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Vitamin A Deficiency in a Hemodialysis Patient – A Case Review

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This article has been approved for 2.0 CPE units. The online CPEU quiz and certificate of completion can be accessed in the Members Only section of the RPG web site via the *My CPEU* link. In addition, this CPE offering is available to current RPG members only and the expiration date is June 30, 2012.

Introduction

This article reviews the function of vitamin A and examines a case review of vitamin A deficiency in a hemodialysis patient, as well as his treatment and outcomes.

Background (1)

Vitamin A is a fat soluble vitamin and plays an essential role in vision, cellular differentiation, growth, immunity, bone development, and has antioxidant properties, among others. It is a collective term for several related, biologically active molecules called retinoids (preformed vitamin A)—retinol, retinal, retinyl esters, and retinoic acid—that comprise the active forms of vitamin A.

- Retinol is necessary for reproduction and is found in animal tissues as retinyl esters with long-chain fatty acids. Animal sources of vitamin A are found primarily in liver, eggs, and milk (see Table 1). Since animal or supplement sources of vitamin A are preformed, toxicity is more likely to occur (2).
- Retinal is an aldehyde derived from the oxidation of retinol. It is necessary for low-light or color vision.
- Retinoic acid is derived from the oxidation of retinal. It is necessary for cell maturation, differentiation and reproduction. It cannot be reduced in the body and therefore cannot give rise to either retinal or retinol (see Diagram 1).

Carotenoids, called provitamin A carotenoids, are plant-based precursors of vitamin A. Of the provitamin A carotenoids, beta-carotene is most efficiently made into retinol and thereby possesses the most provitamin A activity. Metabolism of provitamin A carotenoids into active vitamin A is highly regulated, so toxicity is unlikely from plant sources (2). One exception, is the overconsumption of beta carotene from supplements which acts as a pro-oxidant.

The recommended daily allowance (RDA) for vitamin A is provided as retinol activity equivalents A (RAE). One RAE = 1 mcg retinol = 3.3 International Units (IU) (2). The RDA's are divided into gender and age groups and are listed as micrograms of RAE's to account for the differing biological activities of provitamin A carotenoids and retinols (see Table 2) (3). Tolerable Upper Intake Levels (ULs) were established to prevent toxicity.

Vitamin A Metabolism (1)

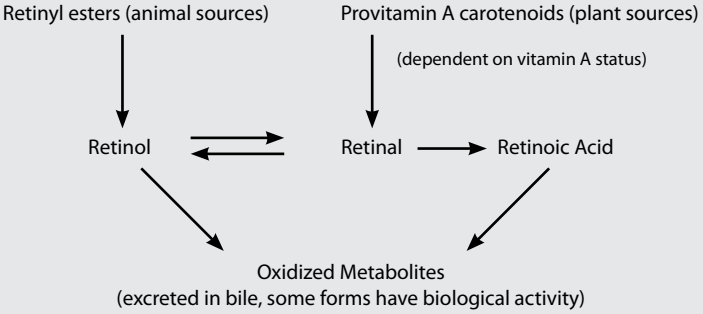
After some digestion in the stomach, retinol is esterified and packaged with chylomicrons in the small intestine, while some carotenoids are metabolized to retinoids and then esterified. Retinoic acid, on the other hand, enters the portal vein and tightly binds to albumin. Pancreatic and intestinal hydrolases act on the retinyl esters, freeing carotenoids and retinols to remain solubilized in micelle solutions. These are absorbed in the duodenum and jejunum, incorporated into chylomicrons, and transported to extrahepatic tissues. Those not taken up into tissues are then transported to the liver for storage or further metabolism. Roughly 50-85% of the total body retinol is stored in the liver (2).

Table 1
Food Sources of Vitamin A (3)

Animal Sources	Vitamin A (IU)*
Liver, beef, cooked (3 oz)	27,185
Milk, fortified skim (1 cup)	500
Cheese, cheddar (1 oz)	284
Milk, whole (1 cup)	249
Egg, fried (1 large)	362
Plant Sources	**Vitamin A (IU)**
Carrots, boiled (1/2 cup)	13,418
Spinach, frozen, boiled (1/2 cup)	11,458
Kale, frozen, boiled (1/2 cup)	9,558
Carrots, 1 raw (7 ½ inches)	8,666
Cantaloupe (1 cup)	5,411
Spinach, raw (1 cup)	2,813
Apricots, raw (1 cup)	3,178
Peach, 1 medium	319

*IU = International Units.

Diagram 1
Vitamin A Conversions



Note: conversion from retinol to retinal is reversible whereas the pathway from retinal to retinoic acid is not.

