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Hypercalcemia and vitamin A: A vitamin to keep in mind

ABSTRACT

Vitamin A, like many things in life, should be consumed in appropriate amounts. Excessive intake of preformed vitamin A, such as that found in supplements and animal sources (animal liver, fish liver oil, dairy, and eggs), is associated with multisystem effects that can include bone resorption and hypercalcemia. Hence, vitamin A toxicity should be explored in unexplained cases of parathyroid hormone-independent hypercalcemia. Serum retinol levels can be helpful in the diagnosis, but the results must be interpreted with caution since they do not always reflect total body levels. Treatment involves supportive care and withdrawal of vitamin A sources, especially preformed ones. Given the long half-life of retinol, normalization of serum levels can take several months.

KEY POINTS

Vitamin A is present in two forms, ie, preformed (retinoids) or as a precursor (carotenoids).

Vitamin A toxicity occurs only from over-ingestion of preformed vitamin A, found in animal sources, supplements, and medications, because absorption of preformed vitamin A is under minimal regulation at the level of the small intestine.

Acute vitamin A toxicity can present with multisystem manifestations including hepatic, neurologic, skin, mucous membrane, and musculoskeletal damage.

Chronic ingestion of vitamin A beyond the recommended daily amount can be associated with increased bone resorption, reduced bone formation, hypercalcemia, and increased risk of fractures.

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VITAMIN A TOXICITY IS OFTEN overlooked in the diagnostic evaluation of hypercalcemia, which itself is often detected incidentally during unrelated laboratory testing.^{1,2} The diagnostic evaluation of hypercalcemia starts with establishing the role of parathyroid hormone (PTH) in its pathogenesis. An elevated PTH level may indicate primary hyperparathyroidism, tertiary hyperparathyroidism, or familial hypocalciuric hypercalcemia. A low PTH should trigger an evaluation for hypercalcemia induced by PTH-related peptide (PTHrP). Vitamin A toxicity should be considered in the diagnostic workup along with malignancy, bone metastasis, vitamin D or calcium toxicity, increased 1,25-hydroxyvitamin D production (eg, from granulomatous disorders and lymphomas), hyperthyroidism, monoclonal gammopathy, and immobility.³

In this article, we explore vitamin A toxicity in the differential diagnosis of hypercalcemia.

■ A CASE SCENARIO: AN ELDERLY WOMAN WITH HYPERCALCEMIA

An elderly woman presented to our outpatient endocrinology practice with mild asymptomatic hypercalcemia. She reported taking 2 different multivitamin tablets for many years. On laboratory testing, her PTH level was suppressed, PTHrP was normal, 1,25-hydroxyvitamin D and thyroid function tests were normal, and serum and urine electrophoresis did not reveal monoclonal gammopathy (Table 1). She was not taking any prescription medications that could cause hypercalcemia.

After an extensive workup, her serum vitamin A (retinol) levels were found to be elevated to almost twice the upper limit of normal, indicating vitamin A toxicity. Her multivita-

TABLE 1
Results of initial laboratory tests

Comprehensive metabolic panel	Value ^a	Reference range
Protein	7.2 g/dL	6.3–8.0
Albumin	4.6 g/dL	3.9–4.9
Calcium	10.6 mg/dL	8.5–10.2
Bilirubin	0.7 mg/dL	0.2–1.3
Alkaline phosphatase	77 U/L	34–123
Aspartate aminotransferase	26 U/L	13–35
Alanine aminotransferase	24 U/L	7–38
Glucose	155 mg/dL	74–99
Blood urea nitrogen	23 mg/dL	7–21
Creatinine	1.08 mg/dL	0.58–0.96
Sodium	138 mmol/L	136–144
Potassium	4.0 mmol/L	3.7–5.1
Chloride	104 mmol/L	97–105
Bicarbonate	21 mmol/L	22–30
Parathyroid hormone (PTH), intact	14 pg/mL	15–65
Calcium, ionized	1.42 mmol/L	1.08–1.30
Vitamin D (25 hydroxy)	38.2 ng/mL	31–80
Vitamin D (1,25 dihydroxy)	29.7 pg/mL	15–60
PTH-related peptide	< 2.0 pmol/L	0.0–3.4
Thyroid stimulating hormone	1.1 μU/mL	0.27–4.2
Vitamin A/retinol	1.99 mg/L	0.3–1.2
Protein electrophoresis urine	No definitive M protein identified	
Protein electrophoresis serum	No definitive M protein identified	

^aSignificant values are in boldface.

