

ARTICLE



Vitamin A deficiency and the retinal “double carrot” sign with optical coherence tomography

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BACKGROUND: Spectral-domain optical coherence tomography (SD-OCT) and full-field electroretinography (ERG) allow retinal assessment with vitamin A deficiency (VAD). Using SD-OCT, this study aimed to characterize and follow a novel retinal abnormality in patients with VAD and intramuscular supplementation.

METHODS: Patients with VAD were retrospectively reviewed, including SD-OCT and electroretinography.

RESULTS: Three patients had VAD following bariatric or colon surgery and varying supplementation. All had nyctalopia, extinguished scotopic rod-specific function with ERG, and decreased serum vitamin A. None demonstrated surface abnormalities. All received intramuscular vitamin A with subjective resolution of symptoms. On SD-OCT, four of six eyes exhibited homogenous foveal hyperreflectivity anterior to retinal pigment epithelium-Bruch complex, reminiscent of a “double carrot”, which improved following supplementation. ERG findings demonstrated improved scotopic rod-specific function in all cases; however, photopic function remained diminished in two cases.

CONCLUSIONS: Structural improvement of the proposed “double carrot” sign occurs soon after vitamin A supplementation. While scotopic function improves rapidly following supplementation, cone function recovers more slowly. Therefore, foveal changes such as the “double carrot” sign suggest that structural recovery of cones precedes functional recovery.

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INTRODUCTION

Early work linking vitamin A to retinal function by George Wald and colleagues was recognized by the 1967 Nobel Prize in Physiology or Medicine, and shared with Haldan Hartline and Ragnar Granit, for their collective discoveries of visual processes [1]. However, decades later, vitamin A deficiency (VAD) remains a leading cause of blindness in the underdeveloped world, and is increasing in developed countries with gastric bypass surgery popularity in the setting of rising obesity [2]. There is concern that a substantial proportion of these patients, and others at high risk including those with inflammatory bowel disease and colon resections, may unknowingly suffer from VAD with visual impairment. Vision loss from VAD occurs from two different mechanisms: 1. keratinization and drying of ocular surface epithelium [3], and 2. impairment of the visual cycle [4]. Severe ophthalmic complications can include bilateral conjunctival and corneal xerosis, bilateral corneal scarring, and nyctalopia [5]. While screening cost-effectiveness is unclear [6], VAD can be detected clinically before late manifestations, often prompted by referrals

from non-ophthalmologists including clinical nutritionists and dietitians [7, 8].

Since nyctalopia is often the first presenting sign of VAD [9], early diagnosis can be achieved with techniques like full-field electroretinogram (ERG) and microperimetry that specifically assess retinal function [10]. Additionally, the ability to evaluate retinal structure with VAD has been advanced through imaging with spectral-domain optical coherence tomography (SD-OCT). Specifically, SD-OCT has allowed for discovery of abnormal features in the retina that can associate with VAD [11]. The goal of this study was to describe an additional novel feature readily detectable in multiple eyes with SD-OCT, and characterize it in the context of the overall clinical evaluation and treatment of VAD.

MATERIALS/SUBJECTS AND METHODS

Subjects

Retrospective review of three patients with diagnosed VAD. All patients were evaluated at Columbia University Irving Medical

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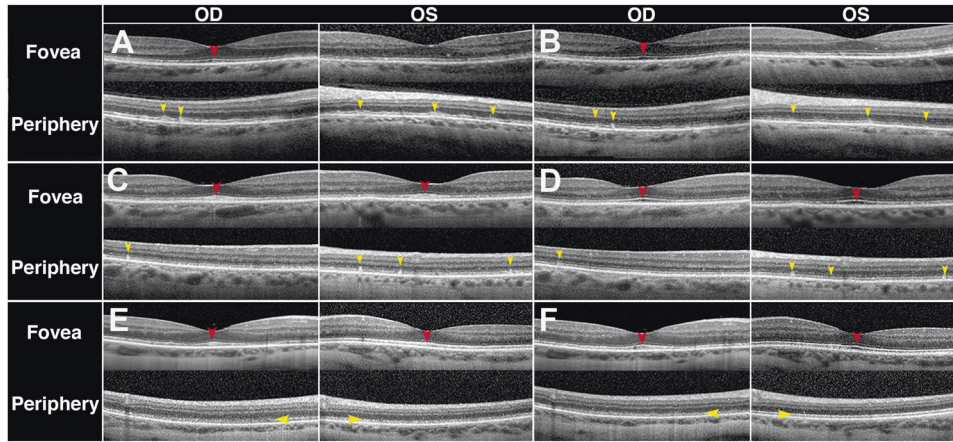


