

Nutritional Therapies for Ocular Disorders: Part Three

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Abstract

Parts one and two of this series discussed nutritional and botanical treatments for cataracts, glaucoma, and retinal diseases (macular degeneration, diabetic retinopathy, retinopathy of the newborn, and retinitis pigmentosa). This review discusses nutritional treatments for asthenopia, blepharitis, chalazion, conjunctivitis (including giant papillary conjunctivitis), gyrate atrophy of the choroid and retina, keratoconus, myopia, sicca syndrome (dry eyes), and uveitis. The evidence presented in this three-part series indicates natural medicine has an important role to play in the practice of ophthalmology. (*Altern Med Rev* 2008;13(3):191-204)

Introduction

Ophthalmologists generally receive minimal training in nutrition. Consequently, they typically believe that, with a few exceptions (such as night blindness and macular degeneration), nutritional factors have little or no role to play in the prevention and treatment of diseases encountered in their practice. However, a substantial body of research indicates dietary modifications and nutritional supplements can ameliorate certain common and uncommon ocular conditions. Appropriate use of nutritional therapy has the potential to improve outcomes and decrease the need for, and therefore the side effects from, conventional therapies. Parts one¹ and two² of this series discussed nutritional and botanical treatments for cataracts, glaucoma, and retinal diseases (macular degeneration, diabetic retinopathy, retinopathy of the newborn, and retinitis pigmentosa).

This article discusses other ocular disorders that may respond to nutritional therapy. These conditions are presented below in alphabetical order.

Asthenopia

Asthenopia is defined as weakness or fatigue of the eyes, often accompanied by eye pain, red eyes, headache, and dimming or blurring of vision. These symptoms tend to occur after tedious visual tasks such as reading or computer work. Asthenopia may be due to refractive errors or abnormalities of binocular vision. Conventional treatments include the use of appropriate eyeglasses, convergence exercises, and surgery.

Flavonoids (*Anthocyanoside Oligomers*)

In a double-blind trial, administration of an anthocyanoside preparation improved subjective symptoms and objective contrast sensitivity in patients with asthenopia associated with myopia. Sixty patients (mean age 38.6 years) with symptoms of asthenopia, poor nocturnal vision, and low-to-moderate myopia were randomly assigned to receive, in double-blind fashion, 100 mg twice daily of an anthocyanoside preparation (Eyezone) or placebo for four weeks. Eyezone (Hanmi Pharmaceuticals; Seoul, Korea) consists of 85-percent anthocyanoside oligomers (i.e., small anthocyanidin glycoside polymers; mainly dimers, trimers, tetramers, and pentamers). It is produced by fermentation of anthocyanoside monomers obtained from grape

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Figure 1. *Vaccinium myrtillus*

pulp and skin. After four weeks, symptoms improved in 73.3 percent of patients receiving anthocyanosides and in 3.3 percent receiving placebo ($p < 0.0001$). Contrast sensitivity levels improved significantly in the group receiving anthocyanosides and remained stable in the placebo group ($p < 0.0001$ for the difference in the change between groups).³

Bilberry (Figure 1) preparations are a more widely available source of anthocyanoside oligomers than the product used in this study and should therefore be considered as a potential treatment for asthenopia.

Blepharitis

Blepharitis is a chronic condition characterized by inflammation of the eyelids. Symptoms include redness, dryness, burning, itching, and irritation of the eyes. Anterior blepharitis affects the outer side of the lid and is frequently caused by *Staphylococcus* or seborrheic dermatitis of the scalp. Posterior blepharitis affects the inner eyelid and is often a manifestation of rosacea or is caused by seborrheic dermatitis of the scalp. Conventional therapy includes keeping the lids clean, applying warm compresses, using dandruff shampoo, and when necessary, administration of antibiotics or steroid eye drops. Treatment rarely resolves blepharitis completely, and the condition tends to recur. Table 1 summarizes nutritional treatment for blepharitis.

