Hypocalcemia Causes

Hypocalcemia is defined as serum calcium < 8.5 mg/dL. Parathyroid hormone (PTH), albumin, vitamin D, magnesium and phosphate are all involved in calcium homeostasis, and derangements in their levels can cause changes in total and active calcium levels. Acid-base changes due to medications or critical illness alter calcium binding. Critical illness such as sepsis or severe burns also cause hypocalcemia through actions on calcium homeostasis and end-organ effects. Many medications, including calcium chelators, bisphosphonates, and chemotherapeutic agents can cause hypocalcemia through effects on calcium binding and homeostasis.

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Hypoalbuminemia

Hippo-album

Total body calcium is comprised of both free and bound calcium. 45% of body calcium is in the active form, which is free or ionized. 40% of calcium circulates bound to plasma proteins such as albumin, with a small portion bound to phosphate and citrate. When albumin levels fall due to liver disease or other causes, total calcium levels also fall. Serum calcium concentration decreases by 0.8 mg/dL for every 1 g/dL decrease in the serum albumin concentration. Drops in albumin do not affect the level of active, free calcium, so measured serum calcium should be corrected for hypoalbuminemia.

Hypomagnesemia (Less Common Hypermagnesemia)

Hippo-magnesium-magazine

Hypoparathyroidism can be caused both by hypomagnesemia and hypermagnesemia. These derangements are seen with a magnesium (Mg) level of <1 mg/dL, or with acute and very severe hypermagnesemia above >6 mg/dL. Hypomagnesemia is most often caused by malabsorption, chronic alcoholism, and treatment with the drug cisplatin; however diuretics, aminoglycosides, and prolonged administration of parenteral fluids are other potential causes. Severe acute hypermagnesemia leads to hypocalcemia through suppression of PTH secretion. This is generally iatrogenic and can be seen in pregnant women who are given large doses of magnesium to treat eclampsia.

Hypovitaminosis D

Hippo with Viking Daisy

Vitamin D plays an important role in calcium homeostasis through action on the vitamin D receptor at bone, kidney, and intestinal levels. Vitamin D deficiency is caused by poor intake or malabsorption, decreased exposure to ultraviolet light, or decreased production of its activated forms in the liver and kidneys due to underlying organ disease.

Hypoparathyroidism

Hippo-para-thigh-droid

Decreased secretion of parathyroid hormone (PTH) causes decreased bone resorption and decreased absorption of calcium in the gut and kidneys. The most common cause of hypoparathyroidism is surgical, occurring after thyroid, parathyroid, or neck surgery. This drop in PTH may be transient, however it often persists. Immune-mediated destruction of the parathyroid glands can result in permanent hypoparathyroidism, while antibody-mediated stimulation of the calcium-sensing receptor can be reversed. Genetic defects like DiGeorge's syndrome may lead to abnormal gland development and altered regulation of PTH. Rare causes of parathyroid gland destruction include infiltrative diseases such as hemochromatosis, Wilson's disease, and malignancies.

Medications

Med-bottle

Calcium chelators such as citrate, lactate, and the anti-viral medication foscarnet reduce serum levels of ionized calcium, but do not affect total calcium levels. Bisphosphonates and denosumab cause hypocalcemia secondary to decreased osteoclastic bone resorption. Cinacalcet is a calcimimetic drug that is used to control secondary hyperparathyroidism through inhibition of PTH release, which may also lead to hypocalcemia. Chemotherapeutic drugs can cause hypocalcemia, with cisplatin being the most common perpetrator when it induces a state of hypomagnesemia. The combination of 5-fluorouracil and leucovorin has also been identified as a causative agent.

Hyperphosphatemia

Hiker-phosphate-P

High phosphate levels lead to hypocalcemia through increased calcium deposition in bone and extraskeletal tissue. Hyperphosphatemia is caused by increased intake, excessive tissue breakdown, and decreased excretion. Impaired renal function from acute kidney injury or CKD may lead to phosphate retention.

Malnutrition

Nutritional-mallet

Prolonged malnutrition causes overall deficiencies of many vitamins, minerals, and proteins. Insufficient levels of albumin, calcium, and vitamin D all lead to hypocalcemia in the malnourished patient.

Acute Pancreatitis

Acute-angle Pancreas-on-fire

Hypocalcemia in acute pancreatitis is due to precipitation of calcium soaps in the abdominal cavity. This is caused by an excess of saturated free fatty acids that bind calcium and decrease levels in the gut without changing the amount of albumin or phosphate in the blood.

Alkalosis

Elk-loser

Changes in blood pH can have an effect on the equilibrium of albumin-calcium complexes. Alkalosis (pH > 7.45) increases the negativity of albumin and increases its ability to bind positively charged free calcium ions, resulting in a decreased fraction of free circulating ionized calcium without decreasing total calcium concentrations. This is of most significance in critically ill and surgical patients, and in patients where major shifts in pH are likely. Ionized calcium should be directly measured in these patients, as other formulas can not correct for pH related changes.

Sepsis

Sepsis-snake

Over 80% of critically ill patients have some degree of hypocalcemia. This includes patients with sepsis and severe burns. Hypocalcemia is caused by decreased secretion of PTH, as well as decreased calcitriol production secondary to chronic or acute kidney injury. End-organ resistance to PTH action is also seen in critically ill or septic patients, and is related to hypomagnesemia and action of inflammatory cytokines.

Chronic Kidney Disease

Crone Kidney

1,25-dihydroxycholecalciferol (calcitriol) is the active form of vitamin D, and is produced in the kidneys. Chronic kidney disease (CKD) is the most common cause of acquired decrease in renal production of calcitriol, leading to decreased calcium absorption in the intestines, and decreased bone resorption.

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