Fig. 1 Spectral-domain optical coherence tomography (SD-OCT) demonstrates abnormal, outer retinal hyperreflectivity that improved after vitamin A supplementation (OD—right eye, OS—left eye). **A** 57-year-old man (*Case 1*) with 2 years of nyctalopia and prior bilio-pancreatic diversion and duodenal switch surgery exhibited minimal changes of the left fovea, but notable outer retinal hyperreflective changes (yellow arrows) without treatment, and focal hyperreflective thickening in the outer, nasal fovea of the right eye (red arrowhead). **B** Following treatment, resolution of the foveal hyperreflectivity of the right eye is apparent, along with subtle improvement of outer retinal deposits elsewhere in both eyes (yellow arrows). **C** 66-year-old man (*Case 2*) with 2 ½ years of progressive nyctalopia and Crohn’s disease status post multiple small bowel resections demonstrated increased reflectivity in both foveas localizing to the ellipsoid zone (EZ) and appearing as two carrots side-by-side (proposed “double carrot” sign), and granular hyperreflective changes throughout the macula with frank hyperreflective foci that interrupt the interdigitation zone (IZ) and EZ (yellow arrows). **D** Following treatment, normalization of the hyperreflectivity in each fovea (red arrowheads) was observed; the latter improvement was more pronounced than in the rest of the macula (yellow arrows). **E** A 61-year-old man (*Case 3*) with 2 years of nyctalopia and prior bilio-pancreatic diversion with duodenal switch surgery presented with a similar proposed “double carrot” sign (red arrowheads) and granular reflective changes of the EZ in the periphery. **F** After treatment, marked improvement and resolution of the foveal hyperreflectivity was seen, with some improvement of granular changes elsewhere.

Center. The need for patient consent was waived due to minimal risk offered to patients and the retrospective nature of this study design as per Columbia University Institutional Review Board approved protocol AAAR8743. All procedures were reviewed and in accordance with the tenets of the Declaration of Helsinki.

Examination and imaging

Patients underwent ophthalmic examination including measurement of best-corrected visual acuity (BCVA), dilation with topical tropicamide (1%) and phenylephrine (2.5%) followed by multimodal imaging, including SD-OCT and fundus autofluorescence (FAF), and ERG.

Electroretinography

Full-field scotopic and photopic ERG was performed on patients using Dawson, Trick, and Litzkow electrodes and Ganzfeld stimulation using a Diagnosys Espion Electrophysiology System (Diagnosys LLC, Littleton, MA, USA). Rod-specific scotopic ERG was obtained using a white stimulus following 30-min of dark adaptation followed by elicitation of a mixed rod and cone ERG. Single flash cone and 30 Hz flicker responses were recorded following a 10-min period of light adaptation. All procedures were performed in accordance with International Society for Clinical Electrophysiology of Vision standards [12].

RESULTS

Case 1

A 57-year-old man was referred with two-and-a-half-year history of poor night vision. Past medical history was significant for bilio-pancreatic diversion with duodenal switch 15 years prior to presentation, and small bowel resection with exploratory laparotomy the following year. The patient had been taking 20,000 international units of oral vitamin A daily. BCVA was 20/20 in both eyes, and the anterior segments were normal, including cornea and conjunctiva. Clinical examination and SD-OCT revealed hyperreflective outgrowths occupying outer retinal bands, and

undulations of the interdigitation zone (IZ) and ellipsoid zone (EZ), and a subtle foveal abnormality consistent with an emerging proposed “double carrot” sign (Fig. 1A). FAF showed a mottled pattern of hypoautofluorescence in the macula (Fig. 2A). Scotopic ERG demonstrated extinguished scotopic-rod-specific response and diminished maximum response. Both the single flash photopic and 30 Hz flicker amplitudes were also decreased (Fig. 3).