Vitamin A (Topical)

In a 1939 report, an ointment containing vitamin A (500 IU/mL) was said to be useful for ulcerative blepharitis and blepharitis caused by tuberculosis.⁴

More recently, in a case report, treatment with an ophthalmic solution containing vitamin A resulted in a resolution of chronic blepharitis. A 74-year-old woman with chronic blepharitis and xerophthalmia of five years' duration that had failed to respond to topical antibiotics and steroids was treated with eye drops containing 0.012-percent vitamin A and 0.2-percent polysorbate 80 (an emulsifier) (Viva-Drops; Vision Pharmaceuticals). A minimum of six drops were instilled in each eye daily, or more as needed. After two weeks, signs and symptoms markedly improved. The patient continued to use the drops 2-3 times daily, and on follow-up visits four months and one year later she was symptom-free.⁵

N-Acetylcysteine

In a randomized trial of 40 patients with chronic posterior blepharitis, the addition of oral N-acetylcysteine (NAC; 100 mg three times daily) to conventional therapy (topical antibiotics and steroids) significantly increased tear quantity and improved tear quality, compared with conventional therapy alone. The authors suggest NAC's mechanism of action is prevention of the peroxidation of lipids (induced by either *Staphylococci* or normal flora) that contribute to the structural integrity of the lipid layer of tear film. A deficiency of these lipids could result in increased evaporation of tears and dryness.⁶

Essential Fatty Acids

In a controlled trial, supplementation with modest doses of linoleic acid (LA) and gamma-linolenic acid (GLA) enhanced the beneficial effect of eyelid hygiene in patients with meibomian gland dysfunction (a common form of posterior blepharitis).

Fifty-seven patients with meibomian gland dysfunction were randomly assigned to one of three groups. Group 1 received a daily oral supplement containing 28.5 mg LA and 15 mg GLA; group 2 performed eyelid hygiene once daily (warm compresses, eyelid massage, and eyelid margin scrubbing); and group 3 received both treatments. The mean improvements in eyelid margin

Table 1. Nutrients for Blepharitis

Nutrient	Treatment Protocol	Dosage	Results	Strength of Evidence
Topical Vitamin A	Viva-Drops (0.012% vitamin A eye drops)	≥6 drops in each eye daily x 2 wk; 2-3 drops daily for 1 yr	Patient symptom-free on follow-up (4 mo; 1 yr)	Case report
N-Acetylcysteine	Conventional topical ointments w/ or w/o oral NAC	100 mg NAC, 3 times daily	NAC group had >tear quantity and improved tear quality	RCT (n=40)
Essential Fatty Acids (EFAs)	EFAs, eyelid hygiene, or both	28.5 mg LA; 15 mg GLA	Combo tx = sig. improvement compared to either alone	RCT (n=57)

Also, consider a multiple vitamin-mineral formula as deficiencies of vitamin B₆, riboflavin, biotin, and zinc have all been associated with blepharitis.

inflammation and other symptoms were significantly greater in the group receiving combination therapy than the groups receiving either treatment alone ($p < 0.05$).⁷

Other Nutrients

Deficiencies of vitamin B₆,⁸ biotin,⁹ riboflavin,^{10,11} and zinc^{12,13} have each been reported to cause blepharitis in humans and animals. While severe deficiencies of these nutrients are uncommon in otherwise healthy people, marginal deficiencies may be relatively common. A multivitamin-multimineral preparation containing these nutrients should be considered for supportive treatment of patients with blepharitis.

Chalazion

A chalazion is a painless swelling of the eyelid resulting from granulomatous inflammation of a meibomian gland. Chalazia sometimes resolve spontaneously, but tend to recur. Conventional treatment includes application of warm compresses, steroid injections, or surgical removal.