Table 2
RDAs and ULs for Vitamin A* (3)

Age (years)	Children (mcg RAE)	Males (mcg RAE)	Females (mcg RAE)	ULs
1-3	300 (1,000 IU)	n/a	n/a	600 (2,000 IU)
4-8	400 (1,320 IU)	n/a	n/a	900 (3,000 IU)
9-13	600 (2,000 IU)	n/a	n/a	1,700 (5,610 IU)
14-18	n/a	900 (3,000 IU)	700 (2,310 IU)	2,800 (9,240 IU)
19+	n/a	900 (3,000 IU)	700 (2,310 IU)	3,000 (10,000 IU)

* RDA's for pregnancy and lactation and Adequate Intakes for infants are found at http://ods.od.nih.gov/factsheets/vitamina

Within cells, retinol binds to cellular retinol-binding protein (RBP), which may function to regulate cellular levels of free retinol and to direct the vitamin to specific metabolic enzymes. Within the blood, retinol transport requires RBP, transthyretin (TTR, formerly known as prealbumin), and thyroxine. These carrier proteins circulate retinol to the tissues, with a half-life ≤ 15 hours. Once retinol has been deposited, the carrier proteins are filtered in the glomeruli and absorbed in the proximal tubules, making the kidneys indispensable to the process.

Vitamin A Deficiency

Vitamin A deficiency is uncommon in developed countries. Those at risk include preschool children eating inadequate fruit or vegetable intake, the urban poor, the elderly, or those with liver failure. Additionally, individuals with fat malabsorption, such as Crohn's disease, chronic diarrhea, celiac disease, and other disorders, have a higher risk of vitamin A deficiency.

A diagnosis of vitamin A deficiency is generally made by clinical findings but can be supported by serum retinol levels < 20 mcg/L or the ratio of retinol:RBP < 0.8 (2). Serum retinol levels may underestimate vitamin A stores in the setting of severe protein-calorie malnutrition since dietary protein, energy, and zinc are necessary for synthesis of RBP (2). Additionally, serum retinol

levels may be low if infection is present due to decreases in the negative acute phase proteins, such as RBP (2). Notably, vitamin A deficiency decreases the mobilization of iron from stores, leading to microcytic anemia.

Vitamin A Toxicity (1)

In comparison, vitamin A toxicity, or hypervitaminosis A, can result from acute or chronic supplementation. Acute symptoms in adults, possibly resulting from even one large dose of >660,000 IU, can include: nausea, vomiting, headache, blurred vision, and dizziness. Chronic toxicity may result from sustained intake of as little as 3-4 times the RDA. Symptoms include: bone or muscle pain, anorexia, dry/itchy skin, or hair loss. Excess vitamin A can also interfere with vitamin K absorption. Unfortunately, serum levels of retinol are not helpful in diagnosing vitamin A toxicity because most vitamin A is stored in the liver (2).

Vitamin A in Chronic Kidney Disease

In the chronic kidney disease (CKD) population, serum levels of vitamin A and RBP typically run higher than the general population (4) and can remain elevated for two years post-transplant (5,6). Additionally, patients with bilateral nephrectomies may have serum retinol levels elevated above that of hemodialysis (HD) patients (7). Elevated values may result from reduced ability of the kidneys to filter or absorb carrier proteins, as well as impaired conversion of retinol to retinoic acid (4). Additionally, Chen et al. reported elevated vitamin A levels associated with elevated creatinine, cautioning against vitamin A supplementation in the general population, but especially those with chronic renal insufficiency (8).

Vitamin A deficiency is uncommon in the CKD population since dialysis does not interfere with vitamin A status (5,9). Therefore, supplementation of vitamin A is not recommended in CKD (5,6) unless malabsorption is present (5). Notably, although HD does not decrease vitamin A levels, carotenoids have been shown to decline with dialysis (7). Symptoms of vitamin A deficiency in patients with CKD include scalded-appearing skin, hyperkeratosed hair follicles, Bitot's spots in the sclera of eyes, and dry eyes. Each can be monitored with use of the subjective global assessment (SGA) (10). Certainly, any acute changes in vision would be suspicious as well.

A recent study has shown, though, that low levels of vitamin A are an independent predictor of cardiovascular mortality in HD patients (11). Although this study could not identify if the increase in mortality was a result of reduced nutritional intake or vitamin A's role in immunity, there was speculation that the reduced ratio of retinol:RBP may affect the bioavailability of retinol within cells (11).

Conversely, Kalantar & Kopple reported elevated calcium and alkaline phosphatase levels in patients with CKD with intake of only 7,500-15,000 IU/day of vitamin A (7). Therefore, they recommend limiting food and supplemental sources of vitamin A to the RDA for patients with CKD (7). Vitamin A toxicity may also manifest as dark margins along the gums or may be associated with anemia (5,6,7,10).

