Vitamin A-Induced Hypercalcemia in Burn Patients: A Case Study

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Vitamin and steroid supplementation such as oxandrolone are commonly given to speed the recovery process in severe burn injuries. Vitamin A is administered concurrently with steroids because of its pro-inflammatory and positive effects on wound healing. However, vitamin A supplementation warrants caution as hypercalcemia can result from vitamin A overdose. Our case involves an 18-year-old male injured in an oil field explosion who presented with 55% total body surface area (TBSA) partial- and full-thickness burns. Following successful resuscitation, he was given vitamin A, oxandrolone, vitamin C, and zinc sulfate as part of the standard vitamin supplementation. On hospital day (HD) 33, serum calcium levels were noted to be elevated and increased to 13 mg/dL a few days later. Parathyroid hormone and vitamin D levels were found to be within normal range, and urine analysis showed normal calcium excretion. Subsequent assessment of vitamin A levels revealed significantly elevated levels at 93 mcg/dL. Vitamin A supplementation was discontinued, and the patient was discharged on HD 42. At the 1-month follow-up, serum calcium levels were normal, which links the hypercalcemia to vitamin A overdose. This case highlights the importance of considering vitamin A overdose as a cause for asymptomatic hypercalcemia with a normal parathyroid and vitamin D workup. While routine, vitamin A supplementation in burn patients calls for assessment of both serum calcium and vitamin A levels throughout the hospital stay to prevent hypercalcemia and its negative effects.

Burn injuries comprise about one-fourth of total traumas and are increasing in prevalence globally. Severe burn injuries that are over 20% TBSA present unique challenges for burn surgeons as burn-induced catabolism results in decreased muscle mass and wound healing.[1] Standard treatment protocol for burn patients involves steroids and a cocktail of vitamins including vitamin A, vitamin C, and zinc sulfate to help offset the mineral loss commonly seen with severe burns. Vitamin A supplementation supports wound healing by stimulating epithelialization, fibroblast proliferation, collagen synthesis, and deposition, and angiogenesis.[2] Vitamin C and zinc sulfate both reduce oxidative stress and help in wound repair.[3] Steroids are administered to offset the burn-induced catabolism present in these patients, and vitamin A is commonly given with steroids to counter their undesired anti-inflammatory effects.[2] The use of vitamin A in burn patients warrants caution, however, as hypercalcemia has been shown in patients with vitamin A overdose.[2,4] We present a case of an 18-year-old male who presented with a 55% TBSA burn and developed hypercalcemia secondary to hypervitaminosis A.

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CASE

An 18-year-old male presented to the emergency department from an oil field explosion with a 55% TBSA thermal burn involving partial- and full-thickness burns to the face, anterior and posterior torso, and bilateral upper and lower extremities. He had a low BMI of 17 kg/m^2, which remained throughout the hospital stay (Figure 1). The patient underwent successful resuscitation for burn shock. Following successful resuscitation, the patient was given the standard burn vitamins including 1000 mg of vitamin C, 10,000 units of vitamin A, and 220 mg of zinc sulfate daily to help with wound healing and counteract vitamin and mineral loss from the burn injury itself. Notably, vitamin A administration was started on the day of admission and continued largely throughout his hospital stay. In addition, the steroid analog oxandrolone was started on HD 2. Over the next 3 weeks, the patient underwent successful debridement and wound grafting including biodegradable temporizing matrix and skin grafts. Other than an episode of hemorrhage which was quickly controlled, the surgeries were all successful and uncomplicated.

On HD 33, serum calcium levels were noted to be elevated at 10.6 mg/dL and increased to 13 mg/dL over the next week. Intravenous (IV) fluids were administered to the patient to correct this asymptomatic hypercalcemia, and calcium levels decreased to the normal range. However, once the IV fluids were discontinued, the hypercalcemia recurred. Parathyroid hormone (PTH) and vitamin D levels were assessed and found to be within the normal range. A urine calcium level was ordered to assess calcium excretion but was found to be normal as well. Vitamin A levels were then assessed on HD 39 and noted to be significantly elevated at 92