Vitamin A

One practitioner noted the pathological changes of chalazion are identical to those seen in fatty tissues exposed to vitamin A deficiency. In his experience, supplementation with 50,000-100,000 IU vitamin A daily for several weeks caused early chalazia to disappear. Vitamin A supplementation also appeared to prevent recurrences following removal of involved meibomian glands. Vitamin A was ineffective against chalazia that had persisted for several months.¹⁴

While spontaneous remission cannot be ruled out in the cases reported above, short-term treatment with vitamin A is relatively safe and therefore may be considered for patients with chalazia. Early warning signs of vitamin A toxicity include fatigue, headache, joint pain, muscle aches, bone pain, and dry skin. These side effects are reversible upon discontinuation of the vitamin. A patient receiving high doses of vitamin A should have periodic measurement of serum calcium and aminotransferases (liver enzymes). Alcoholics, elderly individuals, and patients with liver disease have increased susceptibility to vitamin A toxicity.

Case Report

A 65-year-old woman came to the author's office with recurrent and persistent chalazia. Although she had experienced recurrences for many years they had become worse in the preceding few years. She also had a history of chronic sinusitis. Physical examination revealed a chalazion on the left upper eyelid (which had been present for several months) and general dryness of the skin suggestive of essential fatty acid deficiency.

The patient was treated with 50,000 IU vitamin A daily for four weeks, followed by 25,000 IU per day five days a week. Vitamin E (800 IU daily) was added to enhance the effect of vitamin A.¹⁵ She also underwent an allergy elimination diet because of chronic sinusitis and received 3 g vitamin C daily, 1 tablespoon flaxseed oil per day for six weeks, and a high-potency multivitamin-multimineral. The chalazion improved dramatically within four weeks.

It is unclear which components of the treatment program played a role in the improvement. Food allergy could conceivably be a contributory factor in any chronic inflammatory condition. Although vitamin A alone has been reported to be ineffective in patients with long-standing chalazia (see above), combining vitamin A with other nutrients and dietary changes might enhance its efficacy.

Conjunctivitis

Conjunctivitis is an inflammation of the conjunctiva of the eye usually caused by a viral or bacterial infection or an allergic reaction. Ocular symptoms may include redness, itching, burning, and discharge. Conventional treatment varies according to the etiology and may include topical antimicrobial agents, decongestants, anti-inflammatory drugs, and anti-allergy medications. Giant papillary conjunctivitis is discussed later in this article. Table 2 summarizes possible nutritional interventions for conjunctivitis.

Food Allergy

Conjunctivitis has been mentioned as a manifestation of food allergy.¹⁶ In the author's experience, food allergy is a contributing factor in some cases of conjunctivitis even if the clinical history suggests the condition is due to environmental allergens or irritants. Allergenic foods can be identified in most cases

by means of an elimination diet, followed by individual food challenges.

Vitamin C

One practitioner reported eye drops containing vitamin C (100-125 mg/mL in sterile water) are usually effective for both allergic and viral conjunctivitis.¹⁷ The recommended dosage regimen is 1-2 drops 3-5 times daily. Treatment is tapered or discontinued after improvement occurs. Transient stinging occurs with each application but no other adverse effects were reported.

Case report: The author saw a 57-year-old woman who had experienced itching and burning in the eyes since childhood. She had been treated with sulfacetamide/prednisolone (Vasocidin) eye drops for four years. This treatment helped control her symptoms but they recurred within 36 hours whenever she discontinued the drops. She was prescribed vitamin C eye drops (100 mg/mL, as described above). Improvement occurred within four days, and after two weeks she noted her ocular symptoms had disappeared for the first time since childhood. She discontinued the vitamin C eye drops after three weeks and remained symptom-free (without the use of Vasocidin) for an additional three weeks, after which she was lost to follow-up.

While its mechanism of action is not certain, vitamin C has demonstrated anti-allergy and antiviral effects *in vitro*. Vitamin C eye drops can be prepared, with or without preservatives, by a compounding pharmacist. The solution should be produced under sterile conditions and adjusted to physiologic pH. It is recommended that preservative-free eye drops be refrigerated and discarded within 30 days.

