Hypercalcemia Causes

Dysfunction of several pathways can lead to high levels of calcium circulating in the blood. Calcium homeostasis is regulated by calcium absorption in the intestines, bone turnover, and reabsorption and excretion of calcium in the kidneys. Bone resorption is stimulated by increased levels of vitamin D and parathyroid hormone (PTH). Calcium absorption in the intestines is stimulated by vitamin D and high calcium intake. Renal excretion of calcium is mediated by PTH and vitamin D, and can be affected by many disease states. Malignancy is another important cause of hypercalcemia due to direct osteolytic effects on bone as well as hormonal changes in calcium homeostasis.



PLAY PICMONIC

Two CHIMPANZEES Acronym

Two Chimpanzees

The causes of hypercalcemia can be remembered with the mnemonic: “Two CHIMPANZEES” The letters stand for: Thyroid Disorders, Calcium supplementation, Hyperparathyroidism, Iatrogenic, Milk-alkali syndrome, Paget’s disease of bone, Adrenal insufficiency/Acromegaly, Neoplasm, Zollinger-Ellison syndrome, Excessive vitamin A, Excessive vitamin D, and Sarcoidosis/other granulomatous diseases.

Thyroid Disorders

Thigh-droid

In thyrotoxicosis (an acute elevation of circulating thyroid hormone due to physiological stressors), there is a thyroid hormone-induced increase in bone resorption. Chronic hyperthyroidism patients also have elevated bone resorption, and are predisposed to developing hypercalcemia over time.

Calcium Supplements

Calcium-cow Pills

An increase in calcium intake can cause mild hypercalcemia, which can become more severe if mixed with decreased excretion of calcium.

Hyperparathyroidism

Hiker-para-thigh-droid

Parathyroid hormone (PTH) acts at all three major sites of calcium homeostasis. PTH directly stimulates osteoclastic differentiation to increase bone resorption, which releases both calcium and phosphate in the blood. PTH then inhibits phosphate reabsorption in the proximal tubule of the kidney nephron; with less phosphate available to bind calcium, the serum level of calcium increases. In addition, PTH increases calcium reabsorption at the distal convoluted tubule of the kidney. Finally, PTH stimulates the production of activated vitamin D3 (calcitriol), which then increases intestinal calcium absorption. The most common cause of hypercalcemia is primary hyperparathyroidism due to a parathyroid adenoma.

Iatrogenic (Drugs, immobility)

i-at-medic

Several medications can cause hypercalcemia. Lithium causes secondary hyperparathyroidism by interfering with the ability of elevated calcium to inhibit PTH release. Thiazide diuretics cause a decrease in urinary excretion of calcium. Immobility like in a bedridden hospital patient causes increased calcium release due to an increase in bone resorption.

Milk-Alkali Syndrome

Milk Elk

Very high intake of milk or calcium carbonate can cause a syndrome of hypercalcemia, metabolic alkalosis, and renal insufficiency. The alkalosis directly stimulates calcium reabsorption in the distal tubule of the kidneys, worsening the hypercalcemia. The hypercalcemia may cause renal vasoconstriction and structural injury, worsening renal function and exacerbating the underlying issue.

Paget's Disease of Bone

Pageant-sash Skeleton

This disease involves rapid bone modeling and the construction of poor quality bone. One of the diagnostic clues to detecting Paget’s Disease of Bone is a normal calcium and PTH level. However, in cases where a patient suffers multiple fractures or they are immobilized due to the extent of their disease, hypercalcemia will develop.

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Acromegaly or Addison's Disease

A-chrome-mega-man with Add-sun

Hormone excess or deficiency can be another cause of hypercalcemia. Addison’s disease refers to primary adrenal insufficiency, a condition in which adrenal glands do not produce adequate amounts of steroid hormones. The resulting hormone deficiencies can cause increased bone resorption, dehydration/hemoconcentration, and increased reabsorption of calcium in the kidney. Acromegaly is a disease caused by hypersecretion of growth hormone from the anterior pituitary. GH increases bone resorption and thus hypercalcemia eventually.

Neoplasms

New-growths

The mechanism behind hypercalcemia in malignancy varies between types of cancers. Bone metastases cause direct osteolysis, as well as increased release of cytokines such as tumor necrosis factor and interleukin-1, inducing osteoclastic differentiation and therefore increased bone remodeling and resorption. Multiple myeloma causes hypercalcemia through a similar mechanism, driven by cytokines such as lymphotoxin, interleukin-6, and RANK ligand. Secretion of PTH related protein (PTHrP) is the most common cause of hypercalcemia in solid, nonmetastatic tumors such as squamous cell carcinoma of the lung. PTHrP stimulates excess bone resorption by osteoclasts, and reduces calcium excretion at the proximal tubule.

Zollinger-Ellison Syndrome

Zoolander-Elephant

Zollinger-Ellison Syndrome describes a syndrome of gastrin hypersecretion secondary to duodenal or pancreatic neuroendocrine tumors. When these tumors occur in conjunction with multiple endocrine neoplasia type 1 (MEN1) with primary hyperparathyroidism, hypercalcemia is caused by the hyperparathyroidism and causes a downstream calcium-induced increase in gastrin secretion, further worsening GI symptoms.

Excessive Vitamin A

Up-arrow Viking (A) Apple

Ingestion of greater than 50,000 IU of vitamin A per day can cause an increase in bone resorption and lead to hypercalcemia.

Excessive Vitamin D

Up-arrow Viking Daisy

Hypervitaminosis D causes hypercalcemia through several mechanisms. 1,25-dihydroxyvitamin D (Calcitriol) induces a calcium binding protein known as calbindin D-28K; more of this protein means more calcium absorption in the intestinal tract. At the level of the kidneys, calcitriol increases reabsorption of calcium and phosphate. Calcitriol also acts on bone to increase osteoblastic activation of osteoclasts, increasing bone turnover and raising serum calcium.

Sarcoidosis

Shark-koi-fish

Chronic granulomatous diseases, especially sarcoidosis, involve vitamin D activation due to elevated 1alpha-hydroxylase activity within macrophages. Excess vitamin D then leads to hypercalcemia as explained previously.

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