

Nutritional Deficiencies

As the number of bariatric procedures in the US rises, clinicians must be aware of the ocular manifestations of vitamin deficiencies and their treatment.

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There is a well-recognized connection between vitamin deficiencies and ophthalmic disease.¹ Although the reported prevalence of nutritional deficiencies in the US varies depending on the study population and specific nutrients studied,² a deficiency in vitamin A remains the leading cause of preventable blindness in developing countries.³

Vitamin deficiencies commonly result from poor nutrition due to poverty, drug abuse, and alcoholism. Recent reports, however, suggest that nutritional deficiencies due to malabsorption from gastric bypass procedures are increasing in frequency. A prevalence of obesity in the US has increased interest in surgical procedures for weight loss. For instance, the number of gastric bypass surgeries rose more than 600% from 1993 to 2003. Metabolic and nutritional derangements are common sequelae following these procedures. The Roux-en-Y, the gold-standard bariatric surgery, is known to cause vitamin B₁₂, folate, and iron deficiencies; more aggressive diverting procedures may lead to deficiencies in the fat-soluble vitamins A, D, E, and K due to a malabsorption of fat.⁴ Although patients are routinely prescribed multivitamins and supplements following bariatric procedures, inadequate adherence to this therapy would place them at risk for developing metabolic deficiencies.⁵

Vitamin deficiencies may produce a wide range of systemic signs and symptoms. Ophthalmologists must screen for and recognize the ophthalmic manifestations of the various states of deficiency in patients who have undergone gastric bypass procedures. This article discusses general ocular and visual field abnormalities related to nutritional deficiencies involving vitamin A, vitamin B₁₂, folate, and vitamin C as well as adequate replacement therapy.

VITAMIN A

Although vitamin A deficiency is common in the developing world,⁶ it is rarely seen in the US but may

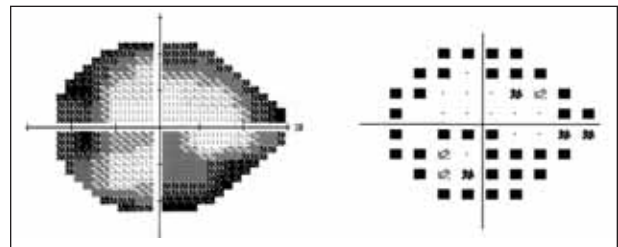


Figure 1. Humphrey Visual Field 24-2 testing (Carl Zeiss Meditec, Inc., Dublin, CA) reveals a peripheral ring scotoma from vitamin A deficiency in the patient's left eye.

become a more clinically recognized phenomenon secondary to malabsorption as the demand for bariatric surgery grows.⁷ This nutritional lack has a wide range of ocular manifestations. Impaired dark adaptation, leading to night blindness (nyctalopia), is the earliest and most common symptom. Up to 60% of patients with vitamin A deficiency due to fat-malabsorption conditions, cholestasis, small-bowel bypass, or inflammatory bowel disease may have subclinical dark-adaptation abnormalities.⁸ Xerophthalmia, which is nearly pathognomonic, results from keratinization of the eyes and involves dehydration of the conjunctiva and cornea. The cornea becomes infiltrated and hazy at an early stage. Keratomalacia involves liquefaction of part of or the entire cornea, which can ultimately lead to phthisis bulbi. In advanced deficiency, Bitot's spots, areas of proliferating abnormal squamous cells and keratinization of the conjunctiva develop and are pathognomonic.⁹

In the retina, vitamin A deficiency preferentially affects the rod photoreceptors. Rods peak in density in a ring pattern 18° or 5 mm from the center of the fovea.¹⁰ As a result, visual field testing will classically reveal a midperipheral ring scotoma (Figure 1). Alternative field abnormalities include the bilateral constriction of the peripher-

al visual fields or generalized depression.¹¹ Scotopic, full-field, electroretinographic wave forms are typically reduced.¹²

The World Health Organization recognizes vitamin A deficiency as the single most important cause of childhood blindness in developing countries. A strategy to combat this global concern is based on its prevention through the fortification, diversification, and supplementation of food as well as public health measures.³ For treatment, the World Health Organization recommends oral vitamin A replacement, from 50,000 to 200,000 IU per day, depending on the age of the patient.¹³ Intramuscular injections in symptomatic patients may help expedite the nutrient's absorption and accelerate the patient's visual recovery.⁷ For individuals with vitamin A deficiencies following bariatric surgery, a complete reversal of the problem's signs and symptoms can occur as quickly as 3 days following treatment.¹¹

VITAMIN B₁₂

Although the prevalence of vitamin B₁₂ deficiency in the general population is unknown, its incidence appears to increase with age. Up to 15% of adults older than 60 years have laboratory evidence of a deficiency in vitamin B₁₂,¹⁴ usually resulting from malabsorption, the inability to split cobalamin from food, or the deficiency of intestinal transport proteins. Gastric atrophy, the chronic carriage of *Helicobacter pylori*, and the use of antacids impedes the enteral absorption of food-bound vitamin B₁₂ in the elderly population. Individuals with small-bowel inflammatory disease or with a history of surgical removal of the small bowel may also experience impeded absorption of vitamin B₁₂.

