

Association Between Vitamin Deficiencies and Ophthalmological Conditions

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Abstract: Vitamin deficiencies can have adverse effects on health, including on the visual system. The ocular manifestations of a vitamin deficiency are related to the underlying biochemical function of the particular nutrient. While vitamin deficiencies are not common in developed countries, they are still prevalent in parts of the developing world and in specific, vulnerable populations. Vitamin deficiencies can cause or contribute to many ophthalmological conditions and eye diseases may even be the first presenting finding of a vitamin deficiency. As such, it is important for ophthalmologists to be aware of the ocular manifestations of vitamin deficiencies, especially given that the complications can be severe and effectively treated if identified early. This review summarizes the literature on the main vitamins known to have characteristic ocular manifestations: vitamins A, B1, B2, B9, B12, C, D, E and K. The function, epidemiology, manifestations, workup, and management of each vitamin is discussed in detail.

Keywords: vitamin A deficiency, vitamin B deficiency, vitamin C deficiency, vitamin D deficiency, vitamin E deficiency, vitamin K deficiency

Introduction

Nutritional deficiencies have adverse effects on systemic health and can lead to end-organ damage if left untreated. Vitamins are the essential constituents of natural food and play a key role in metabolism, cellular integrity and maintenance of homeostasis.¹ Ocular manifestations of vitamin deficiencies is an evolving field as more disease entities are being elucidated by studying the underlying pathophysiology of vitamin level irregularities. In addition, periods of life where growth or increased metabolism are prominent, such as childhood and pregnancy, respectively, can be greatly impacted by altered serum levels of nutrients.² Several vitamin deficiencies have characteristic ocular manifestations, and eye disease can at times be the first presenting signs or symptoms of a vitamin deficiency. As such, a strong understanding of ophthalmological conditions related to nutritional deficits is crucial for the general ophthalmologist. This review outlines the key ophthalmic findings associated with vitamin deficiencies.

Methods

This study is a comprehensive review of the literature. Search engines utilized in this review included: MEDLINE, EMBASE, and Google Scholar. Literature search keywords included: “vitamin” AND “deficiency OR hypovitaminosis” AND “eye OR ocular” AND “manifestation OR presentation OR disease.” Only papers published or available in English were considered for inclusion. Abstracts and full texts were analyzed for relevance to this review.

Results

A total of 487 peer reviewed publications were considered for inclusion, with 46 removed due to either lack of access to the full paper or not available in English. Overall, 159 peer-reviewed publications were included in this analysis. See [Table 1](#) for a summary of ocular manifestations of the vitamin deficiencies discussed in this review.

Table 1 Summary of Ocular Manifestations of Vitamin Deficiencies

Vitamin	Ocular Manifestations	Workup	Treatment
A	Conjunctival and corneal xerosis, Bitot spots, corneal ulceration and scarring, nyctalopia	Serum vitamin A/retinol levels	50,000–200 000 IU IM vitamin A x 1–3 doses based on age
B1	Wernicke's encephalopathy (nystagmus, ophthalmoplegia, diplopia, papilledema)	Thiamine pyrophosphate levels	200 mg IV or oral thiamine TID until symptoms resolve followed by 10 mg daily maintenance
B2	Blurred vision, nyctalopia	Clinical diagnosis, can check urinary excretion rates of riboflavin	5–100 mg oral riboflavin supplementation daily
B9	Optic neuropathy, increased risk of age-related macular degeneration and retinoblastoma	Serum folate (also check B12)	1–5 mg oral folic acid supplementation daily
B12	Optic neuropathy, increased risk of age-related macular degeneration, dry eye disease	Serum B12 (also check folate)	1000 µg B12 IM weekly for up to 4 weeks
C	Hemorrhage (subconjunctival, orbital), exacerbate age-related macular degeneration	Serum vitamin C levels	1–2 g of vitamin C daily for 3 days, then 500 mg for a week, followed by a daily dose of 100 mg for 3 months
D	Dry eye disease, exacerbate diabetic retinopathy, optic neuritis, and thyroid eye disease	Serum 25(OH)D3 levels	Infants – 400 IU daily Adults – 400–2000 IU daily
E	Ophthalmoplegia, strabismus, nystagmus, retinopathy, exacerbate age-related macular degeneration	Serum α -tocopherol level	2000 mg oral vitamin E supplementation
K	Retinal hemorrhages	Prothrombin time (PT) – elevated	Infants – 1 mg IM injection Adults – 90 µg/day oral (women), 120 µg/day (men)

Vitamin A

Function of Vitamin

Vitamin A is a fat soluble nutrient obtained primarily from dietary intake, which is crucial for cellular division, growth, immune system integrity and vision.³ Vitamin A constitutes a group of biochemical compounds, including retinol, retinaldehyde, retinoic acid, and beta-carotene.³ Most pertinent for vision, 11-cis retinaldehyde (or retinal) combines with opsin in the photoreceptor outer segments to create rhodopsin. Once light strikes rhodopsin, 11-cis retinal isomerizes to all-trans retinal, leading to hyperpolarization of the photoreceptor and ultimately, initiation of the visual pathway. 11-cis retinal is regenerated in the retinal pigment epithelium (RPE), to allow the visual cycle to continue. Outside of the retinal photoreceptors, vitamin A maintains corneal and conjunctival epithelial cell integrity. If vitamin A deficiency occurs, these cells undergo metaplasia and keratinization, reducing the amount of mucous secreting epithelial cells on the ocular surface.³

Vitamin A is obtained through leafy greens, fish oils, egg yolks, butter, and orange-coloured vegetables such as carrots.⁴ Once in the digestive tract, pancreatic enzymes break down vitamin A into monomers for absorption within the duodenum; the primary site of storage is in the liver. In times of vitamin A deficiency, this nutrient is released into circulation bound to albumin in a molecule known as transthyretin.⁴ Issues with restricted dietary habits, small intestine disease or liver pathology can lead to vitamin A deficiency. The recommended daily intake of vitamin A is between 700 ug – 900 ug/day in females and males, respectively.⁴

Epidemiology of Disease

The global prevalence of hypovitaminosis A is approximately 30% in those less than 5 years of age and contributes to approximately 2% of deaths for that demographic.⁵ However, there is a large predilection for this disease in developing

countries, as a study in 2013 found only 0.3% prevalence of vitamin A deficiency within the United States of America.⁶ Prevalence of disease though can increase to upwards of 16% in developing countries for those with inflammatory bowel disease such as Crohn's disease,⁷ and an incidence of 70% of hypovitaminosis A has been cited in those with liver cirrhosis due to poor vitamin A storage.⁸

The etiology of hypovitaminosis A can be broken down into three groups: reduced intake, impaired absorption, and reduced storage of vitamin A. Further risk factors include lower socioeconomic status, malnutrition, zinc-deficiency (due to poor hepatic synthesis of retinol-binding protein), and exposure to diarrheal illness.

