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CLINICAL REVIEW: Rare Causes of Hypercalcemia

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Context: Although hypercalcemia is usually caused by primary hyperparathyroidism or malignancy, a number of other conditions can be important to consider. This review considers unusual causes of hypercalcemia that are generally not found in reviews on this subject.

Evidence Acquisition: Articles describing rarely reported associations between hypercalcemia and unusual causes were identified through a computer search of the terms hypercalcemia/etiology and through the references listed in those articles. We grouped the 58 different reports into categories defined by a presumed etiology: increased levels of 1,25-dihydroxyvitamin D or PTHrP, occult milk-alkali syndrome, and undefined mechanisms. Reports in infants and children are listed separately, as are reports of pseudohypercalcemia, situations that are not truly hypercalcemic because the ionized calcium is normal.

Evidence Synthesis: In some situations, as this review points out, a number of unusual causes of hypercalcemia are important to consider. The search for an elusive cause of hypercalcemia is best accomplished by the most likely potential mechanism. An orderly search in this manner is likely to reveal the underlying cause.

Conclusions: That so many patients have been described with rare and usually poorly understood causes of hypercalcemia highlights our incomplete understanding of calcium metabolism in humans and suggests additional areas in which directed clinical investigation might improve our knowledge of the normal metabolism of calcium. **(*J Clin Endocrinol Metab* 90: 6316–6322, 2005)**

HYPERCALCEMIA IS OFTEN a clue to the presence of unsuspected illness. Major textbooks and reviews correctly point out that the great majority of patients with elevated serum calcium will be found to have either primary hyperparathyroidism or malignancy, although the differential diagnosis is much longer. These other causes of hypercalcemia, including vitamin D intoxication, sarcoidosis, tuberculosis, some fungal infections, thyrotoxicosis, Addison's disease, milk-alkali syndrome related to the prescription of absorbable alkali and calcium, vitamin A intoxication, therapy with thiazide diuretics or lithium carbonate, familial hypocalciuric hypercalcemia, prolonged immobilization in patients with high skeletal turnover, and the recovery phase of rhabdomyolysis-associated acute renal failure, all amount to fewer than about 10% of all causes of hypercalcemia. Nevertheless, they are important to consider in certain clinical situations when the underlying cause of hypercalcemia cannot be attributed to primary hyperparathyroidism or overt malignancy. Despite the rather inclusive nature of this list of potential causes of hypercalcemia, there are still other more unusual etiologies reported in single patients or in small groups of patients. In the typical practice of many endocrinologists, patients are seen occasionally for whom the etiology of the hypercalcemia is not attributable to the illnesses listed above and never becomes well defined. In this review, we summarize published reports of patients with hypercalcemia whose etiology is so unusual that it is not listed in many reviews of hypercalcemia and is even more rarely considered in patients with hypercalcemia of obscure etiology. In some reports, a presumed etiology is offered (*e.g.* elevated levels of PTHrP). In others, no presumed mechanism has been defined. Some reports were published before the availability of current methodological tools for investigating hypercalcemia, but have been included because of the unusual clinical circumstances. This review adds to what has previously been reported in the literature for adults and children (1–6).

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Abbreviation: SLE, Systemic lupus erythematosus.

Methods

The reports included in this review were identified through a comprehensive computer-based search for hypercalcemia/etiology and a search of references in the identified reports. We excluded all forms of hypercalcemia of malignancy and hyperparathyroidism. We also excluded reports of hypercalcemia that occurred in patients with unusual medical problems in which the hypercalcemia seemed to be caused by a commonly encountered mechanism [*e.g.* tertiary hyperparathyroidism in Low's syndrome (7)]. We have grouped these reports into categories defined by a presumed etiology, although it is clear in some conditions associated with hypercalcemia that the mechanism underlying the hypercalcemia may differ among patients. For example, hypercalcemia in patients with tuberculosis has been reported to occur in patients with elevated (8), normal (9), or low (10) levels of serum 1,25-dihydroxyvitamin D.