Eighteen months after initial presentation, the patient was given intramuscular vitamin A injection by another physician and described improvement of nyctalopia within a week of administration. ERG performed eight months after treatment revealed improvement of the scotopic rod-specific function, correlating with the patient’s subjective experience (Fig. 3). However, the photopic single flash and 30 Hz flickers remained diminished. SD-OCT following treatment revealed resolution of the emerging “double carrot” sign at the fovea in the right eye as well as improvement of the hyperreflective abnormalities seen elsewhere (Fig. 1B). FAF similarly demonstrated improvement of the hypoautofluorescent mottling following vitamin A supplementation (Fig. 2B).

Case 2

A 66-year-old man presented with a two-and-a-half-year history of slowly progressive nyctalopia. He complained of difficulty driving at night but otherwise had no visual complaints. Past medical history was significant for longstanding Crohn’s disease and multiple small bowel resections, currently managed with biweekly adalimumab injection and daily oral fat-soluble vitamin supplementation. Past ocular history was significant for uncomplicated cataract extraction with intraocular lens implantation. Family history was unable to be determined as the patient was adopted. At presentation, BCVA was 20/25 in the right eye and 20/20 in the left eye. Slit-lamp examination of the cornea, conjunctiva and remaining anterior segment was normal, including absence of Bitot spots, while dilated fundus examination revealed multiple, discrete yellow dots in macula and peripheral retina. In SD-OCT scans, abnormal granular hyperreflectivity extended anteriorly