Oral vitamin C may also occasionally be effective, as suggested by a case report. A woman (age not specified) had a 1.5-year history of excess tearing and eye pain upon exposure to newsprint, photocopied materials, and the print in certain books. Some of these exposures also produced spasm-like blinking. Treatment with antihistamines and decongestants were without benefit. Although dietary vitamin C intake exceeded the Recommended Dietary Allowance, supplementation with 500 mg vitamin C daily was followed by progressive improvement within one week. After continued vitamin C supplementation for six months the woman was nearly asymptomatic.¹⁸

Table 2. Nutritional Approaches to Treatment of Conjunctivitis

Intervention	Protocol/Route of Administration	Dosage	Results	Strength of Evidence
Vitamin C	Eye drops (100-125 mg/mL sterile water)	1-2 drops, 3-5x/d	Improvement in 4 d; no symptoms after 2 wk	Case report
	Oral	500 mg daily	Improvement in 1 wk; nearly asymptomatic after 6 mo	Case report
Vitamin A	Eye drops (1,500 IU/mL better than 500 IU/mL)	4x/d for ≥ 3 mo	Improvement in 83% of subjects	Small open trial (n=12 subj. w/ superior limbic keratoconjunctivitis)
B vitamins	Oral riboflavin and niacinamide	5 mg riboflavin & 25 mg niacinamide, 3x/d	Effective for subjects w/ seasonal conjunc. w/ papillary hypertrophy	Case reports

In addition, an etiology of food allergy should be ruled out.

Vitamin A

Vitamin A promotes the integrity of various types of epithelial tissue, including conjunctiva. Severe vitamin A deficiency can cause redness of the conjunctiva and burning, itching, and excessive dryness; symptoms that can be reversed by vitamin A supplementation.¹⁹ Topical vitamin A has been used successfully to treat superior limbic keratoconjunctivitis, a disorder of unknown etiology characterized by intractable, chronic inflammation of the superior limbic area of the bulbar conjunctiva.

Twelve patients with superior limbic keratoconjunctivitis received vitamin A (retinyl palmitate) eye drops four times daily for at least three months. The treatment produced varying degrees of improvement in 10 cases (83%). A concentration of 1,500 IU/mL was more effective than 500 IU/mL; no side effects were seen. The condition did not recur as long as the treatment continued.²⁰

B Vitamins

Conjunctivitis is one manifestation of severe riboflavin deficiency.^{10,21} In 1949, supplementation with 5 mg riboflavin three times daily was reported to be beneficial for patients with the palpebral form of seasonal conjunctivitis (spring catarrh) with papillary hypertrophy. The addition of niacinamide (25 mg three times daily) appeared to enhance the effect of riboflavin. Riboflavin was not effective for palpebral spring catarrh without papillary hypertrophy or for the bulbar form of spring catarrh.²² This report was published several years after refined grains began to be enriched with B vitamins, so its findings are presumably still relevant.

Giant Papillary Conjunctivitis

Giant papillary conjunctivitis is a common problem in contact lens wearers. Symptoms include itching, redness, irritation, and mucous discharge. The cause appears to be a hypersensitivity reaction to substances that adhere to the surface of the contact lens. Conventional treatment consists of changing the type of lens or, if necessary, discontinuing the use of contact lenses. For patients unwilling or unable to stop using contact lenses, ophthalmic preparations containing cromolyn sodium, antihistamines, or glucocorticoids may be recommended.

Vitamin A (Topical)

In uncontrolled trials, treatment with eye drops containing 0.012-percent vitamin A and 0.2-percent polysorbate 80 (Viva-Drops) resulted in considerable improvement of giant papillary conjunctivitis, without requiring patients to stop using contact lenses.

