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# Confusion and hypercalcemia in an 80-year-old man

A RETIRED 80-YEAR-OLD MAN presented to the emergency department after 10 days of increasing polydipsia, polyuria, dry mouth, confusion, and slurred speech. He also reported that he had gradually and unintentionally lost 20 pounds and had loss of appetite, constipation, and chronic itching. He denied fevers, chills, night sweats, nausea, vomiting, and abdominal pain.

**Medical history.** He had type 2 diabetes mellitus that was well controlled by oral hypoglycemics, hypothyroidism treated with levothyroxine in stable doses, and chronic hepatitis C complicated by liver cirrhosis without focal hepatic lesions. He also had hypertension, well controlled with hydrochlorothiazide and losartan. For his long-standing pruritus he had tried prescription drugs including gabapentin and pregabalin without improvement. He had also seen a naturopathic practitioner, who had prescribed supplements that relieved the symptoms.

**Examination.** The patient was in no acute distress. He appeared thin, with a weight of 140 lb and a body mass index of 21 kg/m<sup>2</sup>. His temperature was 36.8°C (98.2°F), blood pressure 198/82 mm Hg, heart rate 72 beats per minute, respiratory rate 16 breaths per minute, and oxygen saturation 97%. His skin was without jaundice or rashes. The mucous membranes in the oropharynx were dry.

Neurologic examination revealed mild confusion, dysarthria, and ataxic gait. Sensation to light touch, pinprick, and vibration was intact. Generalized weakness was noted. Cranial nerves II through XII were intact. Deep tendon reflexes were symmetrically globally suppressed. Asterixis was absent. The

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remainder of the physical examination was unremarkable.

**Laboratory values in the emergency department.** We initially suspected he had symptomatic hyperglycemia, but a bedside blood glucose value of 113 mg/dL ruled this out. Other initial laboratory values:

- Blood urea nitrogen 31 mg/dL (reference range 9–24)
- Serum creatinine 1.7 mg/dL (0.73–1.22; an earlier value had been 1.0 mg/dL)
- Total serum calcium 14.4 mg/dL (8.6–10.0)

Complete blood cell counts were unremarkable. Computed tomography of the head was negative for acute pathology.

In view of the patient's hypercalcemia, he was given aggressive intravenous fluid resuscitation (2 L of normal saline over 2 hours) and was admitted to the hospital. His laboratory values on admission are shown in Table 1. Fluid resuscitation was continued while the laboratory results were pending.

## CAUSES OF HYPERCALCEMIA

1 Based on this information, which is the most likely cause of this patient's hypercalcemia?

- Primary hyperparathyroidism
- Malignancy
- Hyperthyroidism
- Hypervitaminosis D
- Sarcoidosis

Traditionally, the workup for hypercalcemia in an outpatient starts with measuring the serum parathyroid hormone (PTH) level. Based on the results, a further evaluation of PTH-mediated vs PTH-independent causes of hy-

The hypercalcemia workup in an outpatient starts with measuring PTH

**TABLE 1**

**Our patient’s laboratory values on admission**

Substance	Value	Reference range
Ionized calcium, mmol/L	1.72	1.08–1.30
Phosphorus, mg/dL	7.0	2.5–4.5
Parathyroid hormone, pg/mL	11	15–65
Parathyroid-related hormone, pmol/L	0.3	< 2.0
25-Hydroxyvitamin D, ng/mL	365.5	31–80
1,25-Dihydroxyvitamin D, pg/mL	59.5	15–60
Vitamin A, µg/dL	48	20–120
Thyroid-stimulating hormone, mIU/L	1.380	0.400–5.500
Serum protein electrophoresis and 24-hour urinary protein electrophoresis with immunofixation	No M protein	
Beta-2 microglobulin, mg/mL	6.2	0.3–1.9
Alpha fetoprotein, ng/mL	20.1	< 11
Angiotensin-converting enzyme, mg/L	32	< 40

**Primary hyperparathyroidism and malignancy together account for 90% of all cases of hypercalcemia**

percalcemia would be initiated.

