

# Hypercalcaemia Secondary to Hypervitaminosis A in a Patient with Chronic Renal Failure

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## ABSTRACT

*Vitamin A toxicity is a well-described medical condition with a multitude of potential presenting signs and symptoms. It can be divided into acute and chronic toxicity. Serum vitamin A concentrations are raised in chronic renal failure even with ingestion of less than the usual toxic doses. Hypercalcaemia can occasionally be associated with high levels of vitamin A but it is rare. In this report, we describe a 67-year old female patient with chronic kidney disease who was taking vitamin A supplements for approximately 10 years. The patient had worsening of her chronic kidney disease over the last years and developed chronic hypercalcaemia. Her vitamin A level was elevated with a daily intake of 7000 IU. The vitamin A supplement was stopped. A few months later, vitamin A level diminished substantially and serum calcium levels returned to normal.*

**Keywords:** Chronic renal failure, hypercalcaemia, hypervitaminosis, kidney failure

# Hipercalcemia Secundaria a la Hipervitaminosis A en un Paciente con Insuficiencia Renal Crónica

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## RESUMEN

*La toxicidad de la vitamina A es una condición médica bien descrita que presenta un sinnúmero de potenciales signos y síntomas. Puede ser dividida en toxicidad aguda y crónica. Las concentraciones séricas de vitamina A se elevan con la insuficiencia renal crónica, incluso con la ingestión de dosis tóxicas por debajo de lo habitual. En ocasiones, la hipercalcemia puede estar asociada con altos niveles de vitamina A, pero esto raramente ocurre. En este informe, describimos a una paciente de 67 años de edad con enfermedad renal crónica, que estuvo tomando suplementos de vitamina A por aproximadamente 10 años. La paciente sufrió un empeoramiento de su enfermedad renal crónica en los últimos años, y desarrolló hipercalcemia crónica. Su nivel de vitamina A se elevó con una ingesta diaria de 7000 UI. El suplemento de vitamina A fue suspendido. Unos meses más tarde, el nivel de vitamina A nivel disminuyó sustancialmente, y los niveles de calcio sérico volvieron a la normalidad.*

**Palabras claves:** Insuficiencia renal crónica, insuficiencia renal, hipercalcemia, hipervitaminosis

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## INTRODUCTION

Vitamin A plays an important role in vision, bone growth and cellular differentiation. Vitamin A toxicity has a multitude of potential presenting signs and symptoms. Acute vitamin A toxicity occurs in adults when a single dose of > 660 000 units (> 200 mg) of vitamin A is ingested (1). Chronic toxicity

occurs with long-term ingestion of vitamin A doses higher than 10 times the recommended daily allowance [RDA] (2). It can occur at lower doses in patients with chronic renal failure. Hypercalcaemia is rarely associated with high levels of vitamin A and is thought to be secondary to the effect of vitamin A on bone to stimulate osteoclastic resorption and/or inhibit osteoblastic formation.

## CASE PRESENTATION

We present the case of a 67-year old female patient known to have hypertension and chronic kidney disease stage IV status

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pre-dialysis who was seen in the office for chronic hypercalcaemia. The patient has had hypercalcaemia for the last 10 years with her calcium level ranging between 10.8 mg/dL and 14.8 mg/dL. Her hypercalcaemia was thought initially to be related to secondary hyperparathyroidism. The patient also had multiple hospitalizations for hypercalcaemia with a calcium level around 14 mg/dL improving after hydration.

