REVIEW PAPERS

Hypercalcemia – an underestimated medical problem

Hiperkalcemia – niedoceniany problem medyczny

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- hypercalcemia
- primary hyperparathyroidism
- hypercalcemia of malignancy

Abstract

Hypercalcemia affects approximately 1% of the worldwide population. This electrolyte abnormality is frequent both in out and inpatients (varies from 0,17 to 5% in hospitalized patients, however, incidence increases even up to 7,5% in emergency departments in some populations). Primary hyperparathyroidism (PHPT) and hypercalcemia of malignancy (HCM), account for more than 90 percent of all causes of hypercalcemia. Other causes of hypercalcemia, such as vitamin D intoxication, granulomatous disorders, milk-alkali syndrome, medications, familial hypocalciuric hypercalcemia, and immobilization amount to less than 10% of all causes of hypercalcemia. However, once primary hyperparathyroidism or cancer has been excluded, other causes of hypercalcemia, often life-threatening and requiring appropriate causal management, should be considered. Considering rare etiologies is important, nevertheless, when primary hyperparathyroidism or malignancy do not account for the hypercalcemia. The review describes the pathophysiology, symptoms, and diagnostic approach to the most relevant causes of hypercalcemia.

Słowa kluczowe:

- hiperkalcemia
- pierwotna nadczynność przytarczyc
- hiperkalcemia w przebiegu chorób nowotworowych

Streszczenie

Hiperkalcemia dotyczy około 1% populacji na całym świecie. Jest częstą nieprawidłowością elektrolitową zarówno u pacjentów ambulatoryjnych, jak i hospitalizowanych (waha się od 0,17% do 5% u pacjentów hospitalizowanych; w niektórych populacjach oddziałów ratunkowych występowała nawet u 7,5% badanych). Pierwotna nadczynność przytarczyc (PHPT) i hiperkalcemia nowotworowa (HCM) stanowią więcej niż 90 procent wszystkich przyczyn hiperkalcemii. Inne przyczyny hiperkalcemii, takie jak zatrucie witaminą D, choroby ziarniniakowe, zespół mleczno-alkaliczny, leki, rodzinna hiperkalcemia hipokalciuryczna i unieruchomienie stanowią mniej niż 10% wszystkich przyczyn. W przypadku wykluczenia pierwotnej nadczynności przytarczyc lub nowotworu, należy jednak rozważyć inne przyczyny hiperkalcemii, częstokroć zagrażające życiu i wymagające odpowiedniego postępowania przyczynowego. W przeglądzie opisano patofizjologię, objawy oraz diagnostykę najważniejszych przyczyn hiperkalcemii.

Introduction

The introduction of the automated serum chemistry autoanalyzer in the 1970s brought about a significant advancement in the detection of primary hyperparathyroidism (PHPT), leading to a notable rise in its occurrence by four to five times. Over 75% of patients no longer exhibit the typical symptoms associated with the disease, suggesting that PHPT has transformed or changed from its traditional manifestation (1).

While there is no evidence that Hypercalcemia of Malignancy (HCM) is becoming more prevalent over time, the incidence of HCM may be increasing due to various factors, such as the rising incidence of certain types of cancer, such as multiple myeloma and breast cancer as well as changes in cancer diagnosis and treatment, aging of the population, or increased awareness and reporting of the condition (2, 3).

Other relatively common causes of hypercalcemia include granulomatous diseases hypervitaminosis D, Milk-Alkali

Syndrome, thiazides or lithium administration, and prolonged immobilization (4).

Many previous studies on the incidence and etiology of hypercalcemia have been focused on in-hospital populations and during its course it became apparent, that some cases of hypercalcemia had either been missed or ignored by those managing the patients (in one study even up to 20% of cases), so that no cause for the disorder could be established (5).

Definition

Typically, adults have serum total calcium levels ranging from 8.5 to 10.5 mg/dL (equivalent to 2.12 to 2.62 mM). Any levels surpassing this range are indicative of hypercalcemia. It is classified into mild, moderate, and severe, depending on total calcium values; mild <12 mg/dL (>2.62 and <3 mmol/L), moderate 12-14 mg/dL (3-3.5 mmol/L), and severe >14 mg/dL (>3,5 mmol/L). Approximately 50% of total calcium in the blood is ionized and the remainder is bound to albumin and immunoglobulins (40-45%) in a pH-dependent manner or complexed with small anions such as phosphate, lactate, or citrate (approximately 10%). The usual range for ionized calcium in the body is typically 4.65 to 5.25 mg/dL (equivalent to 1.16 to 1.31 mM), although slight variations may exist between different laboratories. It's important to note that only ionized calcium is metabolically active, meaning it can enter cells and initiate cellular functions. However, many laboratories report total serum calcium concentrations, which include both ionized and non-ionized forms (4, 6, 7).