Reports in Adults

Hypercalcemia mediated by elevated levels of calcitriol (Table 1)

In addition to sarcoidosis, tuberculosis, and some systemic fungal infections, other illnesses in which the pathology is characterized by granuloma formation have been associated with hypercalcemia in association with elevated levels of 1,25-dihydroxyvitamin D. It is presumed that the mechanism is similar to the previously described etiology: namely, in-

TABLE 1. Rare causes of hypercalcemia associated with elevated 1,25-dihydroxyvitamin D

1. Wegener's granulomatosis (11–13)
2. Cat scratch fever (14)
3. Crohn's disease (15)
4. Acute granulomatous pneumonia (16)
5. Hepatic granulomatosis in chronic dialysis (17)
6. Talc granulomatosis (18)
7. Silicone granulomatosis (19)
8. BCG therapy (20)
9. 8-Cl-cAMP therapy (21)
10. Lipoid pneumonia (22)
11. Subcutaneous fat necrosis of the newborn (86)

BCG, Calmette-Guérin bacillus.

creased conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitmin D. The activated macrophages within the granulomas, confirmed only in sarcoidosis-associated granulomas, are believed to contain 1α-hydroxylase activity that is responsible for the enzymatic activation of 25-hydroxyvitamin D.

In Wegener's granulomatosis, hypercalcemia associated with elevated levels of 1,25-dihydroxyvitamin D has been reported on at least three occasions (11, 12). In one patient, serum calcium and 1,25-dihydroxyvitamin D levels changed in parallel with cyclophosphamide and glucocorticoid therapy (13). Identical 18-yr-old male twins with cat scratch fever developed hypercalcemia and hypercalciuria with elevated 1,25-dihydroxyvitamin D levels. In each patient, serum and urinary calcium concentrations returned to normal when the bacterial infection was successfully treated (14). Hypercalcemia has also been described in two patients with Crohn's disease who had typical granulomas on bowel biopsy. With glucocorticoid therapy, the hypercalcemia and elevated 1,25-dihydroxyvitamin D levels both remitted (15). Acute granulomatous pneumonitis, a rare complication of methotrexate therapy, has been reported in association with hypercalcemia and inappropriately elevated levels of 1,25-dihydroxyvitamin D. Glucocorticoid therapy was effective in controlling the hypercalcemia and reducing the 1,25-dihydroxyvitamin D levels (16). Four patients receiving chronic hemodialysis developed hypercalcemia in association with hepatic granulomatosis of obscure etiology. The inappropriately normal PTH levels could well have been due to the accumulation of inactive PTH fragments, but the high-normal 1,25-dihydroxyvitamin D levels argue for a nonrenal source of enzymatic activation. In each instance, hypercalcemia responded promptly to glucocorticoid therapy (17).

Foreign material introduced into the human body often elicits a granulomatous inflammatory reaction. Hypercalcemia associated with elevated levels of 1,25-dihydroxyvitamin D has been reported in patients with granulomatous pneumoconiosis pneumonia caused by talc (18), a granulomatous reaction to silicone injections around the hips (19), and after a systemic reaction to Calmette-Guérin bacillus therapy for bladder cancer complicated by granulomatous hepatitis and marked hypercalcemia (20).

In some situations, the increase in 1,25-dihydroxyvitamin D has not been clearly associated with a granulomatous reaction. For example, an experimental analog of cAMP (8-Cl-cAMP) given to patients with advanced solid malignancies regularly caused hypercalcemia associated with high levels of 1,25-dihydroxyvitamin D (21). Lipoid pneumonia in a man with mental retardation was complicated by recurrent hypercalcemia and elevated levels of calcitriol (22).

Hypercalcemia caused by occult milk-alkali syndrome (Table 2)

Hypercalcemia with hypercalciuria and renal dysfunction is usually easily identified as milk-alkali syndrome in patients who ingest large amounts of calcium and absorbable alkalis (23). Rarely, the diagnosis may be undetected in patients who are either not aware that they are ingesting these substances or who conceal their use. Three patients have been reported from Taiwan who chewed betel nuts along with oyster shell powder, the latter to neutralize the bitter taste of the betel nuts. All patients had findings typical of milk-alkali syndrome (24, 25). Two patients who attempted suicide with buffered aspirin tablets each presented with hypercalcemia reasonably attributed to the associated ingestion of calcium carbonate (26). A woman with a severe eating disorder was hospitalized on three occasions with hypercalcemia caused by massive cheese ingestion in the setting of metabolic alkalosis and dehydration caused by recurrent vomiting and use of a thiazide diuretic (27). Similarly, a nurse with an extensive medical history developed extreme hypercalcemia caused by surreptitious ingestion of large amounts of calcium carbonate with a thiazide diuretic (28).