Primary hyperparathyroidism and malignancy account for 90% of all cases of hypercalcemia. The serum PTH concentration is usually high in primary hyperparathyroidism but low in malignancy, which helps distinguish the conditions from each other.<sup>1</sup>

**Primary hyperparathyroidism**

In primary hyperparathyroidism, there is overproduction of PTH, most commonly from a parathyroid adenoma, though parathyroid hyperplasia or, more rarely, parathyroid carcinoma can also overproduce the hormone.

PTH increases serum calcium levels through 3 primary mechanisms: increasing bone resorption, increasing intestinal absorption of calcium, and decreasing renal excretion of calcium. It also induces renal phosphorus excretion.

Typically, in primary hyperparathyroidism, the increases in serum calcium are small (with serum levels of total calcium rising to no higher than 11 mg/dL) and often intermittent.<sup>2</sup> Our patient had extremely high serum

calcium, low PTH, and high phosphorus levels—all of which are inconsistent with primary hyperparathyroidism.

**Malignancy**

In some solid tumors, the major mechanism of hypercalcemia is secretion of PTH-related peptide (PTHrP) through promotion of osteoclast function and also increased renal absorption of calcium.<sup>3</sup> Hematologic malignancies (eg, multiple myeloma) produce osteoclast-activating factors such as RANK ligand, lymphotoxin, and interleukin 6. Direct tumor invasion of bone can cause osteolysis and subsequent hypercalcemia.<sup>4</sup> These mechanisms are usually associated with a fall in PTH.

Less commonly, tumors can also increase levels of 1,25-dihydroxyvitamin D or produce PTH independently of the parathyroid gland.<sup>5</sup> There have also been reports of severe hypercalcemia from hepatocellular carcinoma due to PTHrP production.<sup>6</sup>

Our patient is certainly at risk for malignancy, given his long-standing history of hepatitis C and cirrhosis. He also had a mildly elevated alpha fetoprotein level and suppressed PTH. However, his PTHrP level was normal, and ultrasonography done recently to screen for hepatocellular carcinoma (recommended every 6 months by the American Association for the Study of Liver Diseases in high-risk patients) was negative.<sup>7</sup>

Multiple myeloma screening involves testing with serum protein electrophoresis with immunofixation in combination with either a serum free light chain assay or 24-hour urine protein electrophoresis with immunofixation. This provides a 97% sensitivity.<sup>8</sup> In this patient, these tests for multiple myeloma were negative.

**Hyperthyroidism**

As many as half of all patients with hyperthyroidism have elevated levels of ionized serum calcium.<sup>9</sup> Increased osteoclastic activity is the likely mechanism. Hyperthyroid patients have increased levels of serum interleukin 6 and increased sensitivity of bone to this factor. This cytokine induces differentiation of monocytic cells into osteoclast precursors.<sup>10</sup> These patients also have normal or low PTH levels.<sup>9</sup>

Our patient was receiving levothyroxine for hypothyroidism, but there was no evidence

that the dosage was too high, as his thyroid-stimulating hormone level was within an acceptable range.

**Hypervitaminosis D**

Vitamin D precursors arise from the skin and from the diet. These precursors are hydroxylated in the liver and then the kidneys to biologically active 1,25-dihydroxyvitamin D (Figure 1).<sup>11</sup> Vitamin D's primary actions are in the intestines to increase absorption of calcium and in bone to induce osteoclast action. These actions raise the serum calcium level, which in turn lowers the PTH level through negative feedback on the parathyroid gland.

Most vitamin D supplements consist of the inactive precursor cholecalciferol (vitamin D<sub>3</sub>). To assess the degree of supplementation, 25-hydroxyvitamin D levels, which indicate the size of the body's vitamin D reservoir, are measured.<sup>11,12</sup>

Our patient's 25-hydroxyvitamin D level is extremely elevated, well beyond the 250-ng/mL upper limit that is considered safe.<sup>13</sup> His low PTH level, lack of other likely causes, and history of supplement use point toward the diagnosis of hypervitaminosis D.