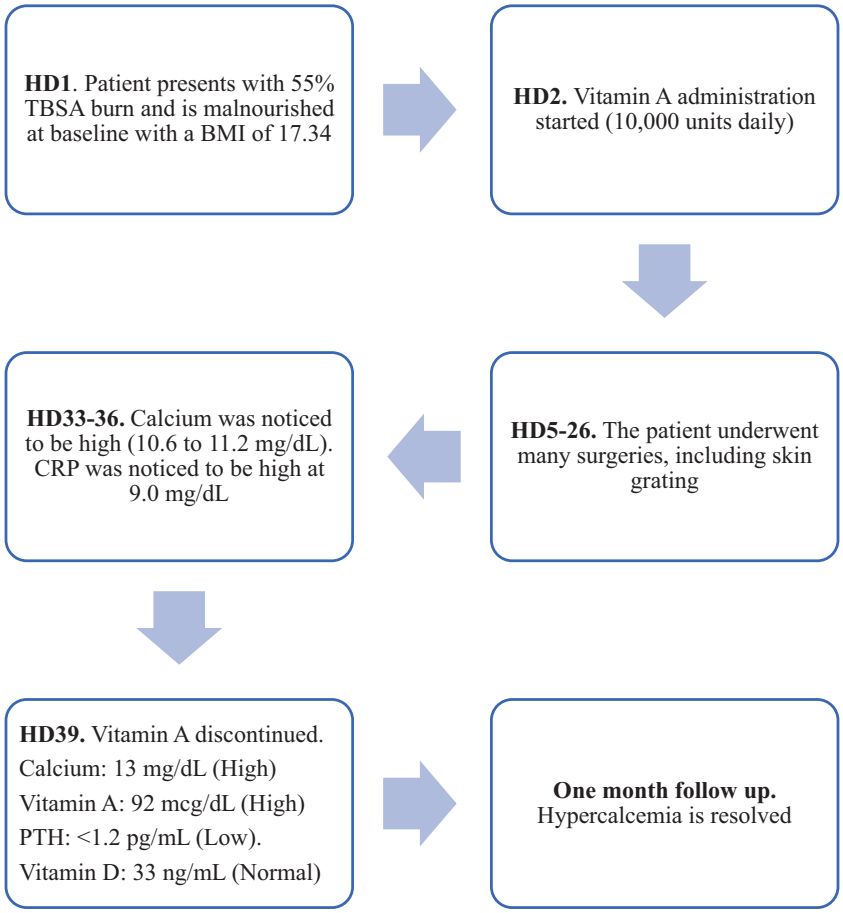

Figure 1. Case timeline.

mcg/dL (normal range 26–72 mcg/dL). Vitamin A supplementation was discontinued. On HD 42, he was discharged to rehabilitation. Serum calcium remained elevated and was to be re-assessed at the 1-month follow-up. At the 1-month follow-up, serum calcium levels were normal. These findings, paired with our normal workup during his hospital stay, confirm that the hypercalcemia was attributed to a vitamin A overdose. At the 2-month follow-up, the patient's serum calcium levels remained normal and there were no further issues.

DISCUSSION

Burns are significant physiologic stressors on the body. Following the initial response of tissue hypoxia and low metabolic rate, hypermetabolism, hypercatabolism, and increased oxygen consumption occurs. This is mediated through increased release of catecholamines, endogenous glucocorticoids, and cytokines that initiate proteolysis, lipolysis, and glycogenolysis.[5,6] The hypermetabolism and hypercatabolism can ultimately become detrimental as catabolism of muscle protein occurs at a higher rate than anabolism resulting in erosion of lean body mass.[6,7] To counteract this, corticosteroids are supplemented to suppress the catabolic response. They reduce inflammatory cell infiltration, collagen deposition and synthesis, fibroblast proliferation, and angiogenesis, which ultimately inhibits wound healing.[8,9] In particular, oxandrolone, a testosterone analog, is commonly given to burn injury patients. Oxandrolone has good oral bioavailability and can exhibit up to 10 times higher anabolic and 10 times lower androgenic effects on the body compared to testosterone.[5,6]