Total serum calcium concentration will change in parallel to the albumin concentration and may not accurately reflect the ionized form, which may remain relatively stable; in other words, it may be more/less total calcium in the blood, but not the ionized form, which is physiologically tightly regulated by parathyroid hormone (PTH) and vitamin D, and can be modified by a variety of factors (see below) (7).

Various formulas have been employed to adjust the total calcium levels based on serum albumin concentrations. However, none of these formulas seems to be universally agreed upon when assessed for their association with ionized calcium. One commonly used equation in clinical settings assumes that for every 1 g/dL (10 g/L) decrease in serum albumin concentration, the serum calcium level decreases by 0.8 mg/dL (0.2 mM) (8):

$$\text{Corrected calcium (mg/dL)} = \text{Serum calcium} + 0.8 \times (4 \text{ g/dL} - \text{Serum albumin})$$

When significant changes occur in serum protein or pH levels, it is advisable to directly measure the ionized calcium level to accurately diagnose hypercalcemia. Ionized form measurement is indicated in hospitalized patients with critical illness and/or patients with advanced-stage chronic kidney disease (CKD) and/or patients with multiple myeloma (MM) (6, 7).

Pathophysiology

Minute-to-minute regulation of the ionized calcium concentration is tightly maintained within a very narrow range mainly by PTH, the most important of calciotropic hormones, modulating calcium and phosphate homeostasis. An increase in PTH secretion increases tubular calcium reabsorption and enhances bone resorption and calcium release from the skeleton, increasing ECF (serum) calcium concentration within minutes. Moreover, increased PTH secretion activates renal 1α hydroxylase (CYP27B1) and enhances the production of 1,25(OH)$_2$D (calcitriol) in the kidney resulting in increased calcium intestinal absorption, however, this effect occurs days after PTH secretion increases. Consequently, the opposite sequence of events occurs in the case when the serum calcium is raised above the normal range unless pathological PTH secretion or 1,25(OH)$_2$D overproduction is the cause of the hypercalcemia (4, 9).

Although the renal 1α hydroxylase [1α(OH)ase] is the major source of circulating hormonal 1,25(OH)$_2$D, a variety of extra-renal cells synthesize calcitriol. The non-renal tissues that produce 1,25(OH)$_2$D can release it in a paracrine or autocrine manner, meaning it acts locally to regulate cell growth, differentiation, and local function. In this context, 1,25(OH)$_2$D does not typically participate in the systemic control of calcemia and is metabolized within the same tissue where it is produced. However, in pathological conditions that run with a significant overproduction of calcitriol, as in sarcoidosis or lymphomas, this can lead to hypercalcemia (4).

In 1979, Parfitt proposed three different mechanisms of hypercalcemia: "equilibrium" hypercalcemia typically occurs in patients with mild, asymptomatic PTHP and is caused by an increased serum calcium release from bone, which is balanced by an increased renal tubular calcium excretion Serum calcium is little above the upper normal or in upper normal. "Disequilibrium" hypercalcemia refers to a condition where there is a sudden surge in the level of calcium in the bloodstream, which occurs due to a significant increase in bone resorption coupled with the kidney's inability to effectively eliminate the excess calcium burden. This condition can manifest in two ways: either as a result of an existing "equilibrium" hypercalcemia being disrupted by an advancing disease or it can originate as a primary disruption of calcium balance and bone remodeling right from the start. An example of the latter is seen in cases of humoral hypercalcemia of malignancy (HCM) where the levels of parathyroid hormone-related protein (PTHrP) are elevated. "Hyperabsorption" hypercalcemia, is a pattern due to increased intestinal calcium absorption and positive calcium balance, e.g. in Milk-Alkali syndrome or vitamin D intoxication (10).

Symptoms of hypercalcemia

The symptoms and signs of hypercalcemia are determined by the severity of hypercalcemia however, the clinical manifestation of hypercalcemia depends more on the rapidity of the increase in serum calcium concentration than on its absolute serum concentration (6, 7).