Vitamin A toxicity could change cell membranes and transportation of ions, such as calcium, disrupting the normal intracellular groupings (12). Conversely, despite the elevated serum vitamin A values in HD patients, Aguilera et al. speculated that physiological or intracellular signs of hypovitaminosis A exist possibly due to a change in vitamin A receptors or the vitamin:carrier complex, leading to lower bioavailability and reduced retinol intracellularly (13). Thereby, the risk of vitamin A toxicity may be greatly reduced in the HD population. Additionally, they pondered whether more accurate vitamin A results could be obtained by checking vitamin:carrier-complex levels, rather than serum vitamin A levels (13).

Case Review—Patient M

Patient M is a 60 year old male who has been on in-center hemodialysis since 54 years of age in November 2004. His CKD is due to chronic interstitial nephritis. He also has a medical history of coronary artery disease, hypertension, debilitating gout, Crohn's disease resulting in colectomy in 1979 and small bowel resections with an ileostomy in 1990. Until the initiation of dialysis, he worked full-time as a chef.

Beginning in January 2005, he reported seeing black spots when standing too quickly or when getting up at night to go to the bathroom. At that time, it was attributed to dehydration and low blood pressure, resulting in an increase in his dialysis dry weight. By early February, he experienced "loss of vision in twilight hours" and difficulty distinguishing objects in low light. His vitamin A levels were checked and were normal at 398 mcg/L (see Table 3), so he was referred to Neurology and Ophthalmology.

By mid-March, his vision continued to deteriorate despite follow-up with a second ophthalmologist and a consult in neuro-ophthalmology with no conclusive diagnosis. Numerous medications were discontinued or substituted and he purchased new glasses, without improvement. Within the next two weeks, he could no longer drive at night. He was also having difficulty at work and, without improvement, would need to consider disability.

A recheck of the patient's vitamin A on April 1st, 2005 was low at 272 mcg/L and was associated with his night-blindness,

Table 3 - Laboratory Results & Vitamin A Supplementation

Date	Vitamin A Free Retinol (mcg/L)	Vitamin A* Free Retinol (mcg/L)	Vitamin A Supplement (IU/day)	Calcium (mg/dL)	Alkaline Phosphatase (U/L)
Reference/Range	**360-1200**	**325-780**	**n/a**	**8.9-10.1**	**45-115**
11/29/2004	n/a	n/a	0	10.5	60
2/10/2005	398	n/a	0	11.3	n/a
4/1/2005	272	n/a	0	n/a	n/a
4/18/2005	2160	n/a	100,000	10	n/a
4/27/2005	2061	n/a	50,000	n/a	n/a
5/11/2005	n/a	n/a	50,000	10.4	98
9/12/2005	646	n/a	Unknown	10.7	n/a
11/9/2005	n/a	n/a	Unknown	10.6	168
5/10/2006	n/a	n/a	As Needed	9.8	82
3/21/2007	75	n/a	0	10.3	110-137
4/3/2007	647	n/a	25,000 + 2 ADEK	10.2	117
11/28/2007	n/a	n/a	0	10.1	148
2/11/2008	n/a	672	0	10.8	n/a
5/21/2008	n/a	n/a	0	10.3	194
11/11/2008	n/a	n/a	0	10	284
3/18/2009	n/a	281	0	9.8	n/a
5/20/2009	n/a	747	10,000	8.9	137
6/17/2009	n/a	737	10,000	9.4	n/a
11/11/2009	n/a	n/a	10,000	8.3	84
5/19/2010	n/a	n/a	10,000	9.8	87
11/17/2010	n/a	n/a	10,000	8.2	154

*Change in assay by the laboratory

despite the previous value being within normal limits. Medication records indicate that he was prescribed 50,000 IU of vitamin A twice daily (100,000 IU/day) for one week. He was maintained on 50,000 IU/day for another month. His vision problems improved immediately and serum levels rose to over 2,000 mcg/L.

The patient reported resolution of his vision problems until mid-July when he started seeing black spots, so he independently increased his dose of vitamin A to two tablets daily (100,000 IU per day) for at least a week. Unfortunately, at this time his medical condition and well-being became complicated with headaches of such intensity that they kept him up at night and worsened when he leaned forward or in the heat of the kitchen at work. He also continued to have hydration issues due to his high output ostomy.