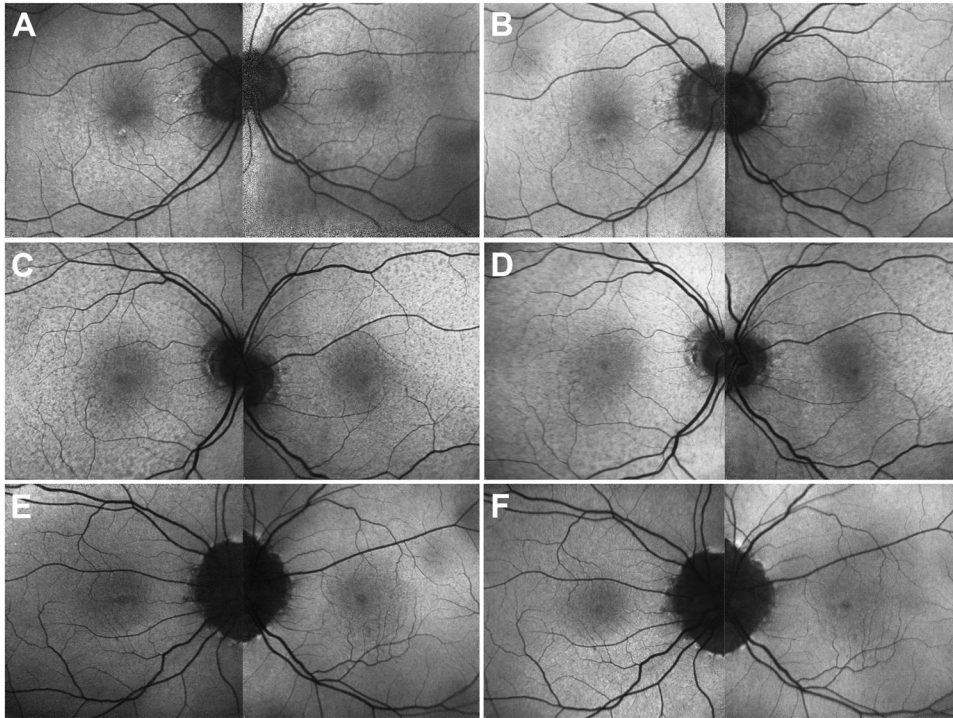


Fig. 2 Fundus autofluorescence (FAF) before and after intramuscular supplementation of vitamin A. **A** FAF of P1 revealed a similar mottled pattern of hypoautofluorescence in the macula that **B** improved following supplementation of vitamin A. **C** FAF of P2 before treatment revealed dense speckled patches of hypoautofluorescence across the macula that **D** decreased in appearance following treatment. **E, F** FAF of P3 demonstrated peripapillary atrophy but did not reveal any substantial changes in the macula.

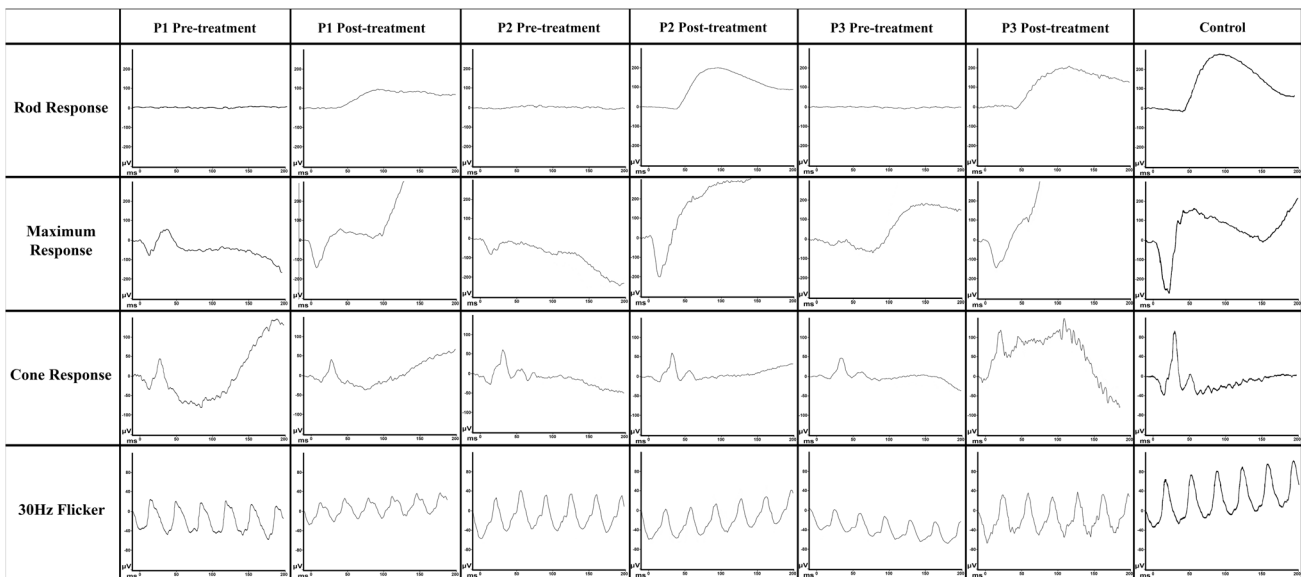


Fig. 3 Scotopic electroretinogram (ERG) recovery following vitamin A supplementation in three patients. Full-field ERG study of the right eye of three patients with vitamin A deficiency (P1-P3) demonstrated fully extinguished rod-specific scotopic response in P1-P3 and an electronegative mixed rod and cone response in P2 and P3. Single flash cone response and 30-Hz flicker amplitudes were diminished in all cases. Following treatment with intramuscular vitamin A, repeat full-field ERG revealed improvement of both the rod-specific scotopic responses and maximum responses in P1-P3. Cone response and 30 Hz flicker responses improved in P3 but remained diminished in P1 and P2.