**Sarcoidosis**

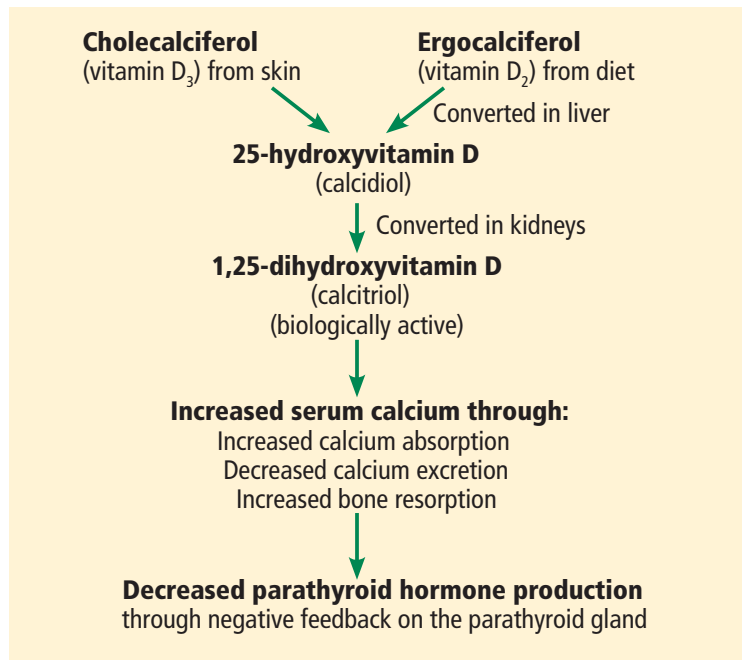
Up to 10% of patients with sarcoidosis have hypercalcemia that is not mediated by PTH. Hypercalcemia in sarcoidosis has several potential mechanisms, including increased activity of the enzyme 1-alpha hydroxylase with a subsequent increase in physiologically active 1,25-dihydroxyvitamin D<sub>3</sub> production.<sup>14</sup>

Our patient had elevated levels of 25-hydroxyvitamin D, but his biologically active 1,25-dihydroxyvitamin D level remained within the laboratory's reference range.

**LESS LIKELY CAUSES OF HYPERCALCEMIA**

**2** Which of the following would be least likely to cause hypercalcemia?

- Thiazide diuretics
- Over-the-counter antacid tablets
- Lithium
- Vitamin A supplementation
- Proton pump inhibitors



**FIGURE 1.** Vitamin D metabolism.

**Thiazide diuretics**

This class of drugs is well known to cause hypercalcemia. The most familiar of the mechanisms is a reduction in urinary calcium excretion. There is also an increase in intestinal absorption of dietary calcium. Evidence is increasing that most patients (as many as two-thirds) who develop hypercalcemia while using a thiazide diuretic have subclinical primary hyperparathyroidism that is uncovered with use of the diuretic.

Of importance, the hypercalcemia that thiazide diuretics cause is mild. In a series of 72 patients with thiazide-induced hypercalcemia, the average serum calcium level was 10.7 mg/dL.<sup>15</sup>

Our patient was receiving a thiazide diuretic but presented with severe hypercalcemia, which is inconsistent with thiazide-induced hypercalcemia.

**Over-the-counter antacid tablets**

Calcium carbonate, a popular over-the-counter antacid, can cause a milk-alkali syndrome that is defined by ingestion of excessive calcium and alkalotic substances, leading to metabolic alkalosis, hypercalcemia, and renal insufficiency. To induce this syndrome generally requires up to 4 g of calcium intake daily, but even lower levels (1.0 to 1.5 g) are known to cause it.<sup>16</sup>

**The patient had been taking > 60,000 IU of vitamin D per day; the recommended dose is ≤ 4,000 IU/day**

### Lithium

Lithium is known to cause hypercalcemia. Multiple mechanisms have been proposed, including direct action on renal tubules and the intestines leading to calcium reabsorption and stimulation of PTH release. Interestingly, parathyroid gland hyperplasia has been noted in long-term users of lithium. An often-proposed mechanism is that lithium increases the threshold at which the parathyroid glands slow their production of PTH, making them less sensitive to serum calcium levels.<sup>17</sup>

### Vitamin A supplementation

Multiple case reports have linked hypercalcemia to ingestion of large doses of vitamin A. The mechanism is thought to be increased bone resorption.<sup>18,19</sup>

Although our patient reported supplement use, he denied taking vitamin A in any form.