Patients with mild hypercalcemia (serum calcium above the upper limit of normal but <12 mg/dL [3 mmol/L]) may be asymptomatic. Long-lasting hypercalcemia however, can have profound effects on many tissues and organs, including the brain, muscles, heart, and kidneys, and can cause chronic nonspecific symptoms like cognitive dysfunction, anxiety, depression, irritability, muscle weakness, constipation and dyspepsia, anorexia, atherosclerosis, hypertension

and left ventricular hypertrophy, nephrolithiasis, nephro-calcinosis and, finally chronic renal insufficiency. Cases of moderately increased serum calcium, ranging from 12 to 14 mg/dL (3 to 3.5 mmol/L), can be generally well tolerated chronically, but acute rise to these concentrations and above (>3.5 mmol/L) may cause marked, acute symptoms, including altered mental status (confusion, stupor, coma, psychosis, hallucinations), nausea, vomiting, and progressive hyperosmotic dehydration. Acute kidney injury may occur. These symptoms are more specific for HCM than for PHPT; observed also in parathyroid carcinoma cases, where high calcium levels occur. The set of symptoms typical for acute hypercalcemia is also called the hypercalcemic crisis and requires immediate treatment (4, 6, 7, 11).

Hypercalcemia in adults: etiology

Hypercalcemia in adults can be categorized into several main causes, including endocrine disorders, malignant disorders, granulomatous disorders, medication-induced hypercalcemia, and immobilization. The majority of patients, around 90%, who experience hypercalcemia, are diagnosed with either primary hyperparathyroidism (PHPT) or hypercalcemia of malignancy (HCM) (4).

Endocrine disorders associated with excess PTH production

Primary Hyperparathyroidism (PHPT)

Sporadic PHPT with single parathyroid adenoma is the most common (to 80-90%) form of this disease. Polyglandular disease (multiglandular hyperplasia, multiple adenomas) accounts for about 15% of all cases but is more of a hereditary basis, occurring as an isolated familial or syndromic condition, rather than sporadic disease. Functional parathyroid cysts and parathyroid carcinomas are very rare (about 1% of cases) (12).

Three major clinical phenotypes of sporadic PHPT have been described (6). Before the 1970s symptomatic cases were predominant, with symptoms and signs of hypercalcemia, and with overt skeletal and renal complications: classical skeletal symptoms of osteitis fibrosa cystica, bone pain or tenderness, and bone fractures as well as chronic kidney disease, nephrolithiasis and/or nephrocalcinosis (13). Since the 1970s, the clinical presentation of primary hyperparathyroidism (PHPT) has changed due to the routine measurement of serum calcium becoming more common during that time. This led to increased recognition and diagnosis of PHPT, resulting in a four- to five-fold rise in its incidence (1). Nowadays, most patients with PHPT are asymptomatic and exhibit mild hypercalcemia. However, they may show signs of subclinical complications affecting the skeletal system and kidneys, such as osteoporosis, hypercalciuria, vertebral fractures, and nephrolithiasis. These manifestations often go unnoticed as they may be asymptomatic. In the absence of obvious symptoms or signs of hypercalcemia, the disorder is usually detected through biochemical screening. Presently, approximately 80% of sporadic PHPT cases are categorized as mild or "asymptomatic" hyperparathyroidism, where hypercalcemia is borderline or mild, typically less than 1 mg/dL (0.25 mM) above the upper limit of normal or may intermittently appear normal. Excess PTH production can produce

significant bone loss, however, an osteoporosis clinical picture is the most common skeletal manifestation of excess circulating PTH at present (13). While the asymptomatic phenotype is most prevalent today, non-classical symptoms which may be associated with PHPT are described, including subtle gastrointestinal, neuromuscular, and cardiovascular manifestations. Both symptomatic and "asymptomatic" patients can present non-classical symptoms. There is no indication, however, for a gastrointestinal, cardiovascular metabolic, neurocognitive, or neuropsychiatric evaluation, unless the patient has the symptomatic form of the gastrointestinal disease or Zollinger-Ellison syndrome (11).