Throughout the remainder of 2005 and into 2006, he experienced intense headaches, anorexia with unintentional weight loss, hand weakness, and foot pain. By June 2006, he had lost 3.5 kg in 6 months (see Table 4). Thereafter, the patient reported a fairly good appetite with larger and more balanced meals. He continued vitamin A supplementation on an as-needed basis and

Table 4 - Weight Changes

Date	Weight (kg)
11/29/2004	54.5
12/14/2004	55.5
1/25/2005	57
6/6/2005	58.5
8/3/2005	57.5
4/12/2006	54
10/24/2006	48.8
12/4/2006	52.5
4/2/2007	42
8/15/2007	39.5
10/17/2007	44
11/19/2007	46
1/2/2008	43
6/4/2008	49
11/5/2008	55
4/22/2009	56
10/21/2009	58.5
1/20/2010	58.5

his renal multivitamin was increased to twice daily due to his malabsorption and large fluid losses from the high output ostomy. A brief SGA by the dietitian revealed splinter hemorrhages beneath his fingernails, which the patient observed for the past two weeks, a scalloped tongue with red edges (causing no oral side effects), and a red/irritated, itchy scalp. The hemorrhages were thought to be related to vitamin C deficiency and improved with the increase to 2 renal multivitamins daily. His care team associated hyperphosphatemia with the itchy skin condition.

However, by the end of the month, the patient again reported poor appetite and weight loss, which persisted despite a liberalized diet and initiation of 1 Nepro with CarbSteady (Abbott Nutrition, Columbus, OH) nutritional supplement daily. His health continued to decline, his dry weight decreased to 48.8 kg (~10% weight loss in 4 months), and he continued to have debilitating headaches.

His medical course continued to be complicated and anorexia persisted. He had to give up his employment due to his worsening condition, weakness, and pain. His serum vitamin A was very low at 75 mcg/L in March 2007, during which time he had stopped taking vitamin A supplements. He was prescribed 25,000 IU vitamin A plus two ADEK multivitamin tablets daily for one week. After which, he should continue 10,000 IU of vitamin A plus the 2 ADEK tablets daily until assessed in Endocrinology the next month. Following this appointment, the vitamin A and ADEK were discontinued with improved serum vitamin A of 647 mcg/L.

His appetite remained poor with a liberalized diet and weight loss persisted even with intake of 2-3 Nepro Carb Steady (Abbott Nutrition, Columbus, OH) nutritional supplements daily. Due to this, hypoalbuminemia of 2.8 g/dL, and history of bowel resection, he initiated intradialytic parenteral nutrition (IDPN) on April 11, 2007. By this time, his HD dry weight decreased to 42 kg (~20% decrease in 4 months). He had grown quite deconditioned and was admitted to nursing home care for physical therapy. His severe pain now encompassed his back, hips, knees, and ankles and was associated with uremic osteodystrophy, gout, or compressive myelopathy. During this time, he also missed a call for kidney transplant. His nephrologist determined he was not likely a good candidate due to his malnourished state and, as a result, was temporarily inactivated from the transplant list.

In the nursing home, he was advanced to a general diet with increased phosphate binders for his chronic hyperphosphatemia. By November 2007, IDPN therapy continued plus 1 Nepro daily. His appetite improved. His dialysis dry weight increased 4.5 kg in two months, albumin improved to 3.2 g/dL, and he demonstrated improved strength. He hoped to return to his home around the New Year, if strong enough.

In early 2008, he had concerns with poor vision, which his nephrologist suspected was due to worsening cataracts, but a vitamin A level was drawn to rule out deficiency. At 672 mcg/L, his vitamin A status was considered adequate and he continued without vitamin A supplementation.

His condition continued to improve through 2008. He remained in the nursing home for much of the year, gained strength and his weight improved to 55 kg by November 2008. He was able to return to his home in early 2009, with a greatly improved appetite and IDPN was discontinued.

During his February 2009 annual dietitian assessment, it was noted that his vitamin A had not been rechecked in a year. This turned out to be low (281 mcg/L) and the nephrologist prescribed 10,000 IU of vitamin A daily. His albumin also had improved to 3.7 g/dL and he exercised thrice weekly with the dialysis bike. A diet recall indicated that his protein intake was insufficient to meet his needs, so he continued intake of 1 Nepro daily.

By February 2010, his dry weight increased to 58.5 kg for the first time since prior to initiating HD. He regularly achieved adequate protein intake and used Nepro only on an as-needed basis. He remained happily independent at home and again pursued reactivation on the kidney transplant list.

Summary

This case review clearly demonstrates that a HD patient with signs of malabsorption may become symptomatic for hypovitaminosis A with normal serum levels. No changes in calcium or alkaline phosphatase were observed during vitamin A supplementation. This was noted despite numerous other medication changes were also made over time.