Twenty patients with giant papillary conjunctivitis applied Viva-Drops three times daily for 30 or 60 days. Each patient wore contact lenses during the treatment period. After 30 days, examination revealed complete resolution or marked improvement in 23 of 40 eyes (57.5%); after 60 days the response rate increased to 87.5 percent. There were no recurrences on follow-up examinations 3-13 months later.²³

One hundred-fourteen patients with giant papillary conjunctivitis continued to wear contact lenses while applying Viva-Drops four times daily for 30 days or more. Soiled lenses were replaced in 84 percent of patients. Signs and symptoms improved in all cases; examination of the conjunctiva revealed complete resolution or marked improvement in 92 percent of affected eyes.²⁴

Based on these studies, topical vitamin A should be considered as an alternative or adjunct to conventional medication for patients unwilling or unable to discontinue the use of contact lenses.

Gyrate Atrophy of the Choroid and Retina

Gyrate atrophy of the choroid and retina is an inborn error of metabolism characterized by progressive loss of vision, usually culminating in blindness between the ages of 40 and 60. The condition is caused by

a defect in the enzyme ornithine keto acid aminotransferase, which plays a role in ornithine metabolism. Plasma ornithine concentrations in patients with gyrate atrophy are typically 10-20 times above the normal range. The extent of the visual damage varies from patient to patient and appears to depend in part on the severity of hyperornithinemia.

Conventional treatment consists primarily of dietary modification and supplementation with vitamin B₆ (see below). These interventions may slow or halt the progression of the disease by decreasing serum ornithine concentrations.

Dietary Factors

Because arginine is a precursor to ornithine, dietary arginine restriction has been used as a primary treatment for hyperornithinemia.²⁵⁻²⁹ In case reports and uncontrolled trials, consumption of a semi-synthetic low-protein, low-arginine diet decreased plasma ornithine concentrations substantially – in some cases to a level at or just above the upper limit of normal. Treatment with this diet resulted in short-term improvement in visual function in some cases. During follow-up periods of up to 14 years, patients who adhered to the diet had significantly less deterioration of visual function than patients who did not follow the diet.

Unfortunately, a semi-synthetic low-protein, low-arginine diet is highly restrictive and unpalatable, and only about 20 percent of patients are able to adhere to it. For patients unable to follow this diet, arginine intake can be decreased to some extent by consuming a low-protein diet (0.8 g per kg of body weight per day). Serum ornithine concentrations have declined 40-50 percent in patients who followed such a diet. Although ornithine levels remained 7-12 times above the normal range, long-term adherence to a low-protein diet appears to slow disease progression in some cases.^{30,31}

Vitamin B₆

Vitamin B₆ is a cofactor for ornithine keto acid aminotransferase. In about five percent of patients with gyrate atrophy, supplementation with pyridoxine has resulted in decreases in serum ornithine concentrations ranging from 20 percent to more than 50 percent.^{25,32-35} The usual recommended dosage of pyridoxine for patients with gyrate atrophy is 300 mg/day, although



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larger amounts were used in early clinical trials. In patients whose serum ornithine levels decline with pyridoxine supplementation, long-term treatment with the vitamin may slow or halt progression of the disease.³⁶

Lysine

Ornithine and arginine share a common renal transport system with lysine. High blood-lysine concentrations may therefore block reabsorption of ornithine and arginine in the kidney, resulting in increased urinary excretion of ornithine and less arginine being available for ornithine synthesis. In a study of five patients (ages 16-45) with gyrate atrophy, supplementation with 2 g lysine five times daily for seven days increased mean urinary ornithine excretion by 775 percent (range, 20-2,767%) and decreased the mean plasma ornithine concentration by 34 percent (range, 30-39%).³⁷ Administration of 10-15 g lysine daily for 40-55 days to three patients (ages 13-19) with gyrate atrophy decreased plasma ornithine concentrations by 21-31 percent. A daily dose of 15 g was more effective than 10 g.³⁸ In a case report, daily supplementation with 2.5-5 g lysine for periods of 4-12 days reduced plasma ornithine concentrations by 33-50 percent in a four-year-old girl with gyrate atrophy.³⁹

These findings suggest lysine supplementation could enhance the ornithine-lowering effects of pyridoxine and a low-protein diet. Lysine may also be of some benefit for patients who refuse to comply with dietary recommendations, although there is no evidence lysine supplementation by itself would be as effective as diet therapy. Lysine treatment may not be appropriate for patients consuming a semi-synthetic low-protein, low-arginine diet. The addition of lysine to such a diet might cause arginine deficiency, potentially resulting in hyperammonemia, impaired immune function, and other adverse effects.