Ocular manifestations of this entity may occur in concert with megaloblastic anemia but often appear in isolation. Patients typically present with reduced visual acuity that is painless, symmetrical, and progressive, but the optic neuropathy occasionally may be unilateral and subacute. Affected individuals' color vision is frequently impaired, and a relative afferent pupillary defect is often absent due to bilateral impairment. A formal evaluation of the patient's visual fields often reveals central or cecocentral defects (Figure 2). The optic disc may be normal or slightly hyperemic in the early stages of the deficiency. Several months to years later in the course of the disease, disc-related changes involve a loss of the nerve fiber layer in the papillomacular bundle, temporal disc pallor, and optic atrophy.¹⁵ Associated neurologic abnormalities include spastic paraparesis, ataxia, and a loss of vibratory and positional sensation due to subacute combined degeneration of central nervous system myelin.

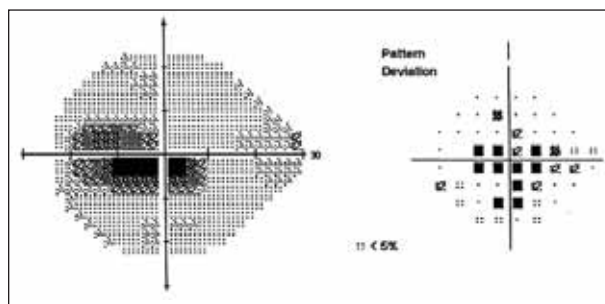


Figure 2. Humphrey Visual Field 24-2 testing shows a cecocentral depression from vitamin B₁₂ in the patient's left eye.

The diagnosis of vitamin B₁₂ deficiency is confirmed by the presence of inadequate serum levels, although the normal levels of this nutrient are quite variable across the adult population. When highly suspicious for clinical disease, therefore, clinicians should obtain methylmalonic acid and homocysteine levels, because the presence of elevated amounts of metabolites is a sensitive marker of functional vitamin deficiency. Standard treatment entails intramuscular injections of 1,000 mcg of vitamin B₁₂; the initial dose is administered daily for 3 days and then monthly for life.¹⁶

FOLATE

The mandatory fortification of cereal-grain products with folic acid began in the US in 1998 to decrease the number of children born with neural tube defects. Subsequently, the prevalence of folate deficiency dropped from 16% to 0.5%.¹⁷ Currently, the most common causes of deficiency are an inadequate intake of this nutrient, usually associated with malnutrition or alcoholism, an increased demand for folate due to pregnancy or lactation, and impaired absorption, as seen with tropical sprue or as a consequence of certain medications (eg, phenytoin).¹⁸ Absorption occurs in the duodenum and upper jejunum, and the liver's stores provide only a 3 to 6 months' reserve.

A lack of folate may produce a megaloblastic anemia and optic neuropathy that is indistinguishable from that caused by low vitamin B₁₂. Clinically, one may be able to distinguish a deficiency in folate versus vitamin B₁₂ by an absence of associated neurologic symptoms, but a lack of vitamin B₁₂ may result in an isolated optic neuropathy. As occurs with low levels of vitamin B₁₂, folate deficiency results in a nutritional optic neuropathy characterized by bilaterally symmetrical, cecocentral vision loss with preferential involvement of the papillomacular bundle.¹⁵

Daily doses of oral folate 400 to 1,000 µg replenish tissues and are usually successful remedies, even if the

patient's deficiency resulted from malabsorption. The normal requirement of folate is 400 µg per day.

VITAMIN C

A recent study determined that the prevalence of vitamin C deficiency in the US is 14% among males and 10% among females.¹⁹ The deficiency occurs in severely malnourished individuals, drug and alcohol abusers, and those living in poverty. Scurvy results from low levels of ascorbic acid, largely due to impaired collagen synthesis, which depends on ascorbate. Symptoms can occur as early as 3 months after deficient intake. Ocular involvement is primarily due to hemorrhages caused by increased capillary fragility. Proptosis secondary to orbital hemorrhage occurs in 10% of cases of infantile scurvy but is rarely seen in adults.²⁰ Petechiae or larger hemorrhages can occur in the conjunctiva, eyelids, orbit, anterior chamber, vitreous, and other ocular structures. Despite the high concentration of ascorbic acid in the crystalline lens, cataracts are not common. There are no known visual field defects that are classically associated with scurvy. Treatment entails the oral replacement of vitamin C with 100 mg four times a day for 10 to 14 days, followed by a maintenance dose of at least 60 mg per day until the recommended dietary allowance (approximately 120 mg per day, depending on the person's sex and age) is resumed.²¹