from retinal pigment epithelium (RPE)-Bruch membrane with focal hyperreflective conical outgrowths penetrating EZ, (Fig. 1C). In the fovea and parafovea of both eyes, there was hyperreflective thickening of EZ (Fig. 1C) resembling a “double carrot” in SD-OCT scans (Fig. 4). FAF imaging revealed diffuse punctate hypoautofluorescent foci across the macula (Fig. 2C). ERG demonstrated

extinguished scotopic rod-specific responses and an electronegative maximum response. Photopic single flash and 30 Hz flicker responses revealed mild decreases in amplitude and implicit time delay (Fig. 3, Table 1). Serum testing revealed vitamin A retinol levels of 0.3–1.2 mg/L (reference 0.3–1.2 mg/L) and retinyl palmitate levels <0.02 mg/L (reference 0–0.1 mg/L).

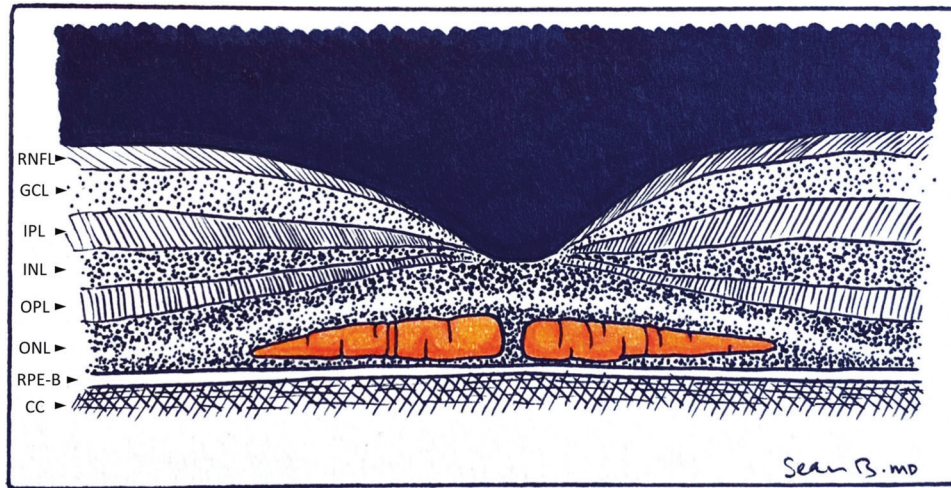


Fig. 4 Schematic cross-sectional illustration of proposed “double carrot” sign relative to macular anatomy. Orange, horizontal “carrots” are metaphorical to central outer retinal hyperreflectivity detected with spectral-domain optical coherence tomography (compare to Fig. 1). RNFL retinal nerve fiber layer, GCL ganglion cell layer, IPL inner plexiform layer, INL inner nuclear layer, OPL outer plexiform layer, ONL outer nuclear layer, EZ ellipsoid zone, RPE-B retinal pigment epithelium-Bruch membrane complex, CC choriocapillaris.

After initial evaluation, the patient increased supplementation of oral vitamin A and received intravenous infusions of multivitamins from his primary care provider. However, the patient experienced continued night vision loss over the following eight months. The patient then received an intramuscular dose of 100,000 international units of vitamin A and experienced rapid symptom resolution over two days. Repeat serum measurement demonstrated vitamin A retinol level of 0.64 mg/L and ERG revealed complete recovery of both scotopic rod-specific and maximum responses (Fig. 3). Photopic single flash and 30 Hz flicker responses remained diminished and implicit time delayed. While some hyperreflective SD-OCT lesions persisted, the “double carrot” abnormality visible with SD-OCT had resolved bilaterally (Fig. 1D) and FAF imaging demonstrated resolution of the hypoautofluorescent speckles (Fig. 2D).