### Proton pump inhibitors

Proton pump inhibitors are not known to cause hypercalcemia. On the contrary, case reports suggest that prolonged use of proton pump inhibitors is associated with hypocalcemia and hypomagnesemia, although the mechanism is still not fully understood. A low magnesium level is known to reduce PTH secretion and also skeletal responsiveness to PTH, which can lead to profound hypocalcemia.<sup>20</sup>

### ■ CASE CONTINUED

On further questioning, the patient revealed that the supplement prescribed by his naturopathic practitioner contained vitamin D. Although he had been instructed to take 1 tablet weekly, he had begun taking it daily with his other routine medications, resulting in a daily dose in excess of 60,000 IU of cholecalciferol (vitamin D<sub>3</sub>). The recommended dose is no more than 4,000 IU/day.

The supplement was immediately discontinued. His hydrochlorothiazide was also held due to its known effect of reducing urinary calcium excretion.

### ■ INITIAL TREATMENT OF HYPERCALCEMIA

**3** Which of the following treatments is not recommended as part of this patient's initial treatment?

- Bisphosphonates
- Calcitonin
- Intravenous fluids
- Furosemide

Our patient met the criteria for the diagnosis of hypercalcemic crisis, usually defined as an albumin-corrected serum calcium level higher than 14 mg/dL associated with multiorgan dysfunction resulting from the hypercalcemia.<sup>21</sup> The mnemonic “stones, bones, abdominal moans, and psychic groans” captures the renal, skeletal, gastrointestinal, and neurologic manifestations.<sup>1</sup>

### Bisphosphonates

Bisphosphonates are analogues of pyrophosphonates, which are normally incorporated into bone. Unlike pyrophosphonates, bisphosphonates inhibit osteoclast function. They are often used to treat hypercalcemia of any cause, although they are currently approved by the US Food and Drug Administration for treating hypercalcemia of malignancy only. As intravenous monotherapy, they are superior to other forms of treatment and are among the first-line agents in management.

Two bisphosphonates shown to be effective in hypercalcemia are zoledronate and pamidronate. Pamidronate begins to lower serum calcium levels within 2 days, with a peak effect at around 6 days.<sup>22</sup> However, in studies comparing the 2 drugs, zoledronate has been shown to be more effective in normalizing serum calcium, with the additional benefit of having a much more rapid infusion time.<sup>23</sup> Zoledronate is contraindicated in patients with creatinine clearance less than 30 mL/min; however, pamidronate may continue to be used.<sup>24</sup>

### Calcitonin

This hormone inhibits bone resorption and increases excretion of calcium in the kidneys. It is not recommended for use alone because of its short duration of action and tachyphylaxis, but it can be used in combination with other agents, particularly in hypercalcemic crisis.<sup>22</sup> It has the most rapid onset (within 2 hours) of the available medications, and when used in combination with bisphosphonates it produces a more substantial and rapid reduction in serum calcium.<sup>25,26</sup>

All management approaches call for fluid repletion as an initial step in hypercalcemia

In a patient such as ours, with severe hypercalcemia and evidence of neurologic consequences, calcitonin should be used for its rapid and effective action in lowering serum calcium as other interventions take effect.

**Intravenous fluids**

Like our patient, many patients with significant hypercalcemia have volume depletion as a result of calciuresis-induced polyuria. Many also have nephrogenic diabetes insipidus from the cytotoxic effect of calcium on renal cells, leading to further volume depletion.<sup>27</sup>

All management approaches call for fluid repletion as an initial step in hypercalcemia. However, for severe hypercalcemia, volume resuscitation alone is unlikely to completely correct the imbalance. In addition to correcting dehydration, giving fluids increases glomerular filtration, allowing for increased secretion of calcium at the distal tubule.<sup>28</sup> The recommendation is 2.5 to 4 L of normal saline over the first 24 hours, with continued aggressive hydration until good urine output is established.<sup>21</sup>

Our patient, in addition to having acute kidney injury thought to be due to prerenal azotemia, appeared to be volume-depleted and was given aggressive intravenous hydration.

**Furosemide**

Furosemide inhibits calcium reabsorption at the thick ascending loop of Henle, but this effect depends on the glomerular filtration rate. While our patient would likely eventually benefit from furosemide, it should not be considered the first-line therapy, as diuretic use in the setting of volume depletion can cause circulatory collapse.<sup>29</sup> A relative contraindication was his presentation with acute kidney injury.