Rapid vitamin and mineral loss as part of the catabolic response in burn injuries prompts vitamin supplementation during the initial resuscitation and throughout the hospital stay. Vitamins A, C, and E are frequently given to burn patients and have been shown to reduce wound healing time and infection rates, and to shorten hospital length of stay.[5,10] Vitamin A supplementation is well documented in burn injuries and is often given concurrently with steroids to offset steroidal anti-inflammatory and anti-wound healing effects. Vitamin A stimulates the immune system, promotes angiogenesis, increases epithelial turnover, and increases collagen and extracellular matrix formation to promote many aspects of wound healing.[2]

This patient with a low body mass index (BMI) of 17 kg/m^2 was baseline malnourished at presentation, resulting in a protein-calorie deficiency. Vitamin A in the form of retinol is transported through the blood bound to retinol-binding protein (RBP)[11,12] (Figure 2). Current literature supports that vitamin A excess can be attributed to deficient RBP.[12] We hypothesized that the low RBP developed from 1) underlying malnutrition and 2) hepatic reprioritization during the inflammatory response. This patient's low BMI can result in

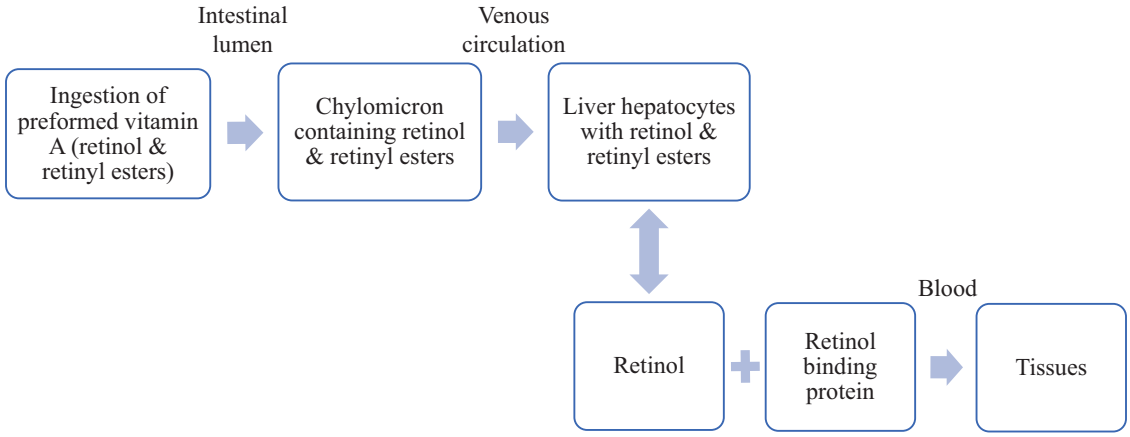

Figure 2. Retinol-binding protein's role in vitamin A transport.

protein deficiency with corresponding low RBP. Additionally, hepatic reprioritization would reduce the synthesis of negative acute phase proteins like RBP with increased synthesis of positive acute phase proteins during the inflammatory response.[13] High levels of C reactive protein, ranging from 5 to 10 mg/dL, (normal range <0.5 mg/dL) confirms the large inflammatory response in this patient. Ultimately, the low RBP led to excess unbound vitamin A in his blood. The excess vitamin A helped heal his burns initially, but he developed hypervitaminosis A once the wounds were largely healed.

Patients with low BMI, or children, are more susceptible to vitamin A toxicity, even with intake as low as 1500 units.[14] This unique case emphasizes the importance of frequent monitoring of vitamin A levels in addition to calcium levels, especially in burn patients who undergo vitamin A supplementation. It is recommended that institutions with a strong nutrition focus or have many patients in need of high-quality nutrition support, should consider bringing these assays in-house.

