when high doses of especially potent bisphosphonates, such as [zoledronic acid](#), are used and in patients with underlying vitamin D deficiency, unrecognized hypoparathyroidism, or impaired renal function. (See "[The use of bisphosphonates in postmenopausal women with osteoporosis](#)", [section on 'Other'](#) and "[Risks of therapy with bone antiresorptive agents in patients with advanced malignancy](#)", [section on 'Hypocalcemia and other electrolyte abnormalities'](#).)

Denosumab — [Denosumab](#) is a fully human monoclonal antibody to the receptor activator of nuclear factor kappaB ligand (RANKL), an osteoclast differentiating factor. It inhibits osteoclast formation, decreases bone resorption, increases bone mineral density (BMD), and reduces the risk of fracture. In patients with conditions that predispose to hypocalcemia, such as chronic kidney disease, malabsorption syndromes, or hypoparathyroidism, symptomatic hypocalcemia may occur. (See "[Denosumab for osteoporosis](#)", [section on 'Hypocalcemia'](#).)

Cinacalcet — Patients receiving a calcimimetic drug (only [cinacalcet](#) is currently available) to help control secondary hyperparathyroidism of renal failure may experience hypocalcemia as a result of acute inhibition of PTH release. Clinically significant hypocalcemia occurs in approximately 5 percent of cases treated with cinacalcet. (See "[Management of secondary hyperparathyroidism and mineral metabolism abnormalities in adult predialysis patients with chronic kidney disease](#)", [section on 'Cinacalcet'](#) and "[Management of secondary hyperparathyroidism and mineral metabolism abnormalities in dialysis patients](#)", [section on 'Calcimimetics'](#).)

Chemotherapy — Hypocalcemia can occur in patients treated with some chemotherapeutic drugs. Among them, [cisplatin](#) is probably most common. As noted above, it causes hypocalcemia by causing hypomagnesemia. Combination therapy with 5-fluorouracil and [leucovorin](#) caused hypocalcemia in 65 percent of patients in one series, possibly by decreasing calcitriol production [26].

Foscarnet — [Foscarnet](#) is a drug used to treat refractory cytomegalovirus and herpes infections in immunocompromised patients. It complexes ionized calcium and therefore lowers ionized calcium concentrations,

potentially causing symptomatic hypocalcemia [27]. Therefore, the ionized calcium concentration should be measured at the end of an infusion of foscarnet.

Fluoride poisoning — Rarely, excess intake of fluoride can cause hypocalcemia [28,29]; this effect is mediated, in part, by the formation of fluorapatite [30].

SPURIOUS HYPOCALCEMIA — Two of the commercially available forms of gadolinium-based contrast agents (used in magnetic resonance angiography), [gadodiamide](#) and [gadoversetamide](#), may interfere with the colorimetric assays for calcium that are frequently used in hospital laboratories [31,32]. This effect is not observed with other gadolinium-based agents: dimeglumine gadopentetate, [gadoteridol](#), or [gadoterate meglumine](#) [31,33].

The interaction can result in a marked reduction in the measured calcium concentration of as much as 6 mg/dL (1.5 mmol/L) if a blood sample is obtained soon after the test [34,35]. This effect is rapidly reversible as the gadolinium is excreted in the urine, and the patient has no symptoms or signs of hypocalcemia. Awareness of this phenomenon is particularly important in patients with renal insufficiency who may retain the contrast agent for prolonged periods. There is no reason to treat this type of hypocalcemia.

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Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "[Patient information: Hypoparathyroidism \(The Basics\)](#)")

SUMMARY AND RECOMMENDATIONS

- Extracellular calcium ions regulate numerous biological processes, including intracellular signaling for secretion of many hormones, muscle contraction, and the coagulation cascade. It is therefore important that serum ionized calcium concentrations be maintained within a very narrow range, which is achieved by the close interrelationship between serum ionized calcium, PTH, and vitamin D. (See '[Calcium homeostasis](#)' above.)
- Hypocalcemia has many causes. It may result from inadequate parathyroid hormone production or secretion, parathyroid hormone resistance, vitamin D deficiency or resistance, abnormal magnesium metabolism, or to extravascular deposition of calcium, which can occur in several clinical situations ([table 1](#)). (See '[Hypocalcemia with low PTH \(hypoparathyroidism\)](#)' above and '[Hypocalcemia with high PTH](#)' above.)
- Among all of the causes of hypocalcemia, postsurgical hypoparathyroidism, autoimmune hypoparathyroidism, and vitamin D deficiency are the most common. (See '[Surgical](#)' above and '[Autoimmune](#)' above and '[Vitamin D deficiency or resistance](#)' above.)

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GRAPHICS

Major causes of hypocalcemia

Low PTH (hypoparathyroidism)

Genetic disorders

Abnormal parathyroid gland development

Abnormal PTH synthesis

Activating mutations of calcium-sensing receptor (autosomal dominant hypocalcemia or sporadic isolated hypoparathyroidism)

Post-surgical (thyroidectomy, parathyroidectomy, radical neck dissection)

Autoimmune

Autoimmune polyglandular syndrome (associated with chronic mucocutaneous candidiasis and primary adrenal insufficiency)

Isolated hypoparathyroidism due to activating antibodies to calcium-sensing receptor

Infiltration of the parathyroid gland (granulomatous, iron overload, metastases)

Radiation-induced destruction parathyroid glands

Hungry bone syndrome (post parathyroidectomy)

HIV infection

High PTH (secondary hyperparathyroidism in response to hypocalcemia)

Vitamin D deficiency or resistance

Multiple causes

Parathyroid hormone resistance

Pseudohypoparathyroidism

Hypomagnesemia

Renal disease

Loss of calcium from the circulation

Hyperphosphatemia

Tumor lysis

Acute pancreatitis

Osteoblastic metastases

Acute respiratory alkalosis

Sepsis or acute severe illness

Drugs

Inhibitors of bone resorption (bisphosphonates, calcitonin, denosumab), especially in vitamin D deficiency

Cinacalcet

Calcium chelators (EDTA, citrate, phosphate)

Foscarnet (due to intravascular complexing with calcium)

Phenytoin (due to conversion of vitamin D to inactive metabolites)

Fluoride poisoning

Disorders of magnesium metabolism

Hypomagnesemia can reduce PTH secretion or cause PTH resistance and is therefore associated with normal, low, or high PTH levels

PTH: parathyroid hormone; HIV: human immunodeficiency virus; EDTA: ethylenediaminetetraacetic acid.

Data from: Thakker RV. Hypocalcemia: Pathogenesis, differential diagnosis, and management. In: Primer on the metabolic bone diseases and disorders of mineral metabolism, sixth edition, American Society of Bone and Mineral Research 2006; 35:213.

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