**LONG-TERM TREATMENT**

**4** In the continued management of a patient with vitamin D toxicity with severe hypercalcemia, which of the following provides prolonged benefit?

- Intravenous hydrocortisone
- Fluid repletion
- Pamidronate
- Calcium-restricted diet

Much has been postulated concerning the mechanism of vitamin D intoxication and subsequent hypercalcemia. Studies have shown it is not an increase in dietary calcium absorption that drives the hypercalcemia but rather an increase in bone resorption. As such, bisphosphonates such as pamidronate have been shown to have a dramatic and rapid effect on severe hypercalcemia from vitamin D toxicity. The duration of action varies but is typically between 1 and 2 weeks.<sup>22,30</sup>

Corticosteroids such as hydrocortisone are also indicated in situations of severe toxicity. They block the action of 1-alpha-hydroxylase, which converts inactive 25-hydroxyvitamin D to the active 1,25-dihydroxyvitamin D. Corticosteroids have also been shown to more directly reduce calcium resorption from bone and intestine in addition to increasing calciuresis.<sup>31</sup> A small study in the United Kingdom noted that while bisphosphonates and steroids were equally effective in reducing serum calcium levels, bisphosphonates accomplished this reduction more rapidly, with a time to therapeutic effect of 9 days as opposed to 22 days.

Fluid hydration, though necessary, is unlikely to produce complete correction on its own, as previously discussed.

**THE PATIENT RECOVERS**

The patient was treated with intravenous fluids over 3 days and received 1 dose of pamidronate. Calcitonin was provided over the first 48 hours after presentation to more rapidly reduce his calcium levels. He was advised to avoid taking the supplements prescribed by his naturopathic practitioner.

On follow-up with an endocrinologist 1 week later, his symptoms had entirely resolved, and his calcium level was 10.5 mg/dL.

**1 week later, his symptoms had entirely resolved, and his calcium level was 10.5 mg/dL**

**TAKE-AWAY POINTS**

- A good medication history includes over-the-counter products such as vitamin D supplements, as more and more people are taking them.
- The level of 25-hydroxyvitamin D should be monitored within 3 to 4 months after initiating treatment for vitamin D deficiency.<sup>11</sup>
- Vitamin D toxicity can have profound

consequences, which are usually seen when levels of 25-hydroxyvitamin D rise above 250 ng/mL.<sup>13</sup>

- The Institute of Medicine recommends that the dosage of vitamin D supplements

be no more than 4,000 IU/day and that doses may need to be lowered to account for concurrent use of hypercalcemia-inducing drugs and other vitamin D-containing supplements.<sup>32</sup>

