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Review

Critical review of hypercalcemia

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Abstract

Hypercalcemia is a clinical condition with an abnormally high serum calcium (Ca) level. Hypercalcemia is associated with many diseases with primary hyperparathyroidism and some malignancies accounting for greater than 90% of cases. Hypercalcemia may be clinically useful as a diagnostic or prognostic marker for these diseases. This paper covers the various etiologies attributing to hypercalcemia, pathogenesis and the differential diagnosis of hypercalcemia. Hypercalcemia is a useful diagnostic marker in hypercalcemia-related diseases such as primary hyperparathyroidism, malignancies and granulomatous disorders. Adequate managements or treatments are aimed to reduce serum Ca levels by preventing bone resorption, enhancing urinary Ca excretion, or preventing intestinal Ca absorption. The optimal choice is dependent on the cause and/or severity of hypercalcemia. Drug treatment or management of hypercalcemia include: Bisphosphonates, Gallium nitrate, Glucocorticoids and Denosumab.

Key words: Serum calcium, Primary hyperparathyroidism, Bisphosphonates, Gallium nitrate, Denosumab, Glucocorticoids

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Hypercalcemia is a clinical condition with an abnormally high serum calcium (Ca) level. Total serum Ca ranges from 8.8–10.4 mg/dL (2.20–2.60 mmol/L) in apparently healthy subjects[1]. Total serum Ca comprises free ions (≈50%), protein-bound complexes (≈40%), and ionic complexes (≈10%)[2]. The free ionic Ca, the physiologic active form, is stringently regulated within a range of 4.4–5.4 mg/dL (1.10 –1.35 mmol/L) so as to avoid Ca toxicity[3]. It is decreased in alkalosis and increased in acidosis[4]. In patients with abnormality of extracellular fluid pH, each 0.1 reduction in pH elevates ionized calcium by approximately 0.2 mg/dl (0.05 mmol/L)[5]. Hypercalcemia is associated with many diseases with primary hyperparathyroidism and some malignancies accounting for greater than 90% of cases[6].

Hypercalcemia may be clinically useful as diagnostic or prognostic marker for these diseases. However, it is non-specific and this may undermine its usefulness as a first-line marker. Patients manifest symptoms with neuromuscular, gastrointestinal, renal, cardiovascular and skeletal involvement[7]. Report showed that the prevalence of hypercalcemia in patients range from 0.17%–2.9% in some hospitals; while surprisingly a higher prevalence of hypercalcemia was reported to vary between

1.07% and 3.9%, in the normal population[8]; and women were reported to be more affected than men[9]. This therefore suggests that its prevalence may depend on the population studied in relation to the underlying disease. Relevant studies to date done on the subject have been considered for this review article. The studies considered for this article are available in various books on the subject and research articles printed or hosted over the internet by reputable online journals.

Interpretation of calcium

In serum, albumin and globulin are the main Ca binding proteins[7]. Because 1g/dL albumin approximately binds 0.8 mg/dl Ca, ionized Ca is estimated from measurements of total Ca and serum albumin; and the ionized Ca concentration adjusted using the formula: Corrected calcium = Measured Ca (mg/dL) + [0.8 × (4 – albumin)] g/dL[10]. However the retrospective study by Steele et al[11] and the prospective study by Slomp et al[12] show that albumin adjusted Ca is a relatively poor indicator of ionic Ca levels in patients that are critically ill. Patients who are hypocalcemic are often underdiagnosed and classified to be hypercalcemic. The use of ward-based analyzers can increase the test sensitivity[11]. Ionized Ca measurement could be of essence in few cases such as in patients with hyperalbuminemia, hypoalbuminemia, Waldenström macroglobulinemia, thrombocytosis, and myeloma[7,10]. In Waldenström macroglobulinemia and myeloma cases, hypercalcemia may be diagnosed but the ionized serum Ca is normal (pseudohypercalcemia)[10].

Pathogenesis of hypercalcemia

Ionized Ca is tightly regulated by the actions of two principal hormones and their receptors: PTH (parathyroid hormone) and PTHR (the PTH receptor)[13] and 1, 25-$[OH]_2$ D (1, 25 – dihydroxy vitamin D3) and VDR (the vitamin D receptor)[14]. Disease(s) which chronically elevate levels of PTH and 1, 25-$[OH]_2$ D may result to increased: bone resorption, releasing Ca; intestinal absorption and renal reabsorption of Ca. The net effect is an increase in plasma Ca above the normal physiological levels leading to the clinical condition known as hypercalcemia[7](Fig 1).