Preformed vitamin A retinoids are derived from animal products; carotenoids occur in plant-based foods

mins were discontinued, resulting in improved retinol and calcium levels several months later.

■ PREFORMED VS PRECURSOR VITAMIN A

Vitamin A supports the integrity of epithelial cells and structural proteins across the human body. It also has a role in normal cellular immunity, supporting the functions of natural killer cells and macrophages. It is vital for vi-

sion and is especially important in pregnancy, as it contributes to organogenesis during early fetal development.⁴⁻⁸

Vitamin A is the term applied to a group of fat-soluble retinoids—retinol, retinal, and retinyl esters. Vitamin A can be ingested as preformed molecules (activated vitamin A), or as vitamin A precursors (“provitamin A”) called carotenoids, which the body converts to reti-

TABLE 2

Vitamin A in various food products and over-the-counter supplements, ranked by % RDI

Food product or supplement	Form of vitamin A	Vitamin A content (µg RAE)	Percentage of RDI for adult men
Beef liver, 3 ounces	Activated (preformed)	6,582	731
Cod-liver oil, 1 tablespoon	Activated	4,080	453
Sunmark One Daily Women's Multivitamin, 1 tablet ^a	Mixed (80% activated, 20% provitamin A)	2,500	277
Sweet potato, 1 whole	Provitamin A	1,403	156
Centrum Silver Adults, 1 tablet	Mixed (60% activated, 40% provitamin A)	750	83
One A Day, Women's Complete Multivitamin ^a	Mixed (90% activated, 10% provitamin A)	700	78
Spinach, ½ cup	Provitamin A	573	64
Ricotta cheese, part skim, 1 cup	Activated	263	31
Egg, boiled, 1 large	Activated	75	8
Broccoli, ½ cup	Provitamin A	60	7
Yogurt, 1 cup	Activated	32	4
Chicken meat, ½ breast piece	Activated	5	1

^a Product used by our patient at the time of presentation.

RAE = retinol activity equivalents; RDI = recommended daily intake

Based on information in references 5, 17, 18, 19, and 20.

Vitamin A toxicity results from excessive intake of preformed vitamin A

noids.^{4,5} Preformed vitamin A is derived naturally from animal products such as dairy, fish oils, eggs, liver, and meat, whereas carotenoids occur naturally in plant-based foods such as carrots, sweet potatoes, and pumpkins.⁴⁻⁶ Preformed vitamin A and carotenoids can be found in the same over-the-counter (OTC) products and in prescription medications such as isotretinoin and tretinoin. If a supplement contains both preformed vitamin A and carotenoids, the ratio is usually reported on the ingredient label on the back of the bottle.

■ THE ROLE OF ABSORPTION IN VITAMIN A TOXICITY

Vitamin A toxicity results from excessive intake of preformed vitamin A, not from expo-

sure to vitamin A precursors because of the way absorption of these substances is regulated at the level of the gut.^{4,5,9,10}

Absorption of vitamin A occurs in the lumen of the small intestine. It is picked up in the duodenum by micelles formed with the aid of bile acids released from the gallbladder.^{4-6,9,10} Retinoids are hydrolyzed further and converted to retinol, and retinol uptake is facilitated through the brush border of the small intestine via transport proteins.