Ocular Manifestations

Xerophthalmia is a term referring to the spectrum of ocular presentations in the setting of hypovitaminosis A. The World Health Organization released a grading system to characterize the grading of the xerophthalmia spectrum of diseases.⁹ The earliest and most benign presentation is conjunctival xerosis, which is characterized by conjunctival wrinkling and ocular surface dryness due to loss of mucin-secreting goblet cells. The next disease in the spectrum is bitot spots, which are triangular patches of white, opaque deposits classically on the temporal bulbar conjunctiva. Bitot spots are keratinized, desquamated conjunctival epithelial cells with overlying *Corynebacterium xerosis* bacteria which produce gas that leads to the typical opaque, rough contour. Corneal xerosis can closely follow, characterized by corneal haze, punctate epithelial erosions, pannus, and neovascularization. With the cornea now affected, patients complain of a decrease in visual acuity. The World Health Organization noted that the corneal xerosis stage is the last where high-dose vitamin A treatment will preserve baseline vision. If left untreated, corneal xerosis can progress to corneal ulceration and keratomalacia secondary to necrosis of limbal stem cells and corneal stroma. Scarring of the cornea is the final stage and would require transplantation for visual recovery.

Hypovitaminosis A also leads to reduced levels of rhodopsin within primarily rod photoreceptors affecting photo-transduction. One of the earliest presentations of xerophthalmia is nyctalopia, or decreased vision in scotopic conditions.⁹ Children may have difficulty verbalizing this symptom; therefore, targeted history taking such as bumping into objects at night or less active in the evenings is important if risk factors for vitamin A deficiency are present.⁹ Fundus changes such as small, white retinal lesions throughout the posterior pole have also been reported, but are far more rare.⁹

More recently, the link between hypovitaminosis A and skull-based bone changes has been reported. Our team published a case of a 12-year-old autistic male with restricted eating habits presenting with bilateral painless vision loss.¹⁰ A CT scan of the orbits demonstrated narrowing of the optic canals due to hyperostosis. He was found to have markedly reduced vitamin A levels.¹⁰ A clinical triad of hypovitaminosis A, hyperostosis, and optic neuropathy has since been postulated by Godfrey et al in 2021 after their publication of 6 cases with restricted eating habits and, similar to our patient, compressive optic neuropathy.¹¹ Early detection and treatment of vitamin A deficiency is crucial to prevent this possibly irreversible loss of vision at a young age.

Workup for Vitamin Deficiency

Hypovitaminosis A has a variety of presentations as outlined above, and treatment success is directly linked to the stage of xerophthalmia that the patient presents with. A patient presenting with risk factors or clinical signs of xerophthalmia must have a targeted history which includes dietary intake, medical history including malabsorption diseases, social history such as access to foods including vitamin A, and issues with vision in low-light conditions. A comprehensive slit lamp anterior segment and dilated fundus examination should follow. If signs or symptoms of hypovitaminosis A are present, serum vitamin A/retinol levels should be measured (reference range 20–60mcg/dL).³ Xerophthalmia typically presents when retinol levels are <10mcg/dL, but levels can be normal due to hepatic maintenance of serum vitamin A.³ The gold standard is quantifying liver retinol concentration through biopsy; however, this is an invasive procedure.¹²

Management

Prompt treatment of xerophthalmia can resolve ocular manifestations without long-term consequences if initiated in the early stages of the disease. Studies have shown conjunctival xerosis, rod function, and night vision can return to baseline within 2 months of treatment.¹³ Treatment for vitamin A deficiency and the ocular manifestations has been outlined by Ross in 2002.¹⁴ Infants up to 5 months old should be administered one dose of 50000IU vitamin A either orally or

intramuscular, with the latter being the more common route of administration. Infants between 6 months to 1 year should receive 100000IU, and children over 1 year should receive 3 doses of 200000IU vitamin A. Management of the ocular surface sequelae should also be considered, including topical antibiotics for corneal ulceration, lubricating eye drops and cyclosporine for dry eye, and corneal transplantation for visually significant corneal scarring. As zinc plays a key role in retinol binding protein levels, zinc supplementation is encouraged for hypovitaminosis A. Family education on how to appropriately supplement vitamin A through diet should be conducted, especially in those children with restricted eating habits.

Vitamin B1 (Thiamine)

Function of Vitamin

Vitamin B1, or thiamine, is a water-soluble vitamin, which is found naturally in foods, such as fish, seeds, green peas, beans and pork.¹⁵ Our bodies do not create thiamine and readily excrete it, therefore having a regular dietary intake is essential in order to maintain normal blood levels.¹⁵ The recommended daily intake for adults over the age of 18 years-old is 1.2mg/day and 1.1 mg/day for men and women respectively.¹⁵

Thiamine has a fundamental role in cellular energy metabolism and is critical in the growth, maintenance and functioning of the body's cells. It can occur in its free form (unphosphorylated) or in 3 different phosphorylated forms: thiamine monophosphate, thiamin pyrophosphate and thiamine triphosphate.^{16,17} Pyrophosphate is the active form, acting as a co-factor for several key enzymes in energy metabolism such as pyruvate dehydrogenase, α -ketoglutarate dehydrogenase complexes, and cytosolic transketolase. A decrease in these metabolic enzyme activities can lead to a selective decrease in adenosine triphosphate levels in the brain, ultimately causing cell death and acidosis.¹⁷

Issues with malabsorption in the gastrointestinal system, low dietary intake of thiamine, increased urine losses and states of increased thiamine utilization can cause thiamine deficiencies. In humans, thiamine deficiencies manifest as cardiovascular, immunological and neurological disorders including dry and wet beriberi (thiamine deficiency disease).¹⁸ Dry beriberi affects the neurological system causing numbness, confusion, difficulty walking.¹⁹ Wet beriberi affects the cardiovascular system causing tachycardia, shortness of breath, edema and congestive heart failure.¹⁹