The patient reported unintentional weight loss of 70 pounds in the last two years, hair loss, generalized fatigue and constipation. She had right nephrectomy in 1984 for renal cell carcinoma, history of recurrent kidney stones and chronic hypercalcaemia. She takes telmisartan (micardis) 80 mg daily, atenolol 100 mg twice daily, furosemide 20 mg daily, clonidine 0.1 mg twice daily, amlodipine 10 mg daily, fenofibrate, fish oil, niacin, aspirin and multivitamins including "ABC plus" (Vitamin A 3500 IU + multivitamin). She reported that she has been taking two tablets of the "ABC plus" which is a total of 7000 IU of vitamin A daily for the last 10 years. She denied calcium supplement intake or Tums<sup>®</sup>. She does not have any family history of hypercalcaemia or recurrent kidney stones. The patient had a blood pressure of 160/80 mmHg, pulse of 78 beats per minute, weight of 120 lbs. Her physical examination was normal except for mild lower extremities pitting oedema. Her blood tests in the office showed: white blood cell (WBC):  $10 \times 10^9/L$ , haemoglobin of 8.8 mg/dL, haematocrit of 26.7 mg/dL, platelet count of  $347/mm^3$ , sodium of 138 mEq/L, potassium of 3.9 mEq/L, creatinine of 5.3 mg/dL (normal range: 0.6–1), calcium 12.7 mg/dL (normal range: 8.5–10.5), ionized calcium 5.9 mg/dL (normal range: 3.8–4.6), phosphorus 7.5 mg/dL, albumin 4.1 g/dL, cholesterol 277 mg/dL (normal range: 180–235), thyroid stimulating hormone (TSH) 1.32 UIU/ml (0.4–4.68), parathyroid hormone (PTH) 11 pg/mL (normal range: 9–78 pg/mL), PTH-related protein (PTHrP) < 0.3 (normal range < 0.3), urinary calcium 79 mg/24 hours, 25-vitamin D 25 (normal range: 10–55) and 1,25 vitamin D 17.2 (normal range: 24–65); serum and urine protein electrophoresis were normal. Dual-energy X-ray absorptiometry (DXA) bone densitometry showed osteoporotic spine. Her vitamin A level was 222 mg/dL (normal range: 30–90). Her normal PTH level ruled out secondary hyperparathyroidism as the cause for her hypercalcaemia since PTH should be elevated in secondary hyperparathyroidism. Also, since she has low urinary calcium but no family history of hypercalcaemia, it is unlikely that she has familial hypercalcaemic hypocalciuric syndrome; in such cases, there should not be a history of recurrent kidney stones. Although malignancy is less likely since the patient had this problem for a long time and an occult malignancy should have been overt by now, a work-up including mammography, Pap smear and computed tomography (CT) of the chest, abdomen and pelvis were normal. The patient had normal colonoscopy two years previously as a work-up for her anaemia. The patient was then diagnosed with hypervitaminosis A and vitamin A supplement was stopped. A few months later, vitamin A and serum calcium levels returned to normal.

## DISCUSSION

In 1953, Shaw and Niccoli (3) first described hypercalcaemia as a complication of hypervitaminosis A. Since that time, few additional cases have been reported with this unique association (4).

Vitamin A is a lipid-soluble compound referred to as retinoic acid. There are two main forms of vitamin A: provitamin A carotenoids (beta-carotene and others), and preformed vitamin A. Provitamin A carotenoids are found in plants and are rarely metabolized to vitamin A, whereas preformed vitamin A (retinol, retinal, retinoic acid and retinyl esters) is mostly found in animal sources of food and in vitamin supplements and represents the most active form of vitamin A. The RDA for vitamin A is given as retinol activity equivalents (RAE), where one RAE = 1 microgram retinol or 3.3 IU. The RDA for adult males is 900 micrograms daily, and for females 700 micrograms daily.

The initial steps in metabolism depend on the type of vitamin A ingested. Usually the excessive intake of vitamin A from plant sources is unlikely to cause toxicity since there are many forms of provitamin A but beta-carotene is the only one that is metabolized by mammals into vitamin A. By contrast, absorption and storage of preformed vitamin A in animal liver or dietary supplements is efficient, and toxicity can occur if excessive quantities are ingested, especially in patients with renal failure.