Although vitamin A toxicity was never diagnosed or recognized, it should be noted that the case review patient's health status began to decline around the time vitamin A supplementation was initiated, or at least when he began self-dosing for improvement of his night blindness. Unfortunately, there is no way to know how much vitamin A he was taking or for what duration. Additionally, there is no longer a record of the content of the ADEK vitamins. Thus the cumulative vitamin A dose during that period is also unknown.

Fortunately, improvement in vitamin A toxicity symptoms can be achieved by simply discontinuing supplementation, which may have been the case for the patient during his 2007-2008 nursing home stay. During this time, medication records reveal that no vitamin A supplementation was prescribed and it was unlikely that the patient was self-dosing in this controlled setting.

There are no clear guidelines regarding safe vitamin A repletion in this population, or the ideal method of supplementation (e.g. water-miscible or other), and this certainly warrants further research. Unfortunately, vitamin A toxicity may be a challenging diagnosis. This may be due to baseline elevated serum retinol values observed in patients with CKD and the non-specific signs and symptoms of vitamin A toxicity. It may be reasonable to consider a large, initial repletion dose of vitamin A. This would then be followed by a lower maintenance dose or staggered maintenance doses. Patients should be discouraged from self-dosing to prevent unwanted side-effects. With close monitoring by a clinician of vitamin A or retinol:RBP levels, and clinical symptoms, patients may be able to safely replete vitamin A stores.

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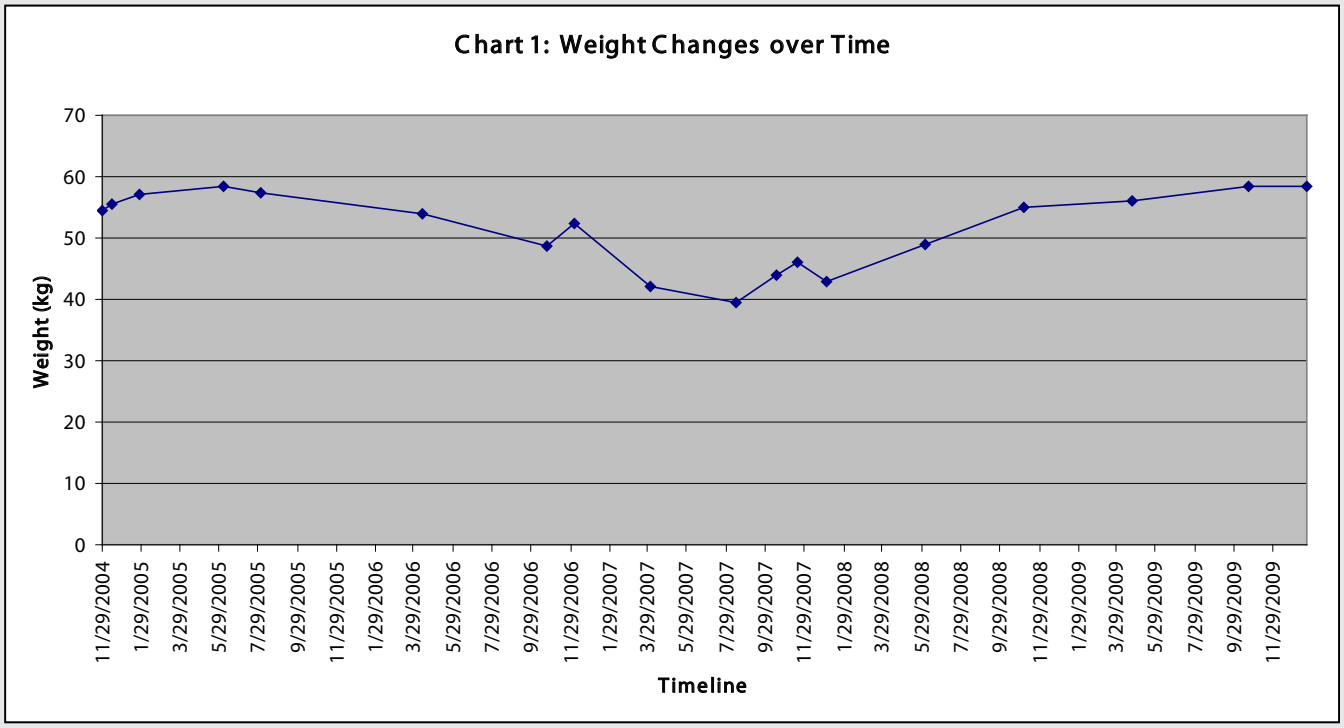
Chart 1
Weight Changes Over Time



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