The long-term safety of high doses of lysine has not been systematically investigated; however, the available evidence suggests 3-6 g of supplemental lysine daily is probably safe for long-term use.⁴⁰ While dosages in that range would be less effective than higher doses for reducing serum ornithine concentrations, they would presumably provide some benefit.

Proline

Decreased proline synthesis has been observed in patients with gyrate atrophy. It has been suggested that proline deficiency in the choroid and retina may cause gyrate atrophy in some patients despite normal serum proline levels.⁴¹ Four patients with gyrate atrophy received 2-10 g proline daily for 2-5 years. During that time, two patients showed no disease progression and the rate of progression was slower than expected in another patient. No adverse effects were reported.⁴¹

While these findings are encouraging, it should be noted that some patients with gyrate atrophy have elevated plasma proline concentrations.⁴² It is not clear whether proline supplementation is appropriate for patients with hyperprolinemia. Plasma proline should be measured (as a component of a plasma amino acid analysis) and the result should be taken into account when considering the use of supplemental proline for gyrate atrophy.

Keratoconus

Keratoconus is a progressive eye disease in which the cornea thins and bulges into a cone-like shape, resulting in a distortion of vision. Risk factors include a history of atopy (particularly ocular allergies), excessive eye rubbing, and the use of rigid contact lenses. The pathogenesis of keratoconus appears to involve a chronic inflammatory process.⁴³

Food Allergy

Because of the association of keratoconus with atopy^{44,45} and inflammation, it might be worthwhile to investigate keratoconus patients for food allergy. Avoidance of allergenic foods might decrease the inflammatory process that appears to play a role in the development of this disease. Avoidance of allergens might also reduce symptoms of ocular allergy, thereby decreasing the need to rub the eyes.

Vitamin D and Calcium

One practitioner treated 11 patients (18 eyes) with keratoconus using a combination of vitamin D (in the form of irradiated ergosterol, a precursor to vitamin D₂) and a calcium preparation containing 64-percent bone meal and 32-percent dicalcium phosphate. The dosage of vitamin D was 15,000 IU per day (larger

doses were used in some cases), taken after breakfast, while the dosage of supplemental calcium was 140-1,260 mg daily, depending on the amount of milk consumed by each patient. The treatment period ranged from three months to three years. All patients showed improvement in vision and a flattening of the cones on ophthalmologic examination. Plaster-of-Paris casts taken of the anterior segment of the eyes of three patients confirmed the improvement noted on ophthalmologic examination.⁴⁶

In his report, this practitioner cited evidence that keratoconus develops in dogs and rats fed a diet low in vitamin D and calcium. The mechanism of action of these nutrients in the treatment of keratoconus is not known.

The high doses of the vitamin D₂ precursor used to treat keratoconus have the potential to cause hypercalcemia and hypercalciuria. However, vitamin D₃ has been found to be 3.4-9.4 times as potent as vitamin D₂ in humans,⁴⁷ and might therefore be an effective treatment for keratoconus at doses well below 15,000 IU daily (i.e., in the range of 1,600-4,400 IU per day). The Tolerable Upper Intake Level for vitamin D established by the Institute of Medicine for humans age one year or older is 2,000 IU per day. Studies in healthy adults suggest 4,000 IU of vitamin D₃ daily for 2-5 months is a safe level of intake.⁴⁸

Vitamins A and E and other Nutrients

Keratoconus developed in rats fed a vitamin A-deficient diet⁴⁹ and, to a lesser extent, in rats fed a vitamin E-deficient diet.⁵⁰

In a case report, a 35-year-old man with keratoconus, posterior subcapsular cataract, severe atopic dermatitis, and asthma was treated daily with 1,200 IU vitamin E, 600 mcg selenium, 80 mg pyridoxine, 15 mg riboflavin, and 2 g vitamin C. Improvement of keratoconus and regression of corneal opacities were seen after two months. Atopic dermatitis and asthma also improved markedly.⁵¹ Additional research is needed to determine whether other patients with keratoconus would benefit from these nutrients.