In centers that focus on metabolic bone diseases and conduct thorough evaluations, a distinct form of primary hyperparathyroidism (PHPT) has been identified. This form is characterized by normal levels of both total and ionized serum calcium. It is known as normocalcemic primary hyperparathyroidism (NPHPT) and can only be diagnosed after ruling out all known causes of secondary hyperparathyroidism. NPHPT may represent the earliest signs of PHPT, often referred to as a "forme fruste" of the disease. Several reports have documented individuals with NPHPT, and some of these patients have progressed to overt hypercalcemia while being monitored by medical professionals (11, 13).

Familial hypocalciuric hypercalcemia (FHH)

Familial Hypocalciuric Hypercalcemia (FHH) is an autosomal dominant disorder caused by genetic mutations in the Calcium-Sensing Receptor (CASR) gene. It is characterized by mild hypercalcemia that persists throughout a person's life, along with normal or slightly elevated levels of parathyroid hormone (PTH) and low urinary calcium excretion. Most individuals affected by FHH do not experience significant symptoms, and their bones and other organs are not adversely affected. It is crucial to differentiate between primary hyperparathyroidism (PHPT) and FHH, as surgery, which is a common treatment for PHPT, typically does not effectively resolve hypercalcemia in FHH and is generally not recommended. FHH should be considered in patients with lifelong hypercalcemia, particularly those under 30 years old or with a family history of hypercalcemia. The diagnosis of FHH is often confirmed when the calcium-to-creatinine clearance ratio (Ca/Cr Cl ratio) is less than 0.01, whereas a Ca/Cr Cl ratio greater than 0.02 is more indicative of PHPT. However, the Ca/Cr clearance ratio may be less than 0.01 in approximately 20 percent of PHPT patients, particularly those with concomitant vitamin D deficiency. Vitamin D repletion always should be provided and 24-hour urinary calcium excretion alongside with Ca/Cr Cl after 3 months reassessed. Genetic testing is indicated when FHH is a consideration (4, 13, 14).

Tertiary hyperparathyroidism

Evolves in the course of longstanding secondary hyperparathyroidism, such as poorly controlled chronic kidney disease or malabsorption syndromes (e.g., active celiac disease, extensive bowel resection, gastric bypass surgery) into a hypercalcemic state as a result of autonomic PTH overproduction. Tertiary hyperparathyroidism is readily identified by the clinical context in which the hypercalcemia presents (4).

Endocrine disorders without excess PTH production

Endocrine disorders that do not involve excessive production of parathyroid hormone (PTH) include hyperthyroidism, hypoadrenalism, or pheochromocytoma. Hypercalcemia has been observed in up to 50% of patients with thyrotoxicosis (15), possibly due to the direct impact of triiodothyronine on bone turnover, leading to increased resorption (16). Pheochromocytomas have also been associated with hypercalcemia, which may be attributed to the excessive production of parathyroid hormone-related protein (PTHrP) (17). While both primary (18) and secondary (19) hypoadrenalism have been linked to hypercalcemia, the underlying causes remain unclear.

Hypercalcemia of Malignancy (HCM)

Hypercalcemia of malignancy (HCM) is more often responsible for hypercalcemia in hospitalized patients than PHPT – up to 65%, while in an ambulatory setting for 31% or less (20). Compared to PHPT, in hypercalcemic cancer patients, the malignancy is generally evident clinically when hypercalcemia occurs and carries a poor prognosis. Hypercalcemia associated with malignancy is generally more acute and severe than in primary hyperparathyroidism and patients with HCM usually have higher calcium concentrations (values above 13 mg/dL [3,25 mmol/L]), which makes them symptomatic more often (21, 22). Hypercalcemia of malignancy (HCM) is the most prevalent metabolic complication observed in cancer patients. However, advancements in chemotherapeutic medications have significantly reduced the mortality rates associated with HCM. It is estimated to affect between 2% and 30% of individuals with cancer, with the occurrence varying depending on the specific type of cancer and the stage of the disease (23).

The most common malignancies associated with hypercalcemia are solid tumors, such as breast, lung and renal cancer, and multiple myeloma (MM) (23). Hypercalcemia of malignancy should be also suspected in patients with otherwise unexplained hypercalcemia and a low-normal or low serum parathyroid hormone (PTH) concentration (e.g. <20 pg/mL) (14, 20).