Epidemiology of Disease

There is a lack of accurate data and reporting on beriberi which makes the global incidence and prevalence difficult to estimate.²⁰ Thiamine deficiency is predominantly due to insufficient dietary intake and therefore is a rare occurrence in food-secure parts of the world.²¹ It occurs mostly in developing regions where diets are centered around low-thiamine rich foods such as polished rice and grains.²¹ In food-secure parts of the world, those who are at risk for thiamine deficiencies are individuals who suffer from alcoholism, chronic illnesses or poor nutritional status.²⁰ Additionally, patients who have had bariatric surgery or are on either long-term peritoneal dialysis or parental feeds are also at risk.²⁰

Both women and men are affected by beriberi equally; however, pregnant women and infants are at higher risk.²⁰ For example, a study by Whitefield et al, analyzed data from the 2014 Cambodian Demographic and Health Survey and found that by using the erythrocyte thiamine diphosphate concentrations cut-off of less than 120 nmol/L, 27% of mothers and 15% of infants from the national population sample were thiamine deficient.²²

Ocular Manifestations

Wernicke's encephalopathy is an acute life-threatening degenerative neurological condition caused by acute thiamine deficiency.²³ It is well established that Wernicke's encephalopathy is characterized by several ocular manifestations including horizontal gaze-evoked nystagmus, primary position upbeat nystagmus, gaze-holding failure, double vision, ophthalmoplegia, conjugate gaze palsies, bilateral impairment of the vestibulo-ocular reflex, loss of visual acuity, papilledema, and changes in the appearance of the optic disc and retina.²³ One of the earliest signs that is helpful in detecting Wernicke's encephalopathy is nystagmus.²⁴ A study by Victor et al found that nystagmus was an early sign found in 97% of patients with thiamine deficiency.²⁵ In addition, several studies have demonstrated a link between ophthalmoplegia associated with Wernicke's encephalopathy.^{26,27} A recent clinical appraisal found that from their 110

included articles, 7% reported oculomotor abnormalities as the main clinical manifestation of pediatric thiamine deficiency in high-income countries.²⁸ A recent study by Mifsud et al retrospectively analyzed 56 cases of thiamine deficiency and found the following clinical manifestations: 35.7% had nystagmus, 7.1% had diplopia, 3.6% had blurred vision, and 1.8% had decreased visual acuity.²⁹

Previous literature reviews and a recent study have found evidence that dietary intake of nutrients such as B1 leads to a decrease in dry eye symptoms.³⁰ There was a randomized control trial by Ren et al, in 2022 which looked at the use of oral vitamin B1 in treatment for dry eye disease (DED).³¹ They found that in their treatment group (oral vitamin B1, mecobalamin and artificial tears), patients with DED significantly ($p < 0.05$) improved in the following outcomes: corneal nerve length, width and neuromas, conjunctival congestion score, symptoms of dryness, pain, photophobia, blurred vision, and total symptoms. They concluded that vitamin B1 is a potential treatment option for DED.³¹

Workup for Vitamin Deficiency

Patients in high-risk groups, those presenting with early symptoms of thiamine deficiency, and those presenting with long-term thiamine deficiency symptoms such as heart-failure and numbness in the extremities should have a targeted history and physical examination.²¹ Wernicke's encephalopathy has been described as a triad of symptoms: nystagmus, confusion and ataxia.²¹ With a high-index of suspicion, routine investigations such as electrolytes, urea and creatinine, blood alcohol content, B12, thiamine pyrophosphate levels, erythrocyte transketolase activity or a computed tomography can be ordered to support diagnosis.²⁸

Management

Management for thiamine deficiencies with evidence of neurological and cardiovascular manifestations should include thiamine supplementation of 200 mg intravenous (IV) or orally 3 times a day until symptoms resolve.^{21,29} A maintenance dose of 10 mg daily should be continued after symptoms have resolved. In an acute crisis, 50 mg of thiamine should be administered intramuscularly (IM) for approximately 2 to 4 days, followed by an oral maintenance period.²¹

Vitamin B2 (Riboflavin)

Function of Vitamin

Vitamin B2 or riboflavin is a water-soluble vitamin found naturally in foods, such as dairy products, eggs, lean beef, salmon and chicken breasts.³² It can also be added to a variety of fortified foods and can be found as an over-the-counter nutrient supplement. Bacteria in our gastrointestinal system can synthesize a small amount of this vitamin but dietary intake is still needed to maintain adequate blood levels.³² The recommended daily intake for adults over the age of 18 years-old is 1.1 to 1.3mg/day and 0.9 to 1.1mg/day for men and women respectively.³³

Riboflavin plays a fundamental role in cellular energy metabolism and the breakdown of fats, steroids and medications.³³ Riboflavin in the body is converted to its two major forms, flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN).³⁴ These electron carriers act as key co-factors in redox reactions in the metabolic pathway.³³ Riboflavin also acts as an antioxidant in our body because glutathione reductase requires riboflavin acts a co-enzyme in order to regenerate the free radical scavenger glutathione.^{33,35} In humans, riboflavin deficiencies typically manifest dermatologically through cheilosis, seborrheic dermatitis, glossitis, conjunctivitis, cataracts anemia, migraines and fatigue.³³

Epidemiology of Disease

Riboflavin deficiency is a rare incidence in food-secure parts of the world and occurs mostly in developing regions such as Asia and Africa.³³ For example, a study by Sivaprasad et al in India found that from 270 health urban dwelling adults aged 30–70 years-old, 50% had a vitamin B2 deficiency.³⁶ Children are a group that is high risk for riboflavin deficiency in developing parts of the world where they are unable to obtain adequate levels of dairy products and meat in their diets.^{33,36} In food-secure parts of the world, those who are at risk for riboflavin deficiencies are individuals who are elderly, patients with eating disorders, patients who have excessive alcohol intake, and those on a vegan diet.^{37,38}

Ocular Manifestations

Although the pathophysiology between impaired vision and riboflavin deficiencies have not been fully understood, there have been a few studies that report loss of vision as a clinical sign of ariboflavinosis.³⁹ Some studies have also linked riboflavin deficiencies to ophthalmological findings such as blurred vision.

Most recently a study by Zhao et al, in 2022 reported on the possible association between riboflavin deficiencies and night-time blindness.⁴⁰ This study identified a key novel retina-specific riboflavin binding protein called retbindin, this binding protein plays an important role in retaining flavin levels in the retina. Their paper suggests that those with riboflavin deficiencies clinically display nyctalopia due to cellular changes in the retina.