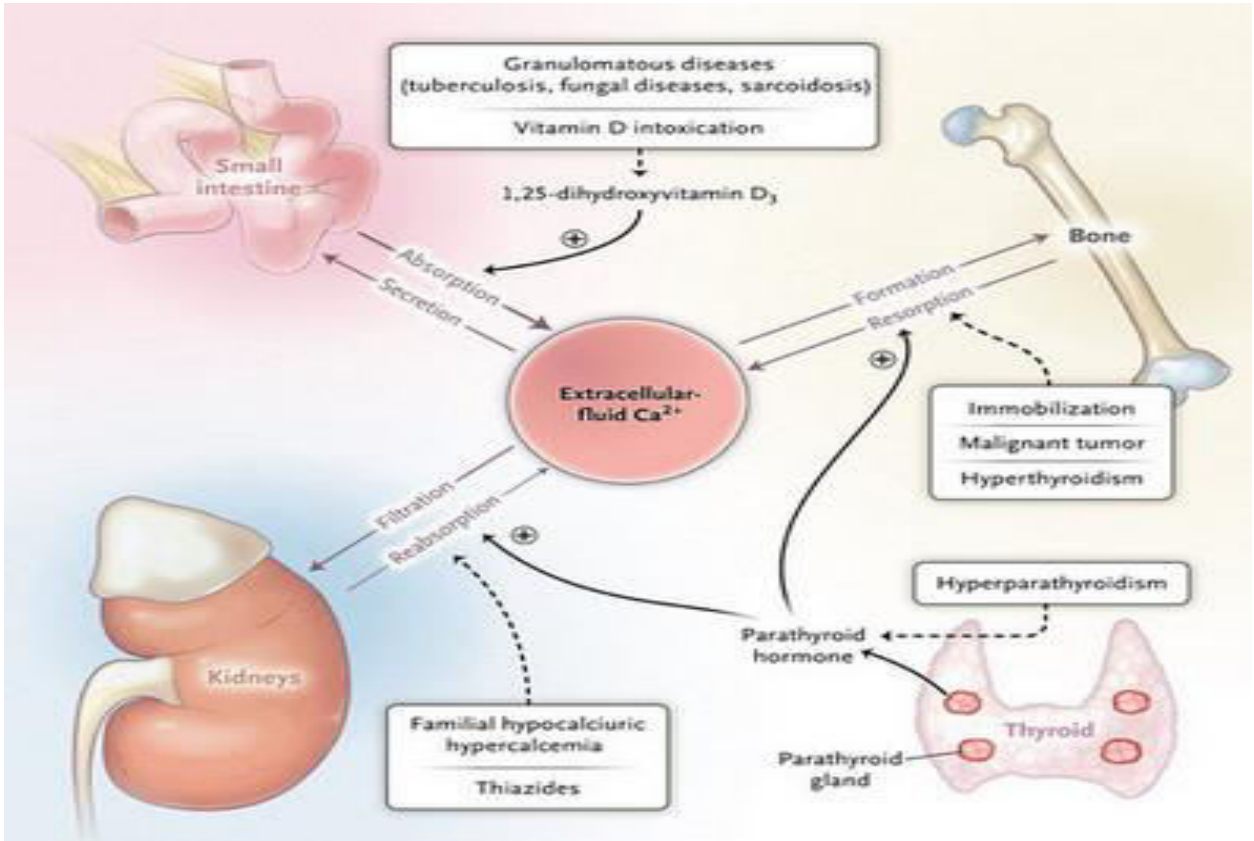

Fig 1. Major etiologies of hypercalcemia. The abnormal rise in the levels of PTH, 1,25-$[OH]_2$ D, or PTH-related proteins (PTHrP) in the blood causes hypercalcemia. Granulomatous diseases such as tuberculosis, fungal diseases or sarcoidosis causes increase in 1, 25- dihydroxyvitamin D_3 (vitamin D intoxication) which enhances intestinal absorption of Ca into the blood. Hyperparathyroidism leads to increased level of circulating PTH which increases renal Ca reabsorption and bone resorption, causing hypercalcaemia. Furthermore, Thiazides (anti-diuretic drugs) can enhance renal Ca reasorption into the extracellular fluid[7].