Standard protocol for burn patients at our institution includes daily assessment of serum calcium. Elevations in calcium levels are very rarely observed, and any hypercalcemia necessitates further workup. Measuring total calcium versus ionized or free calcium is important to consider because total calcium is affected by changes in albumin, pH, and hydration among other factors.[15] Ionized calcium, which is more sensitive to physiologic changes, may have shown hypercalcemia earlier if calcium-binding protein is hypothesized to be low from the large inflammatory response, which forces the liver to shift production to acute phase reactants instead of homeostatic proteins.[16] While more useful and clinically sound, directly measuring ionized calcium is challenging due to lack of standardization, analytical performance, and higher cost.[17] Estimations of ionized calcium from total calcium have been developed to adjust for albumin levels.[17] A broadly used method to calculate ionized calcium from serum/total calcium is the equation: corrected [Ca] = Measured total [Ca] + (0.8 × (4.0 – [albumin])), but other studies have shown it may be more beneficial to develop equations that are derived locally and internally validated.[15,18] Our institution does not regularly measure ionized calcium, but this may have been helpful in this case to detect hypercalcemia earlier, before changes were reflected in total calcium.

Levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, are well-known to be increased during the inflammatory response to burns. Pathologic bone resorption, measured by serum C-terminal telopeptide of type 1 collagen (CTX) assays and upregulated in response to pro-inflammatory cytokines, can further contribute to elevated serum calcium.[19,20] However, our institution does not measure levels of these cytokines and does not regularly measure CTX, and these measurements may not be assessed following detection of vitamin A overdose.

Hypercalcemia can have dangerous effects on the body if left untreated. Symptoms include anorexia, nausea, polyuria, and general weakness when serum calcium levels are elevated between 11.5 and 13 mg/dL. With severe hypercalcemia between 13 and 14 mg/dL, more serious symptoms can arise including lethargy and dehydration, in addition to anorexia, nausea, and vomiting. Electrocardiogram changes are seen with hypercalcemia as well.[21] If the hypercalcemia remains unnoticed, with progressive dehydration, deterioration of renal function, coma, and even death can result.[22] In this case, our patient did not develop any complications from hypercalcemia. Serum vitamin A levels can often be overlooked since initial workup of hypercalcemia involves assessment of serum PTH. Elevated PTH may indicate primary (the most common cause of hypercalcemia in adults) or tertiary hyperparathyroidism.[23,24] Familial hypocalciuric hypercalcemia also should be considered with elevated PTH. If low PTH is observed, hypercalcemia resulting from PTH-related peptide secretion should be investigated. In addition to PTH evaluation, serum vitamin D assessment should follow.

This case demonstrates an opportunity for improvement. We recommend the daily assessment of calcium levels, and elevated serum calcium should raise cause for concern. Once PTH and vitamin D levels are assessed, vitamin A levels should be examined next. It is important to recognize vitamin A overdose early, as vitamin A-induced hypercalcemia has shown to be reversible with discontinuation of vitamin A supplementation. Serum retinol and calcium levels are expected to improve back to normal within a period of weeks to months due to the long half-life of retinol.[2,4,25]

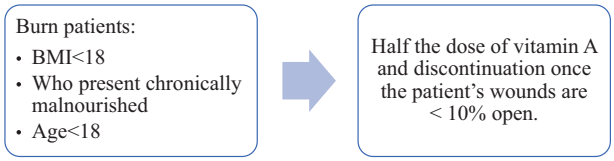

Figure 3. Recommendations for vitamin A supplementation.

CONCLUSION

Steroid and vitamin supplementation are administered to burn patients to facilitate wound healing and prevent muscle breakdown. Vitamin A is part of a standard set of vitamins administered, and physicians should be wary of the potential elevation of calcium levels secondary to vitamin A overdose. Although the mechanism is poorly understood, the hypercalcemia is hypothesized to be due to increased osteoclast activity, hormonal dysregulation of calcium homeostasis, and reduced osteoblast activity.[24] We attribute the hypervitaminosis A to our patient's low BMI causing a protein deficiency including RBP. Based on this case, we believe that burn patients with a BMI under 18, are chronically malnourished, or are under the age of 18 years should be given a dosing reduction plan, such as a half dose of vitamin A daily and discontinuation of vitamin A dosing once the wounds are less than 10% open (Figure 3). Our case highlights the importance of assessing vitamin A levels for burn patients with asymptomatic hypercalcemia and normal PTH and vitamin D levels. Vitamin A supplementation should be discontinued if hypercalcemia is discovered to avoid harmful side effects.