The three major mechanisms responsible for hypercalcemia of malignancy are paraendocrine activity of neoplasm with the systemic secretion of parathyroid hormone-related protein (PTHrP), which can be detected in serum, local release of cytokines (including osteoclast activating factors like PTHrP) by osteolytic metastases, and overproduction of 1,25-dihydroxyvitamin D (calcitriol) in non-Hodgkin's and Hodgkin's lymphoma (22). A significant percentage, up to 80%, of HCM is attributed to an excess of PTHrP in the bloodstream. It is the primary cause of hypercalcemia in patients with non-metastatic solid tumors and can also be a contributing factor in some individuals with non-Hodgkin lymphoma. The overproduction of PTHrP by the tumor cells leads to increased calcium levels and subsequent development of HCM. This condition is also called **"Humoral Hypercalcemia of Malignancy" (hHCM)**. Patients with hHCM most often suffer from squamous cell carcinomas (lung, head, and neck), but also renal, bladder, breast, or ovarian carcinomas as well non-Hodgkin's lymphoma, chronic myeloid and lymphoblastic leukemia and adult T cell leukemia/lymphoma (ATL) were described. Patients usually present with advanced disease and carry a poor prognosis (4, 22, 23).

PTHrP mimics PTH function on bone and kidney and the resultant hypercalcemia suppresses endogenous PTH secretion. Within the bone, PTHrP plays a role in enhancing the production of both the membrane-bound and soluble forms of receptor activator of nuclear factor-kappa B ligand (RANKL). RANKL binds to its corresponding receptor, receptor activator of nuclear factor-kappa B (RANK), located on the surface of osteoclast progenitor cells. This interaction triggers a cascade of events that promote osteoclastogenesis, which is the formation of osteoclasts, and leads to an increased bone remodeling. In the kidney, PTHrP, similarly to PTH increases tubular calcium reabsorption, however is less likely than PTH to stimulate calcitriol production and serum levels of 1,25-dihydroxyvitamin D in patients with PTHrP-mediated hypercalcemia may be variable (4, 22, 23).

Local release of cytokines from osteolytic metastases results in enhanced bone resorption and hypercalcemia in patients with extensive skeletal metastases or marrow infiltration. This mechanism accounts for approximately 20 percent of cases of HCM. Induction of local osteolysis by tumor cells is common with some solid tumors that are metastatic to bone and with Multiple Myeloma (MM). The solid tumor that most often produces hypercalcemia by this mechanism is breast cancer (22, 23). Metastatic malignant cells present in bone tissue may secrete PTHrP into the bone microenvironment which eventually will stimulate osteoblasts to release RANKL ligand (RANKL) resulting in increased skeletal resorption and hypercalcemia. Simultaneously released from the bone growth factors as TGFb, IGF-1 FGF, PDGF, and BMP stimulate further PTHrP release from the tumor, thus setting up a positive feedback loop. This occurs in the absence of high serum PTHrP concentrations, however, in some cases of breast cancer serum PTHrP is elevated, suggesting a systemic effect as well (4, 22, 24). In MM, various studies have shown extensive cytokine secretion, e.g. MIP-1a, IL-1, IL-6, TNF-b (lymphotoxin), and hepatocyte growth factor (HGF) as well as an increase in the soluble form of RANKL production (25). Although bone resorption is increased, the new bone formation is inhibited by Dickkopf-1 (DKK-1), a protein inhibitor of the Wnt pathway, implicated in the suppression of osteoblast differentiation, produced by myeloma cells (26). While osteolysis is a common occurrence in all patients with multiple myeloma (MM), hypercalcemia, on the other hand, only affects approximately 30% of these patients. This difference suggests that as long as kidney function remains intact and there is no increase in renal calcium reabsorption (as myeloma cells rarely produce PTHrP), the kidneys can effectively excrete the excess calcium resulting from excessive local bone resorption. In such cases, renal excretion of calcium is sufficient to handle the increased calcium load (4).