Workup for Vitamin Deficiency

It is rare that patients present with isolated riboflavin deficiency, in most cases these patients will have other vitamin B deficiencies as well.³³ For high-risk groups a targeted history should be taken including dietary intake such as access to food, previous medical history such as malabsorption disease, pregnancy status, previous family history such as genetic conditions, lifestyle and social history such as alcohol intake. On the physical exam, key clinical findings that would lead to suspicion are patients presenting with sore throat, swelling around the throat, hair loss, blurred vision, fatigue, depression and dermatitis around the mouth. Routine investigations such as blood work up for other vitamin B levels, erythrocyte glutathione reductase and anemia can also help solidify the diagnosis.³³ If there is a high-index of suspicion, urinary excretion rates of riboflavin should be measured while the patient is on a therapeutic trial of riboflavin supplements. If the excretion rate is lower than 40 mg then the patient may be deficient.³³

Management

Management depends on the symptoms experienced by the patient. Those who are deficient should take oral riboflavin supplements from 5 to 100 mg daily depending on the severity of their treatments until symptoms have resolved.³³

Vitamin B9 (Folate)

Function of Vitamin

Vitamin B9, also known as folate, is a water-soluble vitamin found naturally in foods, such as dark leafy greens, beans, fresh fruit, whole grains and eggs. It can also be added to a variety of fortified foods and can be found as an over-the-counter nutrient supplement. Our bodies do not create folate and can only store it for short periods of time; therefore, having a regular dietary intake is essential.

In our bodies, folate is present in its non-active form of 5-methyltetrahydrofolate (THFA). Folate has a fundamental role in DNA and RNA synthesis in our bodies because it acts as a co-enzyme during the biosynthesis of purine and pyrimidine nucleotides. Folate also plays a key role in protein metabolism, specifically in the breakdown of homocysteine into methionine.⁴¹ Lastly, folate is involved in the production of red-blood cells in our bodies and this role becomes essential during states where the body needs more red-blood cells such as pregnancy.⁴²

Folate works closely with vitamin B12. Issues with malabsorption in the gastrointestinal system such as celiac disease, alcoholism, pregnancy, and congenital disease can cause folate deficiencies.⁴³ Folate deficiencies can manifest as macrocytic anemia, fetal neural tube defects, depression and diarrhea.⁴³

Epidemiology of Disease

It is estimated that worldwide approximately only 30% of pregnant women take folate supplements before conception.⁴⁴ It is advised women take folate supplements before conception until their 3rd month of pregnancy as scientific evidence shows a decrease in fetal neural defects.⁴⁴ This information changed policies in Europe and North America requiring foods be fortified with folic acid resulting in a lower prevalence of folate deficiencies in the developed world.⁴⁵ Although folate deficiencies are one of the more common vitamin deficiencies, estimates of the global prevalence is limited. A systematic review which analyzed World Health Organization Micronutrient databases on data collected from 2000 to

2014 estimates that prevalence of folate deficiency was greater than 20% in lower income countries and less than 5% in higher income countries.⁴⁶

Ocular Manifestations

Literature has reported that folate deficiency can lead to optic neuropathy. Studies have shown that the deficiency usually appears with a painless bilateral optic neuropathy, with poor colour vision and progressive visual acuity loss.^{47,48} There can be significant visual functioning improvement with folate supplementation.^{49,50}

Folate deficiency has also been linked with age-related macular degeneration (AMD).⁵¹ An epidemiological study in 2013 found that those with vitamin B9 (<11 nmol/L) deficiencies had an 75% and 89% increased risk of early and any form of AMD in 10 years.⁵² The association between B9 and AMD has been supported in subsequent studies.⁵³

Finally, there is an association between folate deficiency and eye cancer. In 2012, Orjuela et al, demonstrated, through a case-control study design, that maternal homozygosity for the gene responsible for converting synthetic folic acid into biologic folic acid was associated with an increased risk of retinoblastoma.⁵⁴

Workup for Vitamin Deficiency

Patients who are being worked up for folate deficiency should also be investigated for vitamin B12 deficiency and macrocytic anemia. A complete blood count (CBC), peripheral smear (PS) and serum folate and vitamin B12 levels should be ordered. Patients who have a serum folate level lower than 2 ng/mL are considered to be deficient.⁴² To confirm the diagnosis, further tests on methylmalonic acid (MMA) and homocysteine levels can be assessed. Normal MMA and elevated homocysteine levels is consistent with folate deficiencies.⁵⁵

An in-depth history on dietary habits, pregnancy, substance use and medications should be taken from all patients. Medications such as methotrexate, phenytoin and trimethoprim can lead to folate deficiencies. Signs and symptoms that can be seen during clinical assessment include, symptoms of anemia, signs of anorexia, glossitis, depression, dementia, and confusion.⁴²

Management

Management involves folic acid supplementation.⁵⁵ Patients are most commonly offered oral supplements ranging from 1 to 5 mg daily.⁴²

Vitamin B12

Function of Vitamin

Vitamin B12 or cobalamin is a water-soluble vitamin found naturally in foods such liver, eggs, fish, and milk products.⁵⁶ The human body relies on dietary intake for adequate blood levels of cobalamin.

Cobalamin has a central cobalt atom in its structure and is found in 2 active forms in our bodies: methylcobalamin and 5-deoxyadenosylcobalamin.⁵⁷ Similar to vitamin B9, cobalamin is essential for our bodies to create healthy red blood cells, DNA and RNA, and is critical for brain health and appropriate nerve cell development.⁵⁷ Cobalamin act as a co-factor for a key reaction that turns homocysteine into methionine. High levels of homocysteine can be toxic for our bodies and damage our blood vessels and nerve cells. The by-products of the reaction that creates methionine are directly used to synthesize pyrimidine for DNA. Additionally, methionine itself is an important methyl-donor that is used in metabolic reactions.⁵⁷

Issues with malabsorption in the gastrointestinal system, impairment in the synthesis and function of intrinsic factor, low dietary intake of cobalamin, Crohn's disease, excessive alcohol intake, pernicious anemia, history of bariatric surgery and strict vegan diets can cause cobalamin deficiencies.⁵⁸ Vitamin B12 is absorbed in the distal ileum through its transportation protein intrinsic factor, those who have had bariatric surgery and issues with intrinsic factor are at a higher risk of deficiency. Signs and symptoms of this vitamin deficiency include macrocytic anemia, depression and abnormal fetal development.⁵⁸