Myopia

Myopia (also called nearsightedness) is a refractive defect of the eye that causes distant images to appear blurred. It usually results from elongation of the eyeball, the cause of which is not known. Myopia is generally treated with eyeglasses, contact lenses, or refractive surgery.

Dietary Factors

In a cross-sectional study of 797 children (ages 10-12 years) in Singapore, the prevalence of myopia was significantly lower in children who had been breastfed than in those who had not (62% vs. 69.1%; $p=0.04$). The duration of breastfeeding (three months or less versus more than three months) was not associated with myopia risk.⁵² Since the incidence of myopia in children in Singapore is among the highest in the world, it is not clear whether these findings can be generalized to other populations. Nevertheless, myopia prevention can be added to the list of the many potential benefits of breastfeeding.

In a 1958 report, treatment of myopic children with a diet containing high amounts of animal protein (10% of energy) appeared to slow the rate of visual deterioration. The best results were seen in those who complied best with the diet. Among boys older than age 12 years who consumed the most animal protein (>8.9% of energy), myopia actually improved.⁵³ Follow-up studies are warranted to determine whether this relatively simple dietary intervention can prevent or treat myopia.

Vitamin D and Calcium

One ophthalmologist found that about one-third of patients with rapidly progressive myopia had an improvement in myopia after treatment with irradiated ergosterol (a precursor to vitamin D₂) and calcium for periods of 5-28 months. Plaster-of-Paris casts of anterior segments of these patients' globes revealed shrinkage of the eyeballs.^{54,55} The dose of irradiated ergosterol was 13,680 IU daily and the dose of calcium was 140-1,260 mg/day, depending on the amount of milk consumed by each patient.

As noted above in the discussion of keratoconus, vitamin D₃ is more potent than vitamin D₂ and might therefore be an effective treatment for myopia at doses well below 13,680 IU per day (i.e., in the range of 1,450-4,400 IU per day).

Sicca Syndrome (Dry Eyes; Keratoconjunctivitis Sicca)

Sicca syndrome (also called dry eyes or keratoconjunctivitis sicca) is characterized by dryness of the conjunctiva and cornea, often accompanied by a decrease in the number of mucus-secreting goblet cells and other histological changes on the ocular surface. The condition may be caused by decreased tear production or by an abnormality of tear composition that results in rapid evaporation of tears. Symptoms include irritation, burning, itching, and a sensation that something is in the eye. Dry eyes may be a symptom of certain autoimmune diseases (e.g., Sjogren's syndrome, rheumatoid arthritis) or other medical conditions; more often it is idiopathic or associated with aging, the use of contact lenses, or some medications. Conventional therapy consists primarily of instilling artificial tears into the eyes every few hours to relieve symptoms. Table 3 summarizes some nutritional treatments for sicca syndrome.

Vitamin A

Severe vitamin A deficiency, which occurs frequently in some developing countries, can cause dryness of the eyes¹⁹ and other, more serious, ocular pathologies. The dryness results in part from a loss of goblet cells, which reappear after vitamin A deficiency is corrected.^{56,57}

In Western societies, vitamin A deficiency severe enough to cause eye disease is uncommon, except among people with chronic liver disease. However, it is possible a localized vitamin A deficiency can develop on the surface of eyes stressed by a harsh environment, chronic inflammation, or use of contact lenses; and that such a deficiency contributes to or exacerbates sicca syndrome. Even in the absence of local vitamin A deficiency, the presence of a high concentration of vitamin A in ocular epithelial cells might enhance the regeneration of goblet cells. In either of these scenarios, topical ophthalmic administration of vitamin A could be beneficial.