Ectopic overproduction of calcitriol is a less common mechanism of HCM and is almost exclusively seen in the course of lymphomas. This accounts for almost all cases of hypercalcemia in Hodgkin lymphoma and approximately one-third of cases in non-Hodgkin lymphoma (22). The exact mechanism would be analogous to overexpression of a 1α-hydroxylase in granulomatous tissue (4). Patients with increased production of calcitriol typically have low or suppressed serum intact PTH and elevated 1,25-dihydroxyvitamin D (20). In certain cases, there have been reports of co-production of PTHrP in malignancies associated with calcitriol-induced hypercalcemia (4, 22). As a result, the production of 1,25-dihydroxyvitamin D (1,25(OH)$_2$D),

lymphoid cytokines and PTHrP collectively contribute to the development of hypercalcemia. These factors work in tandem to disrupt calcium balance and promote elevated levels of calcium in the bloodstream. Hypercalcemia induced by calcitriol (but not PTHrP) usually responds to glucocorticoid therapy – it inhibits the ectopic 1α-hydroxylase, an enzyme produced by malignant lymphocytes, macrophages or both, which, unlike kidney's 1α-hydroxylase, is not under the control of natural feedback limiting the conversion of precursor 25-hydroxyvitamin D to calcitriol. It is important to note that in some cases hypercalcemia may not be effectively resolved despite the use of glucocorticoids. In cases of hypercalcemia mediated by calcitriol, dietary calcium intake needs to be restricted (22, 23).

Hypercalcemia in granulomatous diseases

Hypercalcemia has been described in patients with granulomatous disorders, most commonly sarcoidosis and tuberculosis (27). Hypercalcemia in sarcoidosis and other granulomatous diseases is due to PTH-independent, extrarenal overproduction of calcitriol by activated monocytes or macrophages in the lung and lymph nodes, which promotes mainly intestine calcium absorption, but also bone resorption, similar like in HCM (4, 27). Other granulomatous diseases, described as resulting in hypercalcemia include inflammatory diseases like granulomatosis with polyangitis (GPA), infectious diseases like candidiasis, histoplasmosis, coccidiomycosis or cat-scratch disease (Bartonella Henselae infection) or foreign body-induced granulomatosis like silicone, paraffin talk or berylliosis and many others (6).

Hypercalciuria is observed in approximately 30 to 50 percent of individuals diagnosed with sarcoidosis and hypercalcemia occurs in about 10 to 20 percent of cases. It is important to note that exposure to sunlight can worsen these conditions. Apart from underlying disorder treatment, calcium level abnormalities should be managed by reducing dietary intake of calcium and vitamin D, limiting sunlight exposure, and treating the underlying disease. In more severe cases, bisphosphonates may be helpful (27).

It is believed that in granulomatous disorders (as in malignant lymphoproliferative disease), an extra-renal 1α-hydroxylase produced by macrophages, which are dominant components of the granuloma, is a source of the excess 1,25(OH)₂D. Renal synthesis of hormonal calcitriol is self-regulated by negative feedback with serum calcitriol itself, and by PTH, calcium, phosphorus, and fibroblast growth factor 23 to prevent overproduction of calcitriol and hypercalcemia. However, 1α-hydroxylase produced by macrophages is not regulated as is the renal 1α-hydroxylase, which leads to an uncontrollable overproduction of calcitriol by activated macrophages within the granulomas (4). This macrophage 1α-hydroxylase does however appear to be suppressible by glucocorticoids (28), chloroquine analogs (29), and cytochrome P-450 inhibitors such as ketoconazole (30).

To prevent vitamin D deficiency in patients with sarcoidosis, it may be necessary to administer vitamin D treatment to raise their serum 25-hydroxyvitamin D levels to around 25 ng/mL. However, close monitoring of 25(OH)D concentrations is crucial to avoid complications associated with increased calcium levels – hypercalciuria and hypercalcemia typically occur when the 25(OH)D levels exceed 30 ng/mL in sarcoidosis individuals (31, 32).

Hypercalcemia caused by medications

Hypercalcemia in vitamin D and its analogs intoxication

Excessive intake of vitamin D, calcifediol [25(OH)D], or active analogues: calcitriol alphacalcidol or dihydrotachysterol, can result in hypercalciuria and hypercalcemia by increasing gut absorption of calcium and bone resorption (33). Calcitriol is far more potent than 25(OH)D, but in those who intentionally or accidentally ingest high (mega) doses of cholecalciferol or calcifediol itself, hypercalcemia also may occur (34). According to the Endocrine Society statement, serum levels of 25-hydroxyvitamin D exceeding 100 ng/mL (250 nmol/L) are classified as hypervitaminosis D, indicating an excessive amount of vitamin D in the bloodstream. Furthermore, serum levels exceeding 150 ng/mL (375 nmol/L) have been suggested as the threshold for defining vitamin D intoxication (31). Calcitriol has a relatively short biological half-time and hypercalcemia usually lasts only one to two days, thus stopping the calcitriol and increasing fluid intake may be the only therapy needed. In contrast, 25(OH)D may be stored in fat and released over time, and hypercalcemia caused by cholecalciferol or calcifediol intoxication lasts longer, and more aggressive therapy such as glucocorticosteroids or intravenous bisphosphonates may be necessary (35).