Table 1: Causes of hypercalcemia (Adapted from Endres, 2012[6])

Parathyroid hormone	Primary hyperparathyroidism - Sporadic, familial, MEN I or IIA
	Tertiary hyperparathyroidism
	Coexisting malignancy and primary hyperparathyroidism
	Ectopic PTH in malignancy (very rare)
Cancer	Humoral hypercalcaemia of malignancy - Parathyroid hormone-related protein(PTHrP)
	Local osteolysis - Cytokines, Chemokines, PTHrP
Vitamin D	Granulomatous disease (1,25$[OH]_2$ D) - Sarcoidosis, Tuberculosis, berylliosis, Coccidioidomycosis
	Vitamin D supplements, vitamin D metabolites or analog - (1,25[OH]2D)
Renal failure	Chronic renal failure with treatment with calcium and (1,25$[OH]_2$D) or vitamin D analogs
	Rhabdomyolysis and acute renal failure
	Renal transplant
Other endocrine disorders	Thyrotoxicosis
	Adrenal insufficiency
	Pheomochrocytoma
Medications	Thiazide diuretics
	Lithium
	Milk-alkali syndrome (calcium and antacids)
	Vitamin A
Other	Immobilization
	Familial hypocalcuric hypercalcemia

1, 25$(OH)_2$D = 1,25-dihydroxyvitamin D; MEN = Multiple endocrine neoplasia; PTH = Parathyroid hormone; PTHrP = Parathyroid hormone-related protein

Table 2: Differential diagnosis of hypercalcemia (Adapted from Maier and Levine; 2013[7])

Parathyroid-dependent hypercalcemia	**Parathyroid-independent hypercalcemia**
Primary hyperparathyroidism	Malignancy
• Adenoma	Local osteolitic osteolysis
• Hyperplasia	• Multiple bone metastasis
• Carcinoma (rare)	• Diffuse marrow infiltration
Tetiary hyperparathyroidism	Humoral hypercalcemia of malignancy
Familial hypocalcuric hypercalcemia	• Parathyroid hormone-related protein
Lithium	• 1, 25 Dihydroxyvitamin D
	Granulomatous disease
	Hyperthyroidism
	Adrenal insufficiency
	Medications
	• Thiazide
	• Vitamin D
	• Calcium
	• Vitamin A
	• Teriparatide
	Immobilization

Causes of hypercalcemia

Hypercalcemia is one of the consequences of the pathophysiology of diseases which inappropriately increase the levels of PTH, 1, 25-$[OH]_2$ D, or PTH-related proteins (PTHrP) in the blood[6]. These and other diseases that results to hypercalcemia are listed in table 1.

Differential diagnosis of hypercalcemia

Once hypercalcemia has been established and pseudo-hypercalcemia ruled out, it is very helpful to differentiate those etiologies of hypercalcemia that are PTH dependent as opposed to those that are PTH independent[7] (Table 2).

Hypercalcemia as a marker in hypercalcemia-related diseases

Primary hyperparathyroidism

Primary hyperparathyroidism (PHPT) is a disorder caused by hyperactive parathyroid glands with consequent hypercalcemia[15]. The finding of reproducible hypercalcemia in routine biochemical tests is an indication of PHPT, especially in individuals over 50 years old and in postmenopausal women[16]. Over secretion of PTH from one or more parathyroid glands causes hypercalcemia and constitutes the biochemical characteristic of PHPT[17]. A cohort study based on the population of Tayside used the following biochemical criteria for diagnosing PHPT: albumin-corrected serum calcium > 10.22 mg/dL (8.4-10.22 mg/dL) at least on 2 occasions, with serum PTH > 13.5 ng/L (4.5-31.05 ng/L); or albumin-corrected serum calcium > 10.22 mg/dL on only one occasion with serum PTH > 31.05 ng/l[19]. These values of serum PTH correspond to 20 pg/mL for assays with reference range of 10−65 pg/mL[18]. Although not all patients selected by these criteria and who have serum PTH levels within the reference range have morphological confirmation, it seems reasonable to consider inappropriately normal serum PTH levels, in the presence of hypercalcemia, as indicative of the diagnosis of PHPT.

Malignancies

Hypercalcemia is common in patients with cancer[19]. Cancer-induced bone disease can result from the primary disease itself, either due to circulating bone resorbing substances or metastatic bone disease, such as commonly occurs with breast, lung and prostate cancer[20,21]. They are related to local effects of metastatic deposit in bone and/or to generalized bone loss from tumour-produced systemically circulating bone resorbing hormones or cytokines[21,22]. These comprise parathyroid hormone-related protein (PTHrP), like in lung and breast cancer, or tumor stimulated secretion by the osteoblast of local bone resorbing factors such as receptor activator of nuclear factor kappa-B ligand (RANKL), interleukin (IL)-6 or IL-3, like in multiple myeloma[19,21,22].