CONCLUSION

Clinicians should be aware of the ocular signs and symptoms associated with vitamin deficiencies. Alcohol abuse, inflammatory bowel disease, and tropical sprue are a few conditions known to predispose patients to vitamin deficiencies. A history of bariatric surgery can now be added to this list. The appropriate treatment for vitamin deficiencies requires closely monitored replacement, because excessive supplementation may be toxic, especially with fat-soluble vitamins.²²

A careful clinical examination, formal visual field testing, and laboratory testing are indicated in patients at risk for nutritional deficiencies. The role of imaging to detect early retinal and optic nerve disease remains to be elucidated. Further research examining the utility of intraocular imaging (such as ocular coherence tomography and confocal scanning laser ophthalmoscopy) in patients with nutritional deficiencies may shed light on how these disease states affect the overall health of their retinas and optic nerves. □

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- Hoyt CS. Vitamin metabolism and therapy in ophthalmology. *Surv Ophthalmol*. 1979;24:177-190.
- Alaimo D, McDowell MA, Briefel RR, et al. Dietary intake of vitamins, minerals, and fiber of persons ages 2 months and over in the United States: Third National Health and Nutrition Examination Survey, phase 1, 1988-91. In: *Advance Data*. Centers for Disease Control and Prevention. 1994;258:1-28.
- Indicators for assessing vitamin A deficiency and their application in monitoring and evaluating intervention programmes. Geneva, Switzerland: World Health Organization; 1996.
- Stater GH, Ren CJ, Siegel N, et al. Serum fat-soluble vitamin deficiency and abnormal calcium metabolism after malabsorptive bariatric surgery. *J Gastrointest Surg*. 2004;8:48-55.
- Brolin BE, Leung M. Survey of vitamin and mineral supplementation after gastric bypass and biliopancreatic diversion for morbid obesity. *Obes Surg*. 1999;9:150-154.
- Williams SR. *Nutrition and Diet Therapy*. 8th ed. St Louis, MO: Mosby; 1997:159.
- Chae T, Foroozan R. Vitamin A deficiency in patients with a remote history of intestinal surgery. *Br J Ophthalmol*. 2006;90:955-956.
- Russell RM. The vitamin A spectrum: from deficiency to toxicity. *Am J Clin Nutr*. 2000;71:878-884.
- Sommer A. Xerophthalmia and vitamin A status. *Prog Retin Eye Res*. 1998;17:9-31.
- Curcio CA, Sloan KR, Kalina RE, et al. Human photoreceptor topography. *J Comp Neurol*. 1990;292:497-523.
- Spits Y, De Laey JJ, Leroy BP. Rapid recovery of night blindness due to obesity surgery after vitamin A repletion therapy. *Br J Ophthalmol*. 2004;88:583-585.
- McBain VA, Egan CA, Pieris SJ. Functional observations in vitamin A deficiency: diagnosis and time course of recovery. *Eye*. 2007;21:367-376.
- Andersson M. Vitamin A deficiency control: WHO/UNICEF strategy. Available at: <http://www.euro.who.int/ppt/nut/vad.pdf>. Accessed July 20, 2007.
- Andrés E, Affenberger S, Vinzio S, et al. Food-cobalamin malabsorption in elderly patients: clinical manifestations and treatment. *Am J Med*. 2005;118:1154-1159.
- Sadun AA. Metabolic optic neuropathies. *Semin Ophthalmol*. 2002;17:29-32.
- Hvas A, Nexø E. Diagnosis and treatment of vitamin B12 deficiency—an update. *Haematologica*. 2006;91:1506-1512.
- Pfeiffer CM, Caudill SP, Gunter EW, et al. Biochemical indicators of B vitamin status in the US population after folic acid fortification: results from the National Health and Nutrition Examination Survey 1999-2000. *Am J Clin Nutr*. 2005;82:442-450.
- Rampersaud GC, Kawell GP, Bailey LB. Folate: a key to optimizing health and reducing disease risk in the elderly. *J Am Coll Nutr*. 2003;22:1-8.
- Hampel JS, Taylor CA, Johnston CS. Vitamin C deficiency and depletion in the United States: the Third National Health and Nutrition Examination Survey, 1988 to 1994. *Am J Public Health*. 2004;94:870-875.
- Dunnington JH. Exophthalmos in infantile scurvy. *Trans Am Ophthalmol Soc*. 1931;29:37-47.
- US Department of Health and Human Services and US Department of Agriculture. *Dietary Guidelines for Americans*. 6th ed. Washington, DC: US Government Printing Office; 2005.
- Omaye ST. Safety of megavitamin therapy. *Advances in experimental medicine and biology*. *Adv Exp Med Biol*. 1984;177:169-203.