Case 3

A 61-year-old man presented with a two-year history of night blindness and blurry vision worse in the left eye than right. Past medical history was significant for bilio-pancreatic diversion with duodenal switch 13 years prior to presentation. The patient noted that he was initially supplemented with vitamin A, D, and E following the procedure, but had discontinued treatment before restarting one year ago. Past ocular history included a cataract extraction with three-piece intraocular lens placement in the right eye two years prior, and retinal detachment in the same eye managed with pars plana vitrectomy and gas tamponade two months before presentation. BCVA was 20/60 in the right eye and 20/50 in the left eye. Anterior examination demonstrated 2+ nuclear lenticular sclerosis in the left eye with normal cornea and conjunctiva bilaterally. Fundus examination showed temporal laser scars in the right eye and peripapillary atrophy bilaterally. A hyperreflective prominence extending between ellipsoid and RPE-Bruch membrane complex at the fovea was evident bilaterally with SD-OCT, even in the absence of the conical hyperreflective material protruding through the EZ. However, irregularities and rarefaction of IZ and EZ in the macula, along with thickening and granularity elsewhere, were appreciated on SD-OCT (Fig. 1E). FAF imaging revealed significant peripapillary atrophy but was otherwise unremarkable (Fig. 2E). ERG revealed an extinguished scotopic rod-specific response and an electronegative maximum response. Photopic single flash response and 30 Hz flicker showed diminished amplitudes and implicit time delay (Fig. 3). Metabolic

screening demonstrated diminished serum vitamin A level of 0.08 mg/L (reference 0.24–0.85 mg/L).

The patient returned five months later with complete resolution of his night blindness following treatment with single-dose intramuscular 100,000 international units of vitamin A. An ERG at this visit corroborated complete recovery of scotopic rod-specific function as well as correction of the electronegative maximum response (Fig. 3). Both photopic single flash and 30 Hz flicker amplitudes were improved, however implicit time remained delayed. Limitations of this ERG include blink artifact during the maximum and photopic single flash responses. SD-OCT revealed improvement of the hyperreflective abnormality, specifically in the left more than right fovea (Fig. 1F), while FAF did not reveal any substantial changes following treatment (Fig. 2F).

DISCUSSION

When identified and treated in its early stages, ophthalmic consequences of VAD can be reversible through appropriate vitamin A supplementation. This study supports our understanding of VAD as a disease that can be challenging to diagnose, but one that needs to be considered early in patients at risk, such as those with history of bariatric surgery or bowel resection. Ideally, a registered dietitian remains actively involved in each patient’s ongoing nutritional management. This study serves to expand our knowledge by demonstrating a particular finding, the proposed “double carrot” sign, that can be directly visualized with conventional imaging and, in conjunction with available functional testing, may serve as a valuable biomarker in the treatment of VAD.

The hyperreflective lesions we observed with SD-OCT were found in both the fovea and peripheral retina, and have previously been described in the setting of VAD [11]. Our findings suggest that these outer retinal alterations may reflect a progression of disease severity. Specifically, the SD-OCT in *case 3* revealed a granular IZ and EZ; *case 1* presented with undulations of the IZ and EZ; while intermittent columnar-shaped lesions interrupted outer retina in *case 2*. Similar lesions identified as subretinal drusen deposits, or reticular pseudodrusen, are a phenotype of age-related macular degeneration with distinct prognostic implications [13]. These outer retinal deposits localize between photoreceptors and RPE-Bruch membrane complex as seen with SD-OCT, whereas typical drusen instead localize beneath the RPE-

Table 1. Full-field electroretinogram findings of patients before and after vitamin A supplementation.

Patient ID	Scotopic Response A wave (μV)	Scotopic Response A wave Implicit Time (ms)	Scotopic Response B wave (μV)	Scotopic Response B wave Implicit Time (ms)	Scotopic Response A wave (μV)	Maximum Response A wave (μV)	Maximum Response A wave Implicit Time (ms)	Maximum Response B wave (μV)	Maximum Response B wave Implicit Time (ms)	Cone Response A wave (μV)	Cone Response A wave Implicit Time (ms)	Cone Response B wave (μV)	Cone Response B wave Implicit Time (ms)	30 Hz Flicker (μV)	30 Hz Flicker Implicit Time (ms)
P1	Pre	Extinguished	Extinguished	Extinguished	-78.2	136.9	15	-34.3	39	-34.3	14	79.9	29	65.8	26
	Post	3.6	34	94.3	92	198	15	-17.6	47	-17.6	14	58.9	27	56.0	25
P2	Pre	Extinguished	Extinguished	Extinguished	-82.3	68.5	14	-26.3	39	-26.3	15	89.8	32	82.7	31
	Post	11.9	37	202.4	95	359.7	16	-13.7	50	-13.7	15	74.6	32	63.4	31
P3	Pre	Extinguished	Extinguished	Extinguished	-31.7	298	22	-6.5	42	-6.5	18	54.2	34	42.2	33
	Post	6.8	42	214.5	116	237.1	15	-8.8	50	-8.8	16	129.3	34	100.1	33
Control	20.3	41	270.2	93	-253.1	421.8	15	46.3	43	46.3	15	155.4	29	96.5	27