Epidemiology of Disease

Prevalence estimates of cobalamin deficiencies vary quite a bit and depend on the population that is being assessed. In the general population it is estimated that 1% to 2% of people are vitamin B12 deficient. In one analysis the estimates for cobalamin deficiency

in those older than 60 years in both the United States and the United Kingdom was approximately 6%.⁵⁸ They stated that this prevalence increased to almost 20% as the age of the sample increased. This same study found the prevalence to be significant higher in all age groups in lower income countries. In vegetarians the prevalence of cobalamin deficiency in infants can be as high as 45%, 33.3% in children and adolescent and 39% in pregnant women.⁵⁹ Previous studies have also found that cobalamin deficiencies were higher in those with type 2 diabetes and pernicious anemia.⁶⁰

Ocular Manifestations

Similar to vitamin B9, cobalamin deficiency can lead to optic neuropathy.^{61–64} There can be recovery with supplementation, although it may be partial.^{61,63}

B9 and cobalamin are also similar in that both have been linked with age-related macular degeneration. An epidemiological study in 2013 found that those with vitamin B12 deficiencies (<185 pmol/L) had a higher incidence of early and late AMD diagnosis.⁵² The association between B12 and AMD has been supported in subsequent studies.⁵³

Finally, cobalamin has been linked to dry eye disease and has been used as a treatment for pain associated with dry eye disease.^{65,66} A study by Ozen et al, found that treating vitamin B12 deficiency in patients with dry eye disease in addition to topical treatment improved the neuropathic pain.⁶⁶ Another case report in 2015 of a 28-year-old patient with bilateral burning pain and foreign body sensation in both eyes was found to have cobalamin deficiency.⁶⁷ Resolution of symptoms occurred after cobalamin supplementation and topical treatment.

Workup for Vitamin Deficiency

Similar to vitamin B9, patients who are being worked up for B12 (cobalamin) deficiency should also be investigated for vitamin B9 deficiency, macrocytic anemia and pernicious anemia.⁴² Patients who have a serum cobalamin level lower than 200 pg/mL are considered to be deficient. To confirm the diagnosis, further tests on methylmalonic acid (MMA) and homocysteine levels can be assessed. Elevated MMA and homocysteine levels is consistent with cobalamin deficiency.⁵⁵

An in-depth history on previous gastrointestinal surgeries, dietary habits, substance use and neurological findings should be taken from all patients. Signs and symptoms that can be seen during clinical assessment include, jaundice, peripheral neuropathy, enlarged tongue, diarrhea, headaches, weakness, fatigue, depression, memory loss, ataxia and neuropsychiatric findings.

Management

Management depends on the underlying etiology of the cobalamin deficiency. Most patients are recommended to take 1000 µg of cobalamin intramuscularly once a week for up to 4 weeks.

Vitamin C (Ascorbic Acid)

Function of Vitamin

Vitamin C (or ascorbic acid) is a water-soluble nutrient that is necessary in many biological functions.^{68–70} It can be readily converted from its reduced form, ascorbic acid, to the oxidized form, dehydroascorbic acid.^{68–70} As a result, vitamin C is a very potent antioxidant. As an antioxidant, vitamin C functions in neutralizing reactive oxygen species (ROS) and nitrogen species.⁷¹ This role protects organs which are susceptible to injury from free radicals, such as the eye, brain, and stomach, against oxidative stress.⁷¹ Vitamin C is also involved in the production of collagen, carnitine, catecholamines, cholesterol and some peptide hormones.⁶⁸ Finally, it enhances the absorption of iron from dietary sources.^{68–70}

Epidemiology of Disease

Humans are one of the few animals that do not endogenously synthesize vitamin C from glucose or galactose.⁷⁰ As a result, vitamin C must be obtained from the diet. There are many plant sources with high levels of vitamin C including citrus fruits, peppers, tomatoes, and leafy vegetables. Animal products are poor sources of as vitamin C as it is easily destroyed with heat or cooking. Due to its ready availability in diet, severe vitamin C deficiency is rare.⁷² However, it can be seen in people with poor dietary intake, alcoholism, malabsorption disorders or kidney failure.

Hypovitaminosis C can lead to scurvy, a condition characterized by fatigue, anemia, easy bruising, gum disease and hyperkeratotic hair follicles with hemorrhages.⁷³ Due to the role of vitamin C in synthesis of collagen; areas such as skin, gum, and bones that contain higher collagen levels are susceptible to deficiencies.⁷³ Vitamin C is also involved in other conditions, such as common cold, cardiovascular diseases and neurodegenerative diseases.⁷⁴

Ocular Manifestations

Scurvy is recognized by its hemorrhagic symptoms, and this can be observed as subconjunctival or orbital hemorrhages.⁷⁵ The role of vitamin C as an antioxidant also means that it may play a role in conditions that are linked to ROS, including age-related macular degeneration (AMD), cataracts and glaucoma.

The Age-Related Eye Disease Study (AREDS) investigated the effect of nutritional supplements on AMD.⁷⁶ The AREDS formulation (vitamin C, E, beta carotene, and zinc with copper) reduced the progression of advanced AMD, with these findings persisting up to 10 years after the initial trial.⁷⁶ Furthermore, there is evidence that patients with AMD had lower vitamin C intake or consumed less foods that contain vitamin C than their healthy control counterparts, suggesting that vitamin C intake may be protective against AMD development or its progression.⁷⁷

The AREDS trial also investigated the role of the nutritional supplements on cataracts and found no significant preventative effect of vitamin C on cataract development.⁷⁶ Similarly, the Roche European American Cataract Trial (REACT) also found no benefit in antioxidant supplementation in reducing the risk of cataract progression.⁷⁸

An association between oxidative stress and glaucoma has been established where oxidative stress can lead to damage of the trabecular meshwork resulting in increased intraocular pressure (IOP) and eventually the loss of ganglion cells.⁷⁹ There is evidence that patients with glaucoma have lower vitamin C levels than healthy controls.⁸⁰ There are additional reports showing that vitamin C may have a protective effect against open angle glaucoma (OAG)⁸¹ and that consumption of leafy green vegetable and fruits (rich sources of vitamin C) decrease the risk of glaucoma.⁸²

