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

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 vision 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 retinol.

TABLE 1

Results of initial laboratory tests

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

*Significant values are in boldface.
noids. 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. 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 exposure to vitamin A precursors because of the way absorption of these substances is regulated at the level of the gut.

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. 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 gut wall.
HYPERCALCEMIA AND VITAMIN A

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.4–7 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

TABLE 3
Recommended daily intake of vitamin A

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

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

Based on information in references 4 and 5.
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 diagnosed 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. 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.

REFERENCES

34. Joo NS, Yang SW, Song BC, Yeum KJ. Vitamin A intake, serum


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