Hypercalcemia is a severe complication arising in >80% of acute Adult T-cell leukaemia (ATL) patients and serves as a major prognostic factor for acute ATL disease outcome[23]. Osteolytic bone lesion has been reported in acute ATL patients, along with elevated levels of RANKL, MIP-1α, PTHrP, and IL-6, and is believed to contribute to hypercalcaemia[24]. Wnt-5a, a protein in humans that is encoded by the WNT5A gene, has been shown to increase osteoclastogenesis by enhancing RANKL expression in osteoclast precursors[26]. Recently, Bellon et al[22] demonstrate that ATL cells stimulate osteoclast differentiation and secreted Wnt5a is responsible for increases in RANKL. Therefore, one may reasonably assume that ATL patients may benefit from anti-Wnt5a therapy; as the therapy may also reduce osteolytic bone lesions and hypercalcaemia levels in ATL patients[26,27].

Granulomatous disorders

Hypercalcemia due to extra renal production of 1,25-$[OH]_2$ D has been associated with granulomatous disorders including sarcoidosis and tuberculosis[28,29] and also seen in lymphoma, a non-granulomatous condition[30]. Co-presentation of a parathyroid adenoma and a granulomatous disorder has been reported. However, granulomatous inflammation within a parathyroid adenoma is very rare. Yoshida et al[31] and Chaychi et al[32] reported hypercalcemia due to co-existing parathyroid adenoma and sarcoidosis in a 75-year-old woman and 67-year-old man respectively. Few cases of granulomatous inflammation within the parathyroid adenoma had been reported[33,34]. In these latter cases, the parathyroid glands had been demonstrated to be infiltrated by granulomatous inflammation of tuberculosis within parathyroid adenomas. However, a 50-year-old Caucasian woman with PHPT who was detected to have non-caseating granulomas within her parathyroid adenoma was reported by Anaforoğlu et al[35]. One may reasonably say that non-caseating granulomas could co-exist and also be detected within parathyroid adenoma in the elderly patients; and women may be more affected than men.

Treatment of hypercalcemia

Effective treatments reduce serum Ca by inhibiting bone resorption, increasing urinary Ca excretion,

or decreasing intestinal Ca absorption. The optimal choice varies with the cause and severity of hypercalcemia. Among others are:

Bisphosphonates

Bisphosphonates are potent in the treatment of severe hypercalcemia resulting from excessive bone resorption of any cause including malignancy-related hypercalcemia; and are the preferred agent for the treatment[36]. Zoledronic is among the currently available agents for the treatment of malignancy-associated hypercalcemia. Osteonecrosis of the jaw is a major side effect among others[37].

Gallium nitrate

Gallium inhibits osteoclastic bone resorption, in part via inhibition of an ATPase dependent proton pump on the osteoclast ruffled membrane, without being directly cytotoxic or acting as a metabolic toxin to bone cells[38]. Gallium also inhibits PTH secretion from parathyroid cells in vitro[39]. Unlike bisphosphonates, gallium appears to be effective in both PTHrP-mediated, and non-PTHrP-mediated hypercalcaemia[40]. The disadvantages of gallium include its potential for nephrotoxicity, and the need for continuous infusion over five days[41]. Thus, clinicians may prefer to use bisphosphonates rather than gallium nitrate for the treatment of hypercalcemia due to excessive bone resorption.

Glucocorticoids

Glucocorticoids are used to treat hypercalcemia due to excess availability of 1,25-$[OH]_2$D. Increased 1, 25-$[OH]_2$D production can occur in patients with chronic granulomatous diseases (e.g. sarcoidosis) and in occasional patients with lymphoma. Glucocorticoids (e.g. prednisone) will usually reduce serum calcium concentrations by decreasing 1,25-$[OH]_2$ D production by activated cells[28].

Denosumab

Denosumab is a human monoclonal antibody that binds and neutralizes human RANKL[7]. It prevents RANKL from activating RANK on osteoclasts thereby reducing bone resorption[22]. Therefore, RANKL inhibition through denosumab is a therapeutic target for preventing and treating bone metastases. Osteonecrosis of the jaw and atypical fractures of the femoral shaft have been reported with long-term use[7].

Current investigation and future research

Currently, there is one ongoing clinical trial studying the use of denosumab for refractory hypercalcemia, and the results are pending. Also there are several ongoing trials with an enrolment of over 20,000 patients to evaluate the efficacy of bisphosphonates for prevention of metastases in breast, prostate, and lung cancers; and multiple myeloma[42]. Results from these studies are likely to expand the role of bisphosphonates (especially zoledronic acid) and denosumab in the treatment of hypercalcemia-related disorders.

Conclusion

Hypercalcemia continues to be a clinical condition frequently encountered in both the outpatient and the inpatient setting. However, it is a useful marker for the diagnosis and prognosis of hypercalcemia-related diseases. Establishing a specific aetiology for hypercalcemia is still necessary to provide timely therapy beyond these general measures. Studies evaluating the effectiveness and adverse effects of a new potent inhibitor of osteoclast activity, denosumab, are underway.

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