Workup of Deficiency

Ocular diseases due to vitamin C deficiency usually do not arise in isolation and are typically a result of prolonged and severe deficiency. If a patient's clinical presentation is suspicious for hypovitaminosis C, then serum vitamin C levels should be measured. Vitamin C level is considered normal if above 28 µmol/L, low if 11–28 µmol/L and deficient if <11 µmol/L.⁸³

Management

The recommended daily vitamin C requirement differs in various countries. In the USA and Canada, guidelines recommend 75–90 mg daily and increased dose for smokers.^{83,84} For treatment of ocular hemorrhages, treatment guideline for scurvy is followed: 1–2 g of vitamin C daily for the first 3 days, then 500 mg for the next week, followed by a daily dose of 100 mg for the next 3 months. Symptoms and signs typically resolve within 1–2 weeks of treatment.⁷⁵

Vitamin D

Function of Vitamin

Vitamin D is a fat-soluble prohormone with a main function of maintaining calcium homeostasis, phosphorus absorption, mineral metabolism, and skeletal health.⁸⁵ Specifically, vitamin D aids in increasing intestinal absorption and renal reabsorption of calcium, stimulating osteoclasts activity resorbing calcium from bones, and promoting intestinal phosphorus absorption. Finally, vitamin D is also involved in the immune system, particularly in the inflammatory response.⁸⁶

Vitamin D is synthesized from vitamin D2 (or ergocalciferol) and vitamin D3 (calciferol).⁸⁵ Vitamin D2 is derived from plants and obtained in the diet while vitamin D3 is produced from 1-dehydrocholesterol from the skin after exposure to ultraviolet B radiation (UVB). Vitamin D3 is then transported to the liver where 25-hydroxylase activates it to 25(OH)D3, the main circulating form of vitamin D. Finally, 25(OH)D3 is transported to the kidney where it is further hydroxylated by 1-hydroxylase to the active form of vitamin D1, 25(OH)₂D3, or calcitriol.^{85,86} Finally, vitamin D is

produced locally in the eye. Studies have shown that vitamin D hydroxylases are localized in ocular structures like ciliary body, cornea, and the retina, indicating an important role of vitamin D for ocular health.⁸⁷

Epidemiology of Disease

Vitamin D is derived mainly from diet and the skin. The prevalence of vitamin D deficiency is estimated as 24% in the US, 37% in Canada and 40% in Europe.^{88,89} The most profound disease manifestation of vitamin D deficiency is rickets and osteomalacia.⁹⁰ Rickets (pediatric) and osteomalacia (adult) are bone diseases that result from vitamin D deficiency leading to reduced calcium and phosphorus availability leading to serious bone demineralization. Prevalence of rickets is estimated to be between 9 and 2300 per 100,000 people depending on the country.⁹¹ Vitamin D deficiency also contributes to other conditions, such as cardiovascular diseases, cancers and autoimmune diseases like diabetes, multiple sclerosis, and inflammatory bowel disease.⁹²

Ocular Manifestations

Dry eye disease (DED) is a multifactorial disease that affects up to 5–34% of the general population with incidence increasing with aging.⁹³ Recent studies have shown that DED is a chronic inflammatory disease and, with vitamin D involved in anti-inflammatory processes, it has been implicated in the pathogenesis of DED. Patients with DED have been observed to have lower level of vitamin D than healthy controls.⁹⁴ Moreover, vitamin D supplementation led to improvement of DED symptoms.⁹⁵ Although there has been no established causative relationship between vitamin D and DED, this evidence suggests that vitamin D may have a protective effect against DED.

Diabetic retinopathy is a common neovascular complication of diabetes mellitus (DM) that can lead to blindness. There is an inverse relationship between vitamin D levels and DR prevalence; and the lower the vitamin D level, the more severe the retinopathy.⁹⁶ These findings are consistent in patients with both type 1 and 2 DM.⁹⁷ Vitamin D supplementation may act as a protective factor in the development of diabetic retinopathy. Vitamin D also improves the body's insulin sensitivity, reducing the risk of insulin resistance and development of diabetic retinopathy.⁹⁸

Studies have shown that serum vitamin D levels were lower in glaucoma patients compared to healthy controls although the level of vitamin D did not correlate with glaucoma severity.^{99,100} In non-human primates with glaucoma, calcitriol injection reduced IOP on a dose-dependent, but these results were not observed in a similar human study where patients were given vitamin D supplements for 6 months had no changes in IOP compared to patients receiving placebo.^{101,102}

It has been proposed that vitamin D may be protective against cataracts.¹⁰³ Several studies have shown an inverse relationship between serum 25(OH)D3 levels and the risk of developing nuclear and subcapsular cataracts.^{104–106} Patients with cataracts were observed to have low vitamin D levels.^{104–106} However, the relationship between vitamin D levels and cataract formation has not been well established in high quality, prospective studies to date. There is also evidence that patients with age-related macular degeneration (AMD) have low serum vitamin D with more advanced disease correlating with severe vitamin D deficiency.^{107,108} Vitamin D supplementation may also be protective against AMD.^{109,110}

Multiple sclerosis (MS) is an autoimmune disease that results in the demyelination of central nervous system axons. As vitamin D is an important immunomodulator, it has been implicated in the pathogenesis of MS. Numerous studies have indicated that there is a correlation between vitamin D levels and MS where higher serum vitamin D levels indicate lower risk of developing MS.^{111–114} A Finnish case-control showed that low maternal pre-natal vitamin D levels can increase the risk of MS in the offspring.¹¹⁵ Adequate vitamin intake has also been shown to reduce the activity and progression of MS.¹¹⁶ Lastly, the effect of vitamin D supplementation on MS progression is conflicting with some reports indicating that vitamin D supplementation can reduce the risk of MS relapses, disease activity, and improve quality of life in patients with MS,^{117,118} while other studies have shown no effect of vitamin D supplementation in patients with sufficient serum vitamin D levels.^{119,120} Optic neuritis, a common first symptom of MS, is characterized by demyelination of axons of the optic nerve. Studies have shown that severity of acute optic neuritis (AON) inversely correlated with serum 25(OH)D3 levels, where patients with vitamin deficiency presented with more severe AON suggesting that vitamin may offer neuroprotection in AON.^{121,122}