### REFERENCES

1. Carroll MF, Schade DS. A practical approach to hypercalcemia. *Am Fam Physician* 2003; 67:1959–1966.
2. al Zahrani A, Levine MA. Primary hyperparathyroidism. *Lancet* 1997; 349:1233–1238.
3. Mundy GR, Edwards JR. PTH-related peptide (PTHrP) in hypercalcemia. *J Am Soc Nephrol* 2008; 19:672–675.
4. Ratcliffe WA, Hutchesson AC, Bundred NJ, Ratcliffe JG. Role of assays for parathyroid-hormone-related protein in investigation of hypercalcaemia. *Lancet* 1992; 339:164–167.
5. Hewison M, Kantorovich V, Liker HR, et al. Vitamin D-mediated hypercalcemia in lymphoma: evidence for hormone production by tumor-adjacent macrophages. *J Bone Miner Res* 2003; 18:579–582.
6. Ghobrial MW, George J, Mannam S, Henien SR. Severe hypercalcemia as an initial presenting manifestation of hepatocellular carcinoma. *Can J Gastroenterol* 2002; 16:607–609.
7. Zhao C, Nguyen MH. Hepatocellular carcinoma screening and surveillance: practice guidelines and real-life practice. *J Clin Gastroenterol* 2016; 50:120–133.
8. Rajkumar SV, Kumar S. Multiple myeloma: diagnosis and treatment. *Mayo Clin Proc* 2016; 91:101–119.
9. Burman KD, Monchik JM, Earll JM, Wartofsky L. Ionized and total serum calcium and parathyroid hormone in hyperthyroidism. *Ann Intern Med* 1976; 84:668–671.
10. Iqbal AA, Burgess EH, Gallina DL, Nanes MS, Cook CB. Hypercalcemia in hyperthyroidism: patterns of serum calcium, parathyroid hormone, and 1,25-dihydroxyvitamin D3 levels during management of thyrotoxicosis. *Endocr Pract* 2003; 9:517–521.
11. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357:266–281.
12. Wolpowitz D, Gilchrist BA. The vitamin D questions: how much do you need and how should you get it? *J Am Acad Dermatol* 2006; 54:301–317.
13. Jones G. Pharmacokinetics of vitamin D toxicity. *Am J Clin Nutr* 2008; 88:582S–586S.
14. Inui N, Murayama A, Sasaki S, et al. Correlation between 25-hydroxyvitamin D3 1 alpha-hydroxylase gene expression in alveolar macrophages and the activity of sarcoidosis. *Am J Med* 2001; 110:687–693.
15. Wermers RA, Kearns AE, Jenkins GD, Melton LJ 3rd. Incidence and clinical spectrum of thiazide-associated hypercalcemia. *Am J Med* 2007; 120:911.e9–e15.
16. Patel AM, Goldfarb S. Got calcium? Welcome to the calcium-alkali syndrome. *J Am Soc Nephrol* 2010; 21:1440–1443.
17. Shapiro HI, Davis KA. Hypercalcemia and “primary” hyperparathyroidism during lithium therapy. *Am J Psychiatry* 2015; 172:12–15.
18. Farrington K, Miller P, Varghese Z, Bailod RA, Moorhead JF. Vitamin A toxicity and hypercalcaemia in chronic renal failure. *Br Med J (Clin Res Ed)* 1981; 282:1999–2002.
19. Frame B, Jackson CE, Reynolds WA, Umphrey JE. Hypercalcemia and skeletal effects in chronic hypervitaminosis A. *Ann Intern Med* 1974; 80:44–48.
20. Florentin M, Elisaf MS. Proton pump inhibitor-induced hypomagnesemia: a new challenge. *World J Nephrol* 2012; 1:151–154.
21. Ahmad S, Kuraganti G, Steenkamp D. Hypercalcemic crisis: a clinical review. *Am J Med* 2015; 128:239–245.
22. Nussbaum SR, Younger J, Vandepol CJ, et al. Single-dose intravenous therapy with pamidronate for the treatment of hypercalcemia of malignancy: comparison of 30-, 60-, and 90-mg dosages. *Am J Med* 1993; 95:297–304.
23. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001; 19:558–567.
24. Perazella MA, Markowitz GS. Bisphosphonate nephrotoxicity. *Kidney Int* 2008; 74:1385–1393.
25. Bilezikian JP. Management of acute hypercalcemia. *N Engl J Med* 1992; 326:1196–1203.
26. Ralston SH. Medical management of hypercalcaemia. *Br J Clin Pharmacol* 1992; 34:11–20.
27. Garofeanu CG, Weir M, Rosas-Arellano MP, Henson G, Garg AX, Clark WF. Causes of reversible nephrogenic diabetes insipidus: a systematic review. *Am J Kidney Dis* 2005; 45:626–637.
28. Hosking DJ, Cowley A, Bucknall CA. Rehydration in the treatment of severe hypercalcaemia. *Q J Med* 1981; 50:473–481.
29. Suki WN, Yium JJ, Von Minden M, Saller-Hebert C, Eknayan G, Martinez-Maldonado M. Acute treatment of hypercalcemia with furosemide. *N Engl J Med* 1970; 283:836–840.
30. Selby PL, Davies M, Marks JS, Mawer EB. Vitamin D intoxication causes hypercalcaemia by increased bone resorption which responds to pamidronate. *Clin Endocrinol* 1995; 43:531–536.
31. Davies M, Mawer EB, Freemont AJ. The osteodystrophy of hypervitaminosis D: a metabolic study. *Q J Med* 1986; 61:911–919.
32. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Ross AC, Taylor CL, Yaktine AL, et al, eds. *Dietary reference intakes for calcium and vitamin D*. Washington, DC: National Academies Press (US); 2011.

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