REFERENCES

1. Knuth CM, Auger C, Jeschke MG. Burn-induced hypermetabolism and skeletal muscle dysfunction. Am J Physiol Cell Physiol 2021;321:C58–71.
2. Zinder R, Cooley R, Vlad LG et al. Vitamin A and wound healing. Nutr Clin Pract 2019;34:839–49.
3. Siddiqi M, Evans T, Guiab K et al. Vitamin C in the management of burn patients: a systematic review of the risks and benefits. Am Surg 2022;88:752–7.
4. Baxi SC, Dailey GE, 3rd. Hypervitaminosis A. A cause of hypercalcemia. West J Med 1982;137:429–31.
5. Miller JT, Btaiche IF. Oxandrolone treatment in adults with severe thermal injury. Pharmacotherapy 2009;29:213–26.
6. Gus EI, Shahrokhi S, Jeschke MG. Anabolic and anticatabolic agents used in burn care: what is known and what is yet to be learned. Burns 2020;46:19–32.
7. Hart DW, Wolf SE, Ramzy PI et al. Anabolic effects of oxandrolone after severe burn. Ann Surg 2001;233:556–64.
8. Wicke C, Halliday B, Allen D et al. Effects of steroids and retinoids on wound healing. Arch Surg 2000;135:1265–70.
9. Anstead GM. Steroids, retinoids, and wound healing. Adv Wound Care 1998;11:277–85.
10. Adjepong M, Agbenorku P, Brown P et al. The role of antioxidant micronutrients in the rate of recovery of burn patients: a systematic review. Burns Trauma 2016;4:18.
11. Blaner WS, Li Y, Brun PJ et al. Vitamin A absorption, storage and mobilization. Subcell Biochem 2016;81:95–125.
12. Smith FR, Goodman DS. Vitamin A transport in human vitamin A toxicity. N Engl J Med 1976;294:805–8.
13. Jeschke MG, Lopez ON, Finnerty CC. 24—the hepatic response to thermal injury. In: Herndon DN, editor. Total burn care. 5th ed. Elsevier; 2018. p. 259–67.e3. doi:10.1016/B978-0-323-47661-4.00024-1
14. Hathcock JN, Hattan DG, Jenkins MY et al. Evaluation of vitamin A toxicity. Am J Clin Nutr 1990;52:183–202.
15. James MT, Zhang J, Lyon AW et al. Derivation and internal validation of an equation for albumin-adjusted calcium. BMC Clin Pathol 2008;8:12.
16. Tee MC, Holmes DT, Wiseman SM. Ionized vs serum calcium in the diagnosis and management of primary hyperparathyroidism: which is superior? Am J Surg 2013;205:591–6; discussion 596.
17. Calvi LM, Bushinsky DA. When is it appropriate to order an ionized calcium? J Am Soc Nephrol 2008;19:1257–60.
18. Payne RB, Little AJ, Williams RB et al. Interpretation of serum calcium in patients with abnormal serum proteins. Br Med J 1973;4:643–6.
19. Abdel-Hafez NM, Saleh Hassan Y, El-Metwally TH. A study on biomarkers, cytokines, and growth factors in children with burn injuries. Ann Burns Fire Disasters 2007;20:89–100.
20. Chubb SA. . Measurement of C-terminal telopeptide of type I collagen (CTX) in serum. Clin Biochem 2012;45:928–35.
21. Chorin E, Rosso R, Viskin S. Electrocardiographic manifestations of calcium abnormalities. Ann Noninvasive Electrocardiol 2016;21:7–9.
22. Davis KD, Attie MF. Management of severe hypercalcemia. Crit Care Clin 1991;7:175–90.
23. Minisola S, Pepe J, Piemonte S et al. The diagnosis and management of hypercalcaemia. BMJ 2015;350:h2723.
24. Goltzman D. Pathophysiology of Hypercalcemia. Endocrinol Metab Clin North Am 2021;50:591–607.
25. Borgan SM, Khan LZ, Makin V. Hypercalcemia and vitamin A: a vitamin to keep in mind. Cleve Clin J Med 2022;89:99–105.