Graves' disease is an autoimmune thyroid disease that has been linked to vitamin D deficiency. Several studies indicate that people with Graves' disease have lower vitamin D levels compared to the general population.¹²³ Thyroid eye disease (TED) is an ocular manifestation that develops in up to 25% of people with Graves' disease. Similar to

results seen in Graves' disease, a retrospective case-control study showed that patient with TED had insufficient or deficient vitamin D levels.¹²⁴ Furthermore, Graves' disease patients with lower serum 25(OH)D levels were more at risk to develop TED, suggesting vitamin D may play a protective role in the development of TED.¹²⁵

Vitamin D has been connected to roles in cell differentiation and anti-neoplasm. Since sunlight exposure is necessary for the activation of 25(OH)D, it has been associated with decreased risk for cancer. Cancers, such as retinoblastoma (RB) have been shown to have 25(OH)D receptors which may be how vitamin D mediates its anti-neoplastic effect.¹²⁶ One study showed that combination of vitamin D with chemotherapy significantly reduced tumor growth in patients with RB.¹²⁷ A more recent study showed that infants with higher sunlight exposure had a reduced risk of developing sporadic RB.¹²⁸ Together, these studies suggest a relationship between vitamin D and RB, however, further studies are needed to confirm the association.

Workup of Deficiency

Vitamin D levels are not routinely screened in the general population. When vitamin D deficiency is suspected, the serum 25(OH)D3 level is measured, as it is the major circulating vitamin D.¹²⁹ Serum 1,25(OH)₂D3 is not often measured except in special cases like acquired and inherited vitamin D disorders.¹²⁹ Serum 25(OH)D3 level lower than 20 ng/mL (500 nmol/liter) is considered vitamin D deficient while levels between 21 and 29 (525–725 nmol/liter) is considered vitamin D insufficient.¹²⁹

Management

In Canada and the USA, foods such as cow's milk and margarine are fortified with vitamin D, but may not be sufficient in areas with low levels of sun exposure. A daily 400 international unit (IU) vitamin D is recommended for infants while adults should get 400–2000 IU of vitamin D daily.^{129,130}

Vitamin E

Function of Vitamin

Vitamin E is a term for a group of 8 lipid soluble molecules: four (α , β , δ , γ) each of tocopherols and tocotrienols with α -tocopherol being the most abundant in nature and with the greatest biological activity.¹³¹ Vitamin E was first discovered in 1922 as an essential factor in fertility where deficiency lead to fetal resorption.¹³² Subsequent work has shown that vitamin E is a potent fat soluble antioxidant.¹³³ α -tocopherol, the main vitamin E form for human health, is located primarily in the cell membrane where it protects against lipid peroxidation by reducing the amount of free radicals thus allowing the polysaturated fatty acids (PUFAs) in the membrane to maintain their bioactivity.¹³³

In addition to its role as antioxidant, vitamin E is also involved in reproductive health protecting against loss of spermatogenesis in males and fetal resorption in females.¹³² Other functions include roles in cellular signalling, inhibiting smooth muscle proliferation, protein kinase C activity, and parts of the atherosclerosis process.¹³⁴

Epidemiology of Disease

Vitamin E is the most important lipid soluble antioxidant in the human body. As a result, it has been linked to many chronic diseases, particularly those with oxidative stress involved in their pathogenesis such as cardiovascular diseases, diabetes, and cancer. Vitamin E is obtained in foods such as nuts, seed, oils, and leafy vegetables. The recommended daily allowance (RDA) is 22.5 IU (15 mg).¹³⁵

Although vitamin E is found abundantly in various foods, it is estimated that up to 90% of Americans do not consume their RDA.¹³⁵ However, overt vitamin E deficiency is rare and is more often seen in children due to their reduced stores in comparison to adults. The most common cause of vitamin E deficiency is severe malnutrition and malabsorption disorders (such as cystic fibrosis, short bowel syndrome, chronic liver disease).¹³⁶ Abetalipoproteinemia (ABL), a genetic disorder caused by mutations in the gene for the α -tocopherol transfer protein (α -TTP) can result in a neurological disorder, ataxia with vitamin E deficiency (AVED).¹³⁷

Ocular Manifestations

Patients with abetalipoproteinemia (ABL) lose apolipoprotein B which leads to reduced levels of cholesterol and triglycerides and in turn low absorption of lipid soluble vitamins like vitamin E.¹³⁸ Ocular manifestations of ABL like ophthalmoplegia, strabismus and nystagmus usually appear in childhood.¹³⁹ However, the most profound ocular manifestation is ABL retinopathy, which can eventually lead to reduction in visual acuity. Early treatment with vitamin E supplementation attenuates the severe retinal damage associated with this disorder.^{140,141}

Retinopathy of prematurity (ROP) is another retinopathy associated with vitamin E deficiency. Infants, especially premature newborns, are at higher risk of oxidative damage due to increased exposure to ROS and decreased levels of antioxidants.¹⁴² Premature infants with respiratory distress syndrome (RDS) are at even higher risk as treatment of RDS exposes them to elevated concentrations of oxygen, further increasing the level of free radicals.¹⁴² Prematurity and oxidative damage promote the development of ROP. Due to its function as an effective antioxidant, vitamin E's role in the management of ROP has been studied. Although prophylactic vitamin E in premature infants is inconclusive, there is some evidence that vitamin E supplementation reduces the severity but not total incidence of ROP.^{143–145}

Oxidative stress and inflammation contribute to the pathogenesis of age-related ocular diseases such as AMD and cataracts. As a result, antioxidants such as vitamin E have been studied for their potential role in protecting against these diseases. The landmark AREDS clinical trial investigated the role of antioxidants vitamin C and E, beta-carotene (vitamin A), zinc and copper on the progression of AMD. Their results indicated that the AREDS formulation which contains 400 IU of vitamin E daily (1334% the RDA) reduced the progression of AMD.⁷⁶ Furthermore, patients with AMD had lower levels of serum vitamin E compared to healthy controls.^{146,147}

Workup of Vitamin Deficiency

Severe vitamin E deficiency is more common children compared to adults, likely due to their lower stores. Severe vitamin E deficiency leads to anemia, spinocerebellar ataxia, AVED, neuropathies and myopathies.^{139,140} Patients with malabsorption disorders, α -TTP or signs of severe malnutrition showing symptoms associated with vitamin E deficiency should be tested. Definite diagnosis is made by measuring serum α -tocopherol level. In adults, α -tocopherol <12 mol/L (0.5mg/dL) is considered inadequate or deficient.¹⁴⁸ As vitamin E status is affected by lipid levels, correction of α -tocopherol to lipid concentration is recommended in patients with hyperlipidemia so that the lipid: α -tocopherol ratio is similar to those with normal circulating lipid concentrations.¹⁴⁹