Hypercalcemia caused by PTHrP (Table 3)

Humoral hypercalcemia of malignancy is thought in many instances to be caused by secretion of PTHrP by the tumor (29–31). Although this presentation is now well recognized, hypercalcemia due to high serum levels of PTHrP in the setting of benign disease is very uncommon. A patient with systemic lupus erythematosus (SLE) with renal, central nervous system, and pleural involvement with diffuse lymphadenopathy presented with hypercalcemia accompanied by high levels of PTHrP. Large lymphocytes examined from an excised lymph node contained immunochemically identifiable PTHrP (32). The same group reported a 63-yr-old man with HIV-associated lymphadenopathy and recurrent hypercalcemia of unclear cause, whose cervical lymph node contained large lymphoid cells that stained positively for both PTHrP and its mRNA (33). Another young woman with a known diagnosis of SLE presented with bilateral chylous pleural effusions, diffuse pulmonary calcification, and lymphedematous bilateral breast enlargement. Elevated levels of PTHrP accompanied severe hypercalcemia, and calcium and PTHrP fluctuated in parallel in response to glucocorticoid therapy. Breast tissue did not stain for PTHrP, and no malignancy could be detected over 15 months of observation (34). Massive mammary hyperplasia during pregnancy in a 25-yr-old woman was accompanied by serious hypercalcemia, which responded promptly to bilateral

TABLE 2. Rare presentations of the milk-alkali syndrome

1. Oyster shell calcium in betel nut chewing (24, 25)
2. Overdose with buffered aspirin (26)
3. Massive cheese ingestion (27)
4. Munchausen's syndrome (28)

TABLE 3. Unusual PTHrP-mediated hypercalcemic conditions

1.	SLE (32)
2.	HIV-associated lymphadenopathy (33)
3.	Lymphedema of chest and pleural cavities (34)
4.	Massive mammary hyperplasia during pregnancy (35, 36)
5.	During late pregnancy and lactation in hypoparathyroidism (37–39, 41)
6.	With benign tumors of ovary and kidney, and in benign pheochromocytoma (43–46)

mastectomy (35). Subsequent immunostaining of the excised breast tissue demonstrated PTHrP reactivity in myoepithelial cells, but not in the normal breast tissue (36).

The development of hypercalcemia occurring just before and continuing for weeks after delivery was described in 1969 in two patients with hypoparathyroidism who had previously been well controlled with supplements of ergocalciferol. Neither woman breast fed, and hypercalcemia resolved quickly in one patient after a reduction in the dose of ergocalciferol (37). Hypercalcemia occurred during two successive pregnancies in an otherwise healthy woman with low PTH levels. During the second pregnancy, serum levels of PTHrP were found to be elevated, with persistent elevation of both serum calcium and PTHrP for several months after delivery (38). Another patient with surgical hypoparathyroidism became hypercalcemic while lactating after her first pregnancy, requiring withdrawal of calcium and calcitriol supplements. After a second pregnancy, her serum calcium remained normal off calcitriol and calcium, apparently supported by PTHrP, the serum concentration of which rose immediately after delivery to high levels and remained elevated during lactation for 72 wk (39). A number of groups have demonstrated that serum PTHrP levels are elevated during lactation and probably contribute substantially to the movement of calcium from the maternal skeleton to the mammary glands, causing some suppression of PTH (40, 41). Patients with hypoparathyroidism who are taking pharmacological amounts of vitamin D seem clearly at higher risk for hypercalcemia during the puerperium and lactation and are advised to reduce their intake of vitamin D until they are no longer breast feeding.

It is now clear that PTHrP has other important normal physiological functions (42). It is not surprising therefore to find a few reports of patients whose benign tumor was associated with PTHrP production and hypercalcemia. Benign ovarian tumor (43), renal adenoma (44), and pheochromocytomas (45, 46) have all been reported to be associated with hypercalcemia and elevated levels of PTHrP. When the benign tumor was removed, the hypercalcemia remitted. This syndrome has been dubbed by some humoral hypercalcemia of benignancy (44).