Bruch membrane complex. The progression of subretinal druse-noid deposits has been shown to correlate with clinicopathologic features of age-related macular degeneration [14, 15].

The eyes in this study exhibited a spectrum of changes in fovea which may represent various stages of disease severity. The proposed “double carrot” sign, seen as a hyperreflective lesion that localized to fovea and was positioned anterior to the RPE-Bruch membrane complex was observed most prominently in *case 2* and one we interpreted as emerging in *case 1*. Such disruption of EZ in fovea has been previously demonstrated [16]. In contrast, in *case 3*, this sign was observed less clearly than in *cases 1* and *2*, which may represent more advanced disease and outer retinal damage. Consistent with this hypothesis is the relative deficit in cone function seen in *case 3* as compared to *cases 1* and *2*. Consequently, the phenotype in these three cases may represent a cross-sectional illustration of the various stages of VAD in fovea by severity, with the “double carrot” sign seen more prominently in early stages.

In all eyes of these three successfully treated cases of VAD, disappearance of this abnormality was temporally associated with clinical improvement of nyctalopia. The phenotype of VAD is attributable to an insufficient supply of vitamin A to the visual cycle with resultant deficiency in 11-*cis*-retinaldehyde chromophore of visual pigment in photoreceptor cells, affecting both rod and cone photoreceptors [17, 18]. The formation of a “double carrot” appearance in the fovea rather than radially oriented hyperreflective columns observed elsewhere in the retina in the setting of VAD could be attributable to unique local optical effects imposed by the foveal structure. This is also the basis for the spreading petaloid distribution of Henle’s layer [19].

The ERG findings of all three cases demonstrated extinguished scotopic rod-specific and decreased mixed rod and cone responses at presentation. Photopic single flash and 30 Hz flicker responses were also diminished, corroborating prior reports that both rod and cone photoreceptors are affected by VAD [20, 21]. Improved scotopic rod-specific and maximum responses were observed at 2 days and 5 months respectively following supplementation with vitamin A in *cases 2* and *3*. However, the cone response remained diminished in *case 2* and improved in *case 3*, supporting prior suggestion that functional recovery of the cone response may occur more slowly than that of the rod response [10]. Given the higher density of cone photoreceptors in the fovea, the rapid resolution of the proposed “double carrot” sign seen in our cases suggests that structural recovery of cone photoreceptors on OCT may precede functional improvement on ERG. Consequently, recovery of hyperreflective disruptions in the fovea may serve as an accessible and easily obtained biomarker in disease management. Incorporation of microperimetry in future cases with multifocal ERG [10] may help determine the temporal relationship between improvement in the proposed “double carrot” abnormality and the relatively delayed recovery in central cone function.

Similarly to *cases 2* and *3*, the SD-OCT of *case 1* revealed improvement of both the EZ disruption in the fovea and the reticular pseudodrusen observed in the periphery. However, despite these changes, the ERG demonstrated a more modest recovery in the scotopic rod-specific response and persistently diminished cone response, even several months after supplementation. The absence of significant improvement of photoreceptor function suggests that the supplemented dose of vitamin A may be insufficient, as rod function typically responds rapidly to treatment [21]. Therefore, while SD-OCT may provide an early indication of structural and clinical improvement, functional testing still maintains an important role in determining the adequacy of treatment.