A special group of patients at risk of hypercalcemia are patients with Chronic Kidney Disease (CKD), treated with calcium carbonate and calcitriol in an attempt to reverse both hypocalcemia and secondary hyperparathyroidism (36).

Milk-Alkali Syndrome (MAS)

In the prior absence of renal failure, hypercalcemia can be induced by a high intake of calcium. In the past, a condition known as the milk-alkali syndrome was observed when individuals consumed significant amounts of milk and bicarbonate as a treatment for peptic ulcers. However, in modern times, a similar condition has been identified as a result of using calcium carbonate for the management of osteoporosis or dyspepsia. This modern-day equivalent is believed to arise from the excessive intake of calcium carbonate as part of these treatments. Except from hypercalcemia, historically MAS was accompanied by metabolic alkalosis, nephrocalcinosis, and renal insufficiency. Nowadays, patients are often asymptomatic and the findings are discovered incidentally. PTH levels are generally reduced – this is an important feature that can help distinguish the MAS from PHPT. It is common reversible after cessation of supplementation (37, 38).

Hypercalcemia in vitamin A and its analogs intoxication

Prolonged ingestion of more than 50 000 IU/day vitamin A or administration of retinoic acid to patients with certain tumors, as either cis-retinoic acid or all-trans retinoic acid, causes an increase in bone resorption and hypercalcemia. The preferred treatments seem to be stopping the medication, providing fluids for hydration, and administering an anti-resorptive agent (39).

*Hypercalcemia caused
by thiazide diuretics and lithium*

Thiazides are commonly used to treat hypertension; lithium is used in psychiatric disorders and some cases of hyperthyroidism (14, 20). Both thiazides and lithium carbonate have been reported to produce hypercalcemia. Hypercalcemia is generally reversible with discontinuation of therapy if the drug can be stopped without exacerbating the underlying condition. Persistent hypercalcemia with elevated or high-normal PTH after drug withdrawal suggests that the drug has unmasked PHPT. Lithium can potentially reveal adenomas in individuals with preexisting parathyroid lesions shortly after initiating therapy, or it can lead to parathyroid hyperplasia with long-term use. As a result, lithium is linked to the development of multiglandular primary hyperparathyroidism (PHPT) (13, 40).

Hypercalcemia in prolonged immobilization

Prolonged static position reduces mechanical load on the skeleton, which inhibits bone formation and raises bone resorption; it may manifest as hypercalcemia. This may occur after several states, including hip fracture, bariatric surgery, spinal injury, major stroke, burns and others (41).

Diagnostic approach to hypercalcemia

Primary hyperparathyroidism (PHPT) and hypercalcemia of malignancy (HCM) are the predominant causes of hypercalcemia, constituting over 90 percent of cases (1). The approach to hypercalcemia typically involves distinguishing between PHPT and HCM. Elevated total serum calcium adjusted for albumin in the presence of an elevated or inappropriately normal intact PTH on two occasions at least 2 weeks apart is the diagnostic criteria for PHPT (13). In the ambulatory (outpatient) setting, PHPT accounts for 50-60% of hypercalcemia, while in the hospital for 27% or less (20). Most recent studies revealed that even 90% of all ambulatory chronic hypercalcemia is attributable to PHPT (42).

If hypercalcemia is confirmed and PTH is frankly elevated, PHPT is highly likely. If patients with serum PTH are mid to upper normal or minimally elevated, PHPT is still most likely, but familial hypocalciuric hypercalcemia (FHH) should be considered (14, 20). While sporadic primary hyperparathyroidism (PHPT) is the most common form, it is important to consider familial or inherited syndromic PHPT (such as MEN 1, 2A, and 4, which involve multiple parathyroid glands) as well as non-syndromic familial PHPT for patients below 30 years of age, individuals with a history or imaging indicating multiglandular disease, and those with a family history of hypercalcemia or syndromic diseases (13). Recent findings suggest that family history is the most significant predictor of hereditary PHPT (43). If the PTH is low-normal or low (e.g., <20 pg/mL), PHPT is unlikely and non-PTH mediated hypercalcemia should be evaluated. Without clinically apparent malignancy, PTHrP[1] , $1,25(OH)_2D$ and $25(OH)D$ should be measured. Humoral HCM is more likely while PTHrP is elevated, however granulomatous diseases, lymphoma, or vitamin D intoxication are more likely while $1,25(OH)_2D$ is high (14, 20).