Hypercalcemia caused by medications (Table 4)

Several medications and chemicals other than calcium, vitamins A and D, lithium, and thiazide diuretics have been rarely associated with hypercalcemia. A 31-yr-old woman developed hypercalcemia in the setting of postpregnancy acute interstitial granulomatous nephritis when given omeprazole (47). Theophyline toxicity in 60 patients was complicated in 11 by hypercalcemia with normal levels of PTH, suggesting decreased sensitivity of the parathyroids to ionized calcium (48). High doses of human GH given to severely ill patients in a surgical intensive care unit appeared to cause hypercalcemia, which in some patients was severe, although it is not clear from the report whether parenteral nutrition and immobilization may have contributed to the hypercalcemia in some of the patients (49). Modest hypercalcemia in association with osteomalacia, bone pain, and fractures has been observed in several patients being treated with long-term parenteral nutrition, and in one small study was improved by removing vitamin D from the parenteral nutrition solutions (50). A 44-yr-old man developed polyarthritis and hypercalcemia shortly after his third vaccination for hepatitis B, eventually showing evidence of increased bone turnover and lytic bone lesions. A bone biopsy showed increased osteoclastic bone resorption, and his illness responded well to calcitonin, prednisone, furosemide, and clodronate (51). Although it is more often reported to cause a reduction in ionized calcium related to a chelating effect, foscarnet was believed to be the cause of hypercalcemia in two patients with AIDS complicated by cytomegalic infection (52). Manganese toxicity appears to cause hypercalcemia in addition to a characteristic neurological syndrome (53).

TABLE 4. Medications that have been unusually associated with hypercalcemia

1.	Omeprazole in acute interstitial nephritis (47)
2.	Theophylline toxicity (48)
3.	GH in intensive care unit patients (49)
4.	Parenteral nutrition (50)
5.	Foscarnet (52)
6.	Hepatitis B vaccination (51)
7.	8-Cl-cAMP chemotherapy (21)
8.	Manganese toxicity (53)

Hypercalcemia of unknown mechanism (Table 5)

Hypercalcemia has been reported in several medical settings in which the mechanisms of the hypercalcemia are unknown, either because they were reported before reliable measurements of PTH, PTHrP, or vitamin D metabolites were available or because despite measurements of these

TABLE 5. Rare causes of hypercalcemia in which the mechanism is not known

1.	Eosinophilic granuloma (54)
2.	Leprosy in rheumatoid arthritis (55)
3.	Mycobacterium avium complicating AIDS (56)
4.	Cytomegalic virus infection in AIDS (57)
5.	Chronic berylliosis (58)
6.	Nocardia asteroides pericarditis (59)
7.	Diffuse octeoclastosis (70)
8.	Paraffin granulomatosis (60)
9.	Brucellosis (61)
10.	Isolated ACTH deficiency (62)
11.	Glucocorticoid withdrawal (63)
12.	Hypocaloric diet in hypoparathyroidism (64)
13.	Advanced chronic liver disease (65)
14.	Type I Gaucher's disease with acute pneumonia (66)
15.	Lymphedema in SLE (67)
16.	Juvenile rheumatoid arthritis (68)
17.	Lymphadenopathy with high IL-6 (69)

substances, a mechanism of hypercalcemia could not be defined.

Several conditions characterized by granulomatous pathology have been reported in patients with hypercalcemia in whom 1,25-dihydroxyvitamin D levels were normal or low. Eosinophilic granuloma has been occasionally complicated by hypercalcemia, which has responded to treatment with glucocorticoids (54). A patient with leprosy complicating rheumatoid arthritis developed hypercalcemia in association with low levels of 1,25-dihydroxyvitamin D and responded to dapsone and prednisone (55). In addition to the occasional association of hypercalcemia with *Mycobacterium tuberculosis*, hypercalcemia was also observed in a patient with *Mycobacterium avium* complicating AIDS (56). In other cases of AIDS, hypercalcemia has been described in patients with diffuse cytomegalic virus infection (57). The granulomatous pneumonitis of chronic berylliosis in two patients was found to be associated with hypercalcemia, which resolved spontaneously and without explanation after several months (58). Hypercalcemia complicated pericarditis caused by *Nocardia asteroides* in a patient with hypoparathyroidism (59). It complicated the management of a 63-yr-old male with multiorgan failure histologically associated with the presence of widespread granulomatous lesions associated with paraffin 28 yr after a paraffin mammoplasty (60). Finally, serum calcium levels adjusted for serum albumin were found to be slightly higher in a large group of patients with brucellosis than in a control group, although the differences were small, and additional investigation of mechanisms were not performed (61).