Seventy to ninety per cent of vitamin A from the diet is absorbed in the intestine. Absorption of vitamin A is very rapid, with maximum absorption occurring two to six hours after digestion (5). Within the intestinal lumen, the vitamin is incorporated into a micelle and absorbed across the brush border into the enterocytes. Within the enterocyte, precursors of vitamin A (carotenoids) are converted to active forms of the vitamin. The newly formed products are then packaged into chylomicrons and transported throughout the body (6). After leaving the enterocytes, chylomicrons release triglycerides upon arriving at extra-hepatic cells; however, vitamin A remains within the chylomicron. The chylomicron is then taken up by the liver, metabolized to retinol and stored. When needed, retinol is mobilized from the liver and requires the use of a carrier for transport through the blood. Retinol binding protein (RBP), a single chain polypeptide glycoprotein, is the primary plasma transport protein for retinol (vitamin A); it binds retinol in 1:1 to form RBP-retinol complex. This complex then delivers retinol to specific receptors of the retina, skin, gonads, lungs, salivary glands and other tissues. Tissues are then able to take the retinol up as needed *via* cellular retinoid-binding protein (5). Retinoic acid is believed to be manufactured by the cells as needed. Therefore, transport of retinoic acid is likely not substantial. Instead, the cell possesses intra-cellular proteins that regulate the amount of retinoic acid produced.

The kidneys are the main paths of RBP and retinol excretion from the body. This is achieved mainly *via* renal catabolism and glomerular filtration (5). Those persons suffering

from renal disease often experience elevated serum levels of RBP and retinol and therefore must be more aware of vitamin A toxicity.

Vitamin A toxicity can be divided into acute, chronic or teratogenic. Acute toxicity generally occurs at doses of 25 000 IU/kg while chronic toxicity can occur at 4000 IU/kg daily for six to 15 months (7). Chronic toxicity occurs with long-term ingestion of vitamin A doses in amounts higher than 10 times the daily value (8). It can occur at lower doses in case of renal failure. Several other factors can increase the toxicity of vitamin A, including underlying liver disease, alcoholism, and the use of some drugs, such as tetracyclines. Vitamin A toxicity occurs when the maximum limit for liver stores of retinoids is exceeded so the excess vitamin A enters the circulation causing systemic toxicity. However, in people with renal failure, 4000 IU daily can cause substantial damage (9). In our case, the patient had worsening of her kidney function over the last years which led to increase in vitamin A level and therefore increase in the hospitalizations secondary to hypercalcaemia.

Symptoms and signs of toxicity include dry skin, nausea, headache, fatigue, irritability, anorexia, liver disease and hepatomegaly, hair loss and alopecia, hyperostosis, high cholesterol and increased cerebrospinal fluid pressure [pseudotumour cerebri] (10). In osteoporosis, hypercalcaemia was rarely associated with hypervitaminosis A. In addition, vitamin A toxicity can contribute to hypercalcaemia in patients undergoing haemodialysis, probably by an osteolytic effect. Multivitamin preparations containing vitamin A should therefore be prescribed with caution in these patients (11).

Hypercalcaemia in the setting of vitamin A toxicity has been associated with three groups of patients. The first group of patients is those who receive ATRA (all-trans retinoic acid) therapy for treatment of acute promyelocytic leukaemia (12). The second group involves haemodialysis patients developing vitamin A toxicity related to consumption of nutritional supplements containing pharmacological doses of vitamin A (13). The last group includes few case reports describing hypercalcaemia in association with massive ingestion of vitamin A. One case described vitamin toxicity caused by enteral feeding using commercially available tube-feed formula (4). To our knowledge, this is the first reported case describing hypercalcaemia secondary to vitamin A toxicity in a patient with chronic kidney disease who is not on dialysis.

There is some evidence that intake of vitamin A in the high-normal range may have adverse effects on bone health by reducing bone mineral density that may result in osteoporosis. It is not clear exactly how vitamin A influences bone metabolism; in a prospective cohort study of postmenopausal women, long-term intake of a diet high in retinol (vitamin A) was associated with an increased risk of osteoporotic fractures (14). Similarly, high serum retinol levels were associated with an increased fracture risk in men (15). Vitamin A probably acts directly on bone to stimulate osteoclastic resorption and/or inhibit osteoblastic formation (4). In certain circumstances

such as dehydration, renal failure or immobilization, this could result in hypercalcaemia. Thus high doses of vitamin A may compromise bone health, but the threshold at which clinically relevant effects are seen remains to be determined (16). Whereas the recommended daily requirement of vitamin A in adults is 5000 IU, our patient was taking 7000 IU daily. Although this dose would be unlikely to produce problems in patients with normal renal function, care should be taken in prescribing these vitamins to a patient with impaired renal function.