The efficiency of absorption of preformed vitamin A through gut transport proteins is high—in the range of 70% to 90%—and does not vary based on the ingested amount. Carotenoids, on the other hand, are not transported by carriers but by passive diffusion across the

TABLE 3

Recommended daily intake of vitamin A

Age	Sex, subpopulations	Recommended daily intake of vitamin A (µg RAE)
0–6 months	Male and female	400 ^a
7–12 months	Male and female	500 ^a
1–3 years	Male and female	300
4–8 years	Male and female	400
9–13 years	Male and female	600
14 years or older	Male	900
14 years or older	Female	700
14–18 years	Female – pregnant	750
14–18 years	Female – lactating	1,200
19–50 years	Male	900
19–50 years	Female	700
19–50 years	Female – pregnant	770
19–50 years	Female – lactating	1,300

^aValue extrapolated from vitamin A content of consumed breast milk by healthy infants. RAE = retinol activity equivalents

Based on information in references 4 and 5.

luminal border, and this results in poor absorption efficiency, in the range of 9% to 22%. In addition, upon ingestion of excessive amounts of carotenoids, the efficiency of luminal diffusion decreases, which further protects against toxicity from over-ingestion. Based on this, OTC vitamins containing carotenoids may be safer for patients than those containing preformed vitamin A.¹¹ The patient described in our case scenario was taking a supplement with vitamin A content that was above the recommended daily intake (RDI).

Once absorbed, most vitamin A is stored in the liver and released into the bloodstream, where retinol-binding protein transports it to its target tissues.¹² If the body's supply of vitamin A changes, the liver modifies the release of retinol into the serum to maintain normal plasma retinol levels. However, a normal plasma retinol level does not

always indicate normal total body levels of vitamin A, and low or high retinol levels can indicate a significant abnormality of the body's vitamin A stores.^{12,13} The half-life of vitamin A is estimated to be 128 days, so it can take many months for retinol levels to normalize after vitamin A toxicity.⁴

■ CHALLENGES TO APPROPRIATE VITAMIN A INTAKE

OTC supplements are the most common source of clinically significant preformed vitamin A ingestion. In a national survey, approximately half of the US population reported using an OTC supplement, with 28% to 37% reporting using a multivitamin that contains vitamin A and with a higher proportion in the elderly.¹⁴ This high percentage of use is concerning, given that multivitamin products are not under US Food and Drug Administration regulation, and reported vitamin ingredients are often inaccurate and underestimated.¹⁵ Manufacturers can sell vitamins OTC, often with quantities above the recommended daily intake, and packaging, flavoring, and chewable formulations make the products more desirable, increasing the risk of vitamin A toxicity in children.¹⁶

The proposed standardized measure for vitamin A is retinol activity equivalents (RAE) in micrograms. The RDI of vitamin A is 900 µg RAE for men and 700 µg RAE for women.⁴⁻⁶ The RDI for children varies with age but can range from 300 µg RAE to 700 µg RAE.^{4,5} **Table 2** shows vitamin A content in different food products and supplements and compares them with the RDI.^{5,17-20} **Table 3** shows the RDI of vitamin A based on sex and age groups.^{4,5}

■ CONSEQUENCES OF EXCESSIVE VITAMIN A INTAKE

The tolerable upper daily intake level of vitamin A is approximately 3,000 µg RAE.⁴ Higher levels increase the risk of vitamin A-induced chronic liver damage and fetal teratogenicity.²¹⁻²⁴ Importantly, chronic daily ingestion of preformed vitamin A above the recommended intake (700 to 900 µg RAE) but below the tolerable upper intake (3,000 µg RAE) may still be harmful, especially to the musculoskeletal system.^{5,25,26}

Acute ingestion (ie, a single dose) of more than 200,000 µg RAE of preformed vitamin A is required to cause acute hypervitaminosis A syndrome in adults.⁶ This condition is uncommon and was seen historically in Atlantic explorers who inadvertently ate large amounts of animal livers containing preformed vitamin A.^{5,10}

Acute over-ingestion of vitamin A can affect multiple systems:

- Neurologic—increased intracranial pressure, headaches, dizziness, vomiting, delirium, and confusion
- Hepatobiliary—nausea, vomiting, and jaundice resulting from hepatitis progressing to cirrhosis
- Musculoskeletal—periosteal bone resorption, osteopenia, elevated alkaline phosphatase, and hypercalcemia
- Skin and mucous membranes—dry, fragile skin, brittle nails, loss of hair.^{10,27}

In clinical practice, however, chronic over-ingestion of vitamin A is a much more likely cause of vitamin A toxicity.