Classic endocrine disorders, such as Addison's disease and thyrotoxicosis, are known to be complicated at times by hypercalcemia. In addition, isolated ACTH deficiency can result in hypercalcemia (62), and even glucocorticoid withdrawal after surgical cure of Cushing's syndrome has been associated with persistently elevated serum calcium levels (63). In a patient with hypoparathyroidism and a stable low serum calcium level while taking large doses of vitamin D, a hypocaloric diet was complicated by hypercalcemia sufficiently severe to require treatment with glucocorticoids and iv fluids (64). Advanced chronic liver disease was complicated by hypercalcemia in 10 patients without concomitant malignancy. Most had mild azotemia, and PTH levels were suppressed or in the low-normal range, as were levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D (65).

A patient with type I Gaucher's disease presented with acute pneumonia and hypercalcemia postulated to be caused by pathological activation of osteoclasts via undegraded glucocerebroside activation of proinflammatory cytokines (66). The lymphadema syndrome described above in association with SLE has been reported to occur in the presence of normal levels of PTHrP as well (67). A boy with juvenile rheumatoid arthritis and persistent hypercalcemia had a serum activity that stimulated bone resorption *in vitro* and was neutralized by antibody to IL-1β (68). A 24-yr-old man presented with widespread musculoskeletal pain, lymphadenopathy, hypercalcemia, and hyperphosphatemia. Histological and chemical indices of bone turnover were high, and serum levels of IL-6 were 100-fold higher than normal. The patient improved after administration of iv pamidronate (69). Finally, a 31-yr-old African woman presented with multiple painful, lytic bony lesions associated with systemic inflammatory symptoms responding to glucocorticoids, but eventually died of severe hypercalcemia. Histological examination of three of the lesions showed only intense osteoclastic bone resorption by normal-appearing osteoclasts, with some foci of osteoblastic new bone formation (70).

Diseases Occurring in Childhood (Table 6)

Children present with hypercalcemia probably less frequently than adults, but the causes that we recognize to be common in adults are also common in children. Young children and infants, however, have been reported with hypercalcemia in association with a number of conditions seen almost exclusively in that population.

Heritable diseases of childhood

A number of monogenic heritable disorders are complicated by hypercalcemia. Jansen's disease, a heritable disorder of dwarfism, is characterized by short stature, scoliosis, short limbs, cranial abnormalities, and hypercalcemia in some cases. It is associated with constitutive activation of the PTH/PTHrP receptor (71) and, somewhat surprisingly, is not associated with osteitis fibrosis cystica even after many years (72). Hypophosphatasia is caused by loss of function mutations in the gene for tissue-nonspecific alkaline phosphatase. Phenotypic presentation varies widely, but in the more severe infantile form, extensive demineralization caused by failure of osteoblastic new bone formation leads to multiple fractures and early mortality. Hypercalcemia probably results from failure of bone matrix mineralization in the face of unimpeded osteoclastic bone resorption (73). Williams-Beuren syndrome, an autosomal dominant heritable disorder, causes elfin facies, supravalvular aortic stenosis, stenosis of pulmonary arteries, short stature, and developmental delay and often presents with hypercalcemia during infancy. Deletions in maternal or paternal chromosome 7q11.23 have been identified in most patients (74). Although evidence supporting a mechanism of increased intestinal calcium absorption or reduced calcitonin excretion has been offered, there is at present no defined mechanism causing the hypercalcemia that has gained consensus (75). In most children, the hypercalcemia resolves by 4 yr of age. A child with primary oxalosis who had required both renal and liver transplants developed recurrent hypercalcemia with lytic

TABLE 6. Rare causes of hypercalcemia in infants and young children

Associated with heritable diseases of childhood
1. Jansen's osteodystrophy (71, 72)
2. Hypophosphatasia (73)
3. Williams-Beuren syndrome (75)
4. Primary oxalosis (76)
5. Congenital lactase deficiency (77)
6. Down's syndrome (78, 79)
Associated with acquired diseases of childhood
1. Renal tubular acidosis (80–83)
2. Phosphate depletion in severe prematurity (84)
3. Subcutaneous fat necrosis of the newborn (86)
4. Infantile hypothyroidism (87)

bone lesions. Bone biopsy demonstrated numerous oxalate crystals associated with macrophages and increased areas of bone erosion (76). Infants with congenital lactase deficiency frequently present with hypercalcemia, hypercalciuria, and nephrocalcinosis. The mechanism of the hypercalcemia is unclear, and it quickly resolves on a lactose-free diet (77). Down's syndrome complicated by hypercalcemia has been reported in four patients, probably, but not clearly, on the basis of excessive calcium supplementation (78, 79).