## CONCLUSION

Vitamin A toxicity can occur with long-term ingestion of vitamin A supplements 10 times higher than the recommended daily dose; it can occur at lower doses in patients with chronic renal failure. It is thought that the factors that may contribute to the high vitamin A concentration in patients with chronic renal failure is the diminished metabolism of retinol to retinoic acid, which is excreted by the kidneys (17), and increased concentrations of retinol-binding protein found in chronic renal failure (18). It appears that the high serum vitamin A level that occurs in patients with chronic renal failure has toxic effects. Hypercalcaemia can occur as a consequence of the effect of vitamin A on bone probably by an osteolytic effect, though the precise mechanism is not well understood. Multivitamin preparations containing vitamin A should therefore be prescribed with caution in these patients.

## REFERENCES

1. Olson JA. Upper limits of vitamin A in infant formulas, with some comments on vitamin K. *J Nutr* 1989; **119**: 1820.
2. Penniston KL, Tanumihardjo SA. The acute and chronic toxic effects of vitamin A. *Am J Clin Nutr* 2006; **83**: 191.
3. Shaw EW, Niccoli JZ. Hypervitaminosis A: report of a case in an adult male. *Ann Intern Med* 1953; **39**: 131–4.
4. Bhalla KH, Ennis DM, Ennis ED. Hypercalcaemia caused by iatrogenic hypervitaminosis A. *J Am Diet Assoc* 2005; **105**: 119–21.
5. Ross AC. Vitamin A. In: Shils M, Olson J, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease*. 9<sup>th</sup> edition. Baltimore: Williams & Wilkins; 1999: 305–13.
6. Groff JL, Gropper SS, Hunt SM. The fat soluble vitamins. In: *Advanced Nutrition and Human Metabolism*. Minneapolis: West Publishing Company; 1995: 284–324.
7. Rosenbloom M. Vitamin toxicity. eMedicine. [updated 2013 Jun 3]. Available from: <http://www.emedicine.com/emerg/topic638.htm>
8. Soprano DR, Soprano KJ. Retinoids as teratogens. *Ann Rev Nutr* 1995; **15**: 111.
9. Penniston KL, Tanumihardjo SA. The acute and chronic toxic effects of vitamin A. *Am J Clin Nutr* 2006; **83**: 191–201.
10. Lippe B, Hensen L, Mendoza G, Finerman M, Welch M. Chronic vitamin A intoxication. A multisystem disease that could reach epidemic proportions. *Am J Dis Child* 1981; **135**: 634–6.
11. Farrington K, Miller P, Varghese Z, Bailloled RA, Moorhead JF. Vitamin A toxicity and hypercalcaemia in chronic renal failure. *Br Med J (Clin Res Ed)* 1981; **282**: 1999–2002.
12. Sakamoto O, Yoshinari M, Rikhiishi T, Fujiwara I, Imaizumi M, Tsuchiya S et al. Hypercalcaemia due to all-trans retinoic acid therapy for acute promyelocytic leukemia: a case of effective treatment with bisphosphonate. *Pediatr Int* 2001; **43**: 688–90.
13. Fishbane S, Frei GL, Finger M, Dressler R, Sibiliger S. Hypervitaminosis A in two hemodialysis patients. *Am J Kidney Dis* 1995; **25**: 346–9.

14. Feskanich D, Singh V, Willett WC, Colditz GA. Vitamin A intake and hip fractures among postmenopausal women. *JAMA* 2002; **287**: 47.
15. Michaelsson K, Lithell H, Vessby B, Melhus H. Serum retinol levels and the risk of fracture. *N Engl J Med* 2003; **348**: 287.
16. Crandall C. Vitamin A intake and osteoporosis: a clinical review. *J Women's Health (Larchmt)* 2004; **13**: 939.
17. Kleiner-Bossaler A, Deluca HF. Formation of retinoic acid from retinol in the kidney. *Arch Biochem Biophys* 1971; **142**: 371–7.
18. Smith FR, Dewitt SG. Effects of diseases of the liver, thyroid and kidneys on the transport of vitamin A in human plasma. *J Clin Invest* 1971; **50**: 2426–36.