Typical laboratory findings in patients with humoral HCM include very low or suppressed serum intact PTH (secretion of endogenous PTH is suppressed by PTHrP-mediated hypercalcemia), elevated serum PTHrP, and variable serum calcitriol (22). If serum parathyroid hormone-related protein (PTHrP) and PTH concentrations are both high, then coexisting primary hyperparathyroidism should be considered. However, some cases of tumors simultaneously secreting both PTH and PTHrP have been reported (44). Patients with metastatic bone disease often exhibit the following characteristic findings: decreased or suppressed levels of intact parathyroid hormone (PTH) in the bloodstream, reduced or low-normal levels of 1,25-dihydroxyvitamin D (a form of vitamin D), and decreased or low-normal levels of parathyroid hormone-related protein (PTHrP) in the blood (although PTHrP secreted by bone metastases may not be easily detectable through a serum assay). Additionally, these patients typically demonstrate extensive skeletal metastases or infiltration of the bone marrow (22). If only serum $25(OH)D$ is elevated – vitamin D intoxication is more likely. While both PTH, PTHrP, $25(OH)D$ and $1,25(OH)_2D$ are low/normal, other rare causes of hypercalcemia like MM, thyreotoxicosis, vitamin A intoxication, immobilization, discontinuation of denosumab, as well as unrecognized calcium intake in the face of renal insufficiency (as in the milk-alkali syndrome) must be considered (14, 20).

Hyperparathyroidism and humoral hypercalcemia of malignancy (caused by PTHrP) can lead to noticeable hypophosphatemia or low-normal levels of phosphate in the bloodstream. This occurs due to the inhibition of renal proximal tubular phosphate reabsorption (20), resulting in reduced levels of phosphate in the body. 24-hour urinary calcium excretion may be normal, high-normal, or elevated in hyperparathyroidism without vitamin D deficiency and HCM. In contrast, there are three disorders in which an increase in renal calcium reabsorption leads to relative hypocalciuria [less than 100 mg/day (2.5 mmol/day)]: thiazide diuretics (directly enhance active calcium reabsorption in the distal tubule); FHH and MAS (the last is associated metabolic alkalosis which enhances calcium reabsorption; there is also serum chloride below 103 mEq/L) (20).

Bone radiographs or abdominal CT imaging can be useful. Fractures, nephrolithiasis, or nephrocalcinosis can be detected incidentally and suggest PHPT. Osteolytic lesions suggest metastasis or MM. Bone lesions typical for osteitis fibrosa cystica result from the overproduction of PTH in the setting of primary, secondary, and tertiary hyperparathyroidism (20, 45).

Summary

Hypercalcemia is a relatively common clinical problem. The advent of automated chemistry panels that routinely measure serum calcium concentration caused an increase in reported incidence and prevalence of hypercalcemia (mainly in the course of PHPT) in the United States and Europe; it revealed the broader scale of a problem than it was considered before the 1970s. Hypercalcemia can lower the quality of life or can be life-threatening and should be considered as a surrogate marker of underlying pathology; hence, it needs detailed evaluation to ascertain the etiology

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[1] *The possibilities of determining serum PTHrP in Poland are significantly limited.*

for providing proper treatment of underlying disease. The two most common causes of hypercalcemia are primary hyperparathyroidism and malignancy, which together account for more than 90 percent of cases. When faced with hypercalcemia, the diagnostic process usually involves a combination of clinical assessment and laboratory testing to differentiate between these two causes. The many other causes of hypercalcemia occur less frequently (remaining 10% of patients) but are important to consider in clinical situations when hypercalcemia is not caused by PHPT or HCM. Mild hypercalcemia per se can be asymptomatic, however, long-lasting can have profound effects on many tissues and organs, including the brain, muscles, heart, and kidneys, and can cause chronic nonspecific symptoms. If the patient has acute symptomatic hypercalcemia and/or total calcium > 14 mg/dL (3.5 mmol/L) require immediate treatment for lowering calcemia.

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