■ VITAMIN A AND THE SKELETON: BONE RESORPTION AND HYPERCALCEMIA

The mechanism of vitamin A-induced bone resorption and hypercalcemia is poorly understood. It is hypothesized to be secondary to increased osteoclastic activity, reduced osteoid, suppression of osteoblastic activity, and hormonal dysregulation of calcium homeostasis of parathyroid hormone and vitamin D.^{28–31} Vitamin A and vitamin D exhibit a complex relationship that occurs at the molecular transcription level, where they can have stimulatory or inhibitory effects on each other.^{32–35} However, the effects of vitamin A toxicity on bone resorption have been observed independent of serum calcium, phosphate, and vitamin D levels.³⁶

Results of studies in humans are consistent with those of animals. In a study of 39 pediatric patients treated for neuroblastoma with a high-dose vitamin A derivative, hypercalcemia developed in twelve (31%) patients.³⁷ In a study of adult patients treated for multiple myeloma with all-trans retinoic acid, hypercalcemia was observed in 3 of 6 patients treated.³⁸ Myalgia, arthralgia, and skeletal pain were consistently seen in a case series of patients di-

agnosed with hypervitaminosis A syndrome.³⁹

Animal studies have shown an increased incidence of bone fractures with exposure to large amounts of vitamin A.⁴⁰ In humans, even if the ingestion of preformed vitamin A is increased moderately and incrementally over a long period, skeletal manifestations may occur. In cross-sectional and nested-control studies conducted in 2 counties in Sweden, each 1,000-µg RAE increment intake of daily vitamin A above the 1,500-µg RAE threshold was associated with a 68% increase in the risk of hip fracture.²⁵

In a US study,²⁶ a prospective cohort of 72,337 nurses was followed for 18 years. Those who ingested more than 2,000 µg RAE of vitamin A daily had almost double the risk of hip fracture compared with those who ingested less than 500 µg RAE.²⁶ In another prospective cohort of postmenopausal women followed for a mean duration of 9.5 years in the United States,⁴¹ the risk of hip fracture was 1.18 times greater in those who used a vitamin A-containing supplement, although the difference did not reach statistical significance (95% confidence interval 0.99–1.41). In a longitudinal cohort of 2,322 men followed for a median of 30 years,⁴² a baseline serum retinol level in the upper quartiles was associated with a significantly higher risk of hip fracture and all fractures.

■ TREATMENT RELIES ON ANECDOTAL EXPERIENCE

Treatment of vitamin A toxicity is based on anecdotal data from case reports.^{6,36–38} The recommendation is to withdraw sources of vitamin A, especially of preformed vitamin A, and provide standard supportive treatment for multisystem manifestations. Limited data are available regarding the role of antiresorptive agents in treating vitamin A-related skeletal adverse effects and hypercalcemia. With discontinuation of vitamin A ingestion, retinol and calcium levels are expected to improve within weeks to months, although longitudinal prognostic data are limited.

■ TAKE-HOME MESSAGE: CONSIDER VITAMIN A IN HYPERCALCEMIA

Consumption of plant-derived precursor vitamin A (carotenoids) is harmless, but excessive

Absorption of preformed vitamin A through gut transport proteins is highly efficient

consumption of preformed vitamin A commonly found in OTC supplements and some animal products can have negative multisystem manifestations. Vitamin A is an often overlooked cause of hypercalcemia, thought to stem from its adverse effect on the skeletal system through stimulation of bone resorption and inhibition of bone formation. In the setting of unexplained PTH-independent hypercalcemia, serum retinol levels should be

checked but interpreted with caution, as they do not always reflect total body levels. Treatment involves withdrawal of vitamin A sources and supportive care. Given the long half-life of retinol, normalization can take several months.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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