Many routes and approaches for supplementation and treatment of VAD are available. Typically, intramuscular vitamin A has been demonstrated to be most successful [4], consistent with our

own experience. Two of our patients received 100,000 international units, with dose adjustment in consultation with a gastroenterologist. The single patient who was treated by an outside provider received an unknown dose. Health system-wide difficulties can arise in obtaining this intramuscular formulation as its availability is often limited [4]. Additionally, achieving therapeutic levels from intramuscular vitamin A may be challenging with concurrent problems like primary biliary cirrhosis, also with reduced dosing for pregnant or lactating women, and for children [22]. Decades after early implementation and measurement for deficient neonates [23], intravenous vitamin A continues to demonstrate unpredictable results [24]. Sublingual vitamin A has recently been described as an alternative for patients with contraindications to intramuscular formulation, though its benefit was confounded by simultaneous oral supplementation and required months to achieve sufficient response [21]. Additional investigation may be needed to adequately compare efficacy with intramuscular therapy.

Complicating diagnosis and management is the potential for VAD with normal serum vitamin A levels. A high index of suspicion is thus warranted in patients complaining of night blindness despite reference-range laboratory results. ERG can be essential for establishing the diagnosis and is considered more reliable than serum vitamin A testing for monitoring chronic disease [10, 24]. However, ERG is not accessible for many, if not most, ophthalmologists. The relatively widespread availability of SD-OCT among ophthalmologists and retina specialists provides an important alternative in identifying and monitoring patients with VAD through detection of hyperreflective focal lesions in outer retina and the proposed “double carrot” sign.

VAD is of mounting concern in the developed world due to increased frequency with which bariatric surgery is performed in addition to patients with other complicated gastrointestinal histories. Many authoritative nutrition texts advocate for a basic ophthalmic examination that assess the ocular surface as part of the “nutrition-focused physical examination” in such cases [7, 8]. However, as discussed elsewhere [9] and demonstrated here, many patients exhibit visual impairment from retinal dysfunction with VAD before any signs of corneal or conjunctival abnormalities like Bitot spots or xerophthalmia. It is critical that clinicians involved in caring for these patients are aware of the early manifestations of VAD such as nyctalopia, and the mainstays of treatment including intramuscular vitamin A supplementation. Since not all eyes in this study, or previous reports, have overtly demonstrated the proposed “double carrot” sign, an overreliance on this finding should be cautioned in establishing the diagnosis of VAD. However, the proposed “double carrot” sign shows promise as a robust imaging feature for VAD identification within the proper clinical context.

SUMMARY

What was known before

- Vitamin A deficiency is frequently seen in the setting of gastric bypass surgery due to obesity and colon resection secondary to inflammatory bowel disease. Early detection of vitamin A deficiency can be achieved through the use of ERG, microperimetry, and multimodal imaging.

What this study adds

- The double carrot sign is a feature seen on OCT that may be used as a biomarker of vitamin A deficiency. Structural improvement of this sign occurs rapidly after vitamin A

supplementation, suggesting that structural recovery of cones precedes functional recovery.

DATA AVAILABILITY

Authors can confirm that all relevant data are included in the article and/or its supplementary information files.

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AUTHOR CONTRIBUTIONS

Each author contributed to the manuscript as follows: design and conduct of the study (M.P.B., J.K.O., S.H.T.) collection, management, analysis, and interpretation of the data (M. P.B., J.K.O., J.R.S., S.F., S.H.T.); preparation, review, or approval of the manuscript and decision to submit for publication (M.P.B., J.K.O., S.A.B., J.A.K., R.K., C.M.R. J.R.S., S.F., S.H. T.). At least two authors (M.P.B., J.K.O.) had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The need for patient consent was waived due to minimal risk offered to patients and the retrospective nature of this study design as per Columbia University Institutional Review Board approved protocol AAAR8743. All procedures were reviewed and in accordance with the tenets of the Declaration of Helsinki.

ADDITIONAL INFORMATION

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