Acquired diseases of childhood

In infants, hypercalcemia has been reported to complicate renal tubular acidosis. So-called Lightwood's syndrome is rarely seen now (80), but at times was complicated by hypercalcemia in children not exposed to supplemental dietary calcium (81, 82). Severe hypercalcemia caused hospitalization of a 21-d-old male subsequently shown to have distal renal tubular acidosis, which had not resolved by age 4 yr (83). Very premature infants with sustained hypercalcemia and hypophosphatemia corrected their metabolic abnormalities when phosphate supplements were added to expressed breast milk (84) or total parenteral nutrition supplementation. The authors of this report ascribed the hypercalcemia to severe phosphate depletion syndrome, which has been observed in laboratory rodents, but not in adult humans (85).

Subcutaneous fat necrosis of the newborn, an unusual form of self-limited localized panniculitis, often presents shortly after birth in infants who have sustained prenatal or perinatal complications, especially birth asphyxia and meconium aspiration. The etiology of this condition is unknown, but it is often accompanied by hypercalcemia associated with low levels of PTH and is mediated by elevated levels of 1,25-dihydroxyvitamin D, presumably secreted by macrophages participating in the granulomatous inflammatory process. The presence of hypercalcemia carries with it a mortality as high as 15%, although serum calcium usually is normal by 4 months of age (86)

Hypothyroidism in infants, especially when congenital, is associated with mild hypercalcemia. Increased intestinal calcium absorption secondary to increased sensitivity to vitamin D has been proposed as a mechanism, although levels of vitamin D metabolites are not usually high (87).

Pseudohypercalcemia (Table 7)

Persistently elevated total serum calcium in the presence of a normal ionized serum calcium level is rare and has been termed pseudohypercalcemia. Under normal circumstances about half the serum calcium concentration is bound to albumin. Therefore, in patients with elevations of serum albumin, mild hypercalcemia may be observed in the presence of normal free calcium (88). Two patients with essential thrombocythemia were found to have hypercalcemia that fluctuated directly with changes in platelet counts. The researchers believed that the best explanation for the hypercalcemia was the *in vitro* release of calcium from within activated platelets similar to the phenomenon of *in vitro* hyperkalemia that occurs in such patients (89). Pseudohypercalcemia in the setting of M-protein disorder has been ascribed to abnormal calcium binding by the IgM-κ paraprotein of a patient with Waldenstrom's macroglobulinemia (90) and by the IgG κ (91) and IgG λ (92) paraproteins as well. A well-studied case demonstrated that an IgG λ M protein in a patient with myeloma quantitatively bound 4 mol calcium/mol IgG (93). Two patients with IgM paraproteinemia were found to have pseudohypercalcemia caused by interference by the paraprotein with calcium measurements by an autoanalyzer, probably caused by hyperviscosity.

TABLE 7. Pseudohypercalcemia

1. High serum albumin (88)
2. Thrombocythemia (89)
3. Calcium binding to M-proteins (90, 93)

Conclusion

Successful management of hypercalcemia usually depends upon determining its etiology. In most patients the cause is obvious from the clinical setting and the results of serum assays of PTH, PTHrP, and vitamin D metabolites. The practicing clinician faced with hypercalcemia not attributable to the more common etiologies listed in most reviews of the subject may benefit from considering some of the rarer entities listed above. As presented in this review, the unusual associations between hypercalcemia and a number of diverse disorders demonstrates that our knowledge of the mechanisms of hypercalcemia is far from complete and points, in some cases, to undescribed humoral and cellular processes that may be important in the pathogenesis of hypercalcemia. As we learn more about the mechanisms underlying these associations, it is likely that we will gain new knowledge about the normal physiological processes that control calcium and skeletal metabolism.

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