Management

A daily recommended intake of 12–15 mg of α -tocopherol is recommended for adults. In people with symptomatic vitamin E deficiency, daily vitamin E supplementation up to 2000 mg is given. In patients with ABL, prophylactic vitamin E supplementation is recommended to prevent the development and progression of neurologic symptoms.¹⁵⁰

Vitamin K

Function of Vitamin

Vitamin K is a fat soluble nutrient that is crucial in the biosynthesis of proteins within the clotting cascade, such as prothrombin, proteins C and S and clotting factors II, VII, IX and X.¹⁵¹ Deficiencies of vitamin K may lead to a disease entity known as vitamin K deficiency bleeding (VKDB) due to the disruption in clotting factor homeostasis.¹⁵¹ Neonates contain only a small amount of hepatically stored vitamin K due to the small amount of placental transfer from maternal blood.¹⁵¹ Breastfeeding provides infants modest increased levels and stores of vitamin K, but whole milk contains upwards of 5-times more vitamin K, and formula contains up to 100 times more.¹⁵¹ Therefore, solely breastfed children are at risk of VKDB. To date, there is no direct link towards vitamin K and the anatomical or neurological health of the developing or adult eye. However, deficiencies can predispose neonates or adults to idiosyncratic bleeding events that can have major ramifications on vision.

Epidemiology of Disease

The human gastrointestinal tract produces endogenous vitamin K; however, a diet rich in soybeans, alfalfa, spinach and tomatoes helps meet the adult vitamin K requirements.¹⁵¹ Compared to the previous nutrients discussed, hypovitaminosis K is rare.¹⁵² However, VKDB has been cited in the first week of life to range between 0.25 and 1.7 cases per 100 live births.¹⁵³ This incidence may be misleading though, as prophylactic intramuscular vitamin K has become standard practice in antenatal care, therefore reducing the early VKDB cases in the developed world. Late cases of VKDB, which occurs anywhere between the 2nd week – 6th month of life, is cited to occur in 1/15,000–1/20,000 births, with cases primarily in exclusively breastfed infants or those with gastrointestinal malabsorption diseases.¹⁵²

Ocular Manifestations

Vitamin K deficiency has been linked to ocular hemorrhagic diseases in newborns and adults. Although no large sample studies exist on ocular manifestations secondary to VKDB, many case reports have been published on vitreous and retinal hemorrhages in the setting of hypovitaminosis K. The first case of retinal hemorrhages associated with VKDB was by Wille in 1944.¹⁵³ This patient presented with early-VKDB and flame-shaped pre- and intra-retinal hemorrhages within the posterior pole secondary to birth trauma.¹⁵³ These hemorrhages resolved in 3 months. In 1995, Wetzel et al presented a 10-week-old infant presumed to have non-accidental trauma due to bruises on her hands, thighs and rectum.¹⁵⁴ However, one week after presentation, the patient was unable to be aroused from sleep. A fundus examination demonstrated bilateral flame-shaped and dot-blot hemorrhages throughout the posterior pole that were too many to count.¹⁵⁴ Blood work found factor 7 activity as less than 1% and increased prothrombin time (PT); it was later elucidated that the infant did not receive vitamin K prophylaxis.¹⁵⁴ Long-term visual outcomes were unable to be determined as the patient succumbed to her bleeding disorder.¹⁵⁴ All other case reports with retinal hemorrhages associated with hypovitaminosis K note children are exclusively breastfed, further stressing the importance of prompt vitamin K prophylaxis and monitoring.^{155,156} There have been no reports of retrobulbar or anterior segment hemorrhages linked to VKDB.

Workup for Vitamin Deficiency

Vitamin K deficiency classically leads to elongated PT and bleeding in the setting of minor or absent trauma. PT has been shown to be a more sensitive measure of vitamin K levels as direct measurement of vitamin K demonstrates high variability.¹⁵⁷ Another serum marker for vitamin K levels is known as “Protein Induced by Vitamin K Absence or Antagonism” (PIVKA). PIVKA levels are prominent when patients acquire less than 60mcg vitamin K per day or in newborns without supplementation.¹⁵⁷ Diagnosis of vitamin K deficiency has been defined as a PT level greater than 4 times the normal reference range with one of the following criteria: 1. PT normalization within 30 minutes after IV vitamin K administration, 2. increased levels of PIVKA or 3. Normal platelet count with normal fibrinogen and absence of degradation products.¹⁵⁷

Management

Effective management of hypovitaminosis K requires rapid detection of signs related to clotting disorders. Administration of 0.5–1.0 mg of intramuscular vitamin K has now become the antenatal standard of care, but 2 mg oral vitamin K1 at birth with subsequent 1 mg orally weekly for 3 months has been introduced as an alternative.^{157,158} This has demonstrated a significant decrease in the incidence of VKDB worldwide. For infants who do develop bleeding events in the setting of vitamin K deficiency, 1 mg of intramuscular vitamin K has been shown to restore homeostatic coagulation and reverse increased INR and PTT times.¹⁵⁹ For adults with vitamin K nutritional deficiency, 90 µg/day supplementation for women, and 120 µg/day for men, has been encouraged.¹⁵⁸ If retinal hemorrhages occur in the setting of VKDB, close observation would be warranted to ensure prompt resolution and monitor for amblyopia. Careful observation of low-vision habits in newborns or bleeding events visualized by the parents is crucial in the developing period.

Conclusion

This review summarizes the literature on the main vitamin deficiencies that can cause or exacerbate ophthalmological conditions. Vitamin deficiencies can have many ocular manifestations, including xerosis, encephalopathy, nyctalopia, optic neuropathy, nystagmus, ophthalmoplegia and hemorrhage. Vitamin deficiencies can also exacerbate common eye conditions such as dry eye disease, age-related macular degeneration, and diabetic retinopathy. By describing the function, epidemiology, manifestations, workup and management of each vitamin deficiency, the aim of this review is to give clinicians a practical guide to recognizing, assessing and treating the ophthalmological conditions associated with vitamin deficiencies.

Disclosure

The authors report no conflicts of interest relevant to this study.

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