In an uncontrolled trial, topical ophthalmic application of an ointment containing all-trans retinoic acid (a vitamin A derivative) resulted in clinical improvement and a regeneration of goblet cells in six of six patients with sicca syndrome.⁵⁸ Topical ophthalmic application of vitamin A (retinol palmitate) was also shown in one study to regenerate goblet cells in conjunctival tissue of patients with dry eyes. The dose was

1 drop of a solution containing 1,000 IU/mL vitamin A, administered four times daily for four weeks.⁵⁹

In two uncontrolled trials and one double-blind trial, application of eye drops containing 0.012-percent vitamin A and 0.2-percent polysorbate 80 (Viva-Drops) resulted in improvement in most cases.

One-hundred patients with various dry-eye disorders were treated with Viva-Drops two or three times daily for 30 days; improvement was seen in 95 percent of cases.⁶⁰

Thirty-three patients with dry eyes of various etiologies (including xerophthalmia, erythema multiforme/Stevens Johnson syndrome, keratoconjunctivitis sicca, cicatricial conjunctivitis, drug-induced dry eyes, and contact lens-induced dry eyes) applied Viva-Drops 2-4 times daily for six months; 88 percent of patients experienced symptomatic improvement.⁶¹

Twenty-three patients with dry eyes participated in a double-blind trial, in which 1 or 2 drops of Viva-Drops were instilled into one eye and artificial tears were instilled into the other eye five times daily for four weeks. Subjective improvement occurred in 61 percent of eyes treated with Viva-Drops and 15 percent of eyes treated with artificial tears. Objective improvement was demonstrated by a 132-percent increase in mean tear break-up time in the eyes treated with Viva-Drops, compared with a five-percent increase in eyes treated with artificial tears.⁶²

In the author's experience, Viva-Drops have produced significant improvement in approximately 50 percent of patients with idiopathic sicca syndrome.

Essential Fatty Acids (Linoleic Acid and gamma-Linolenic Acid)

There is evidence that sicca syndrome is caused in part by chronic inflammation of the ocular surface and lacrimal glands. Linoleic acid and gamma-linolenic acid are precursors to the anti-inflammatory prostaglandin, prostaglandin E1, and as such would be expected to have anti-inflammatory activity. In clinical trials, supplementation with the combination of LA and GLA or with evening primrose oil (EPO), which contains both of these fatty acids, resulted in improvement of sicca syndrome.⁶³⁻⁶⁵ The fatty acids were given alone or in combination with vitamins C and B₆, which play a role in essential fatty acid metabolism.

Table 3. Nutritional Treatment of Sicca Syndrome

Nutrient	Protocol/Route of Administration	Dosage/Length of Treatment	Results	Strength of Evidence
Vitamin A	Topical retinol palmitate drops (1,000 IU/mL)	1 drop 4x/d for 4 wk	Regenerate conjunctival goblet cells	Uncontrolled trial (n=29)
	Viva-Drops (0.012% vit A)	2-3x/d for 30 d	Improvement in 95% of cases	Uncontrolled trial (n=100)
		2-4x/d for 6 mo	Improvement in 88% of cases	Uncontrolled trial (n=33)
	Viva-Drops in 1 eye; artificial tears in other eye	5x/d for 4 wk	Sig. subjective improvement and increase in tear break-up time (see text)	RCT (n=23)
EFAs plus vitamins	Evening primrose oil, pyridoxine, vitamin C orally	3 g EPO, 25-50 mg B6, 2-3 g vitamin C daily	Improvement in 1-3 mo	Four cases
		1 g EPO, 50 mg B6, 1 g vitamin C, 3x/d	13/17 subjective improvement; 10/17 increased tear production	Uncontrolled trial (n=17)
EFAs	Linoleic acid plus GLA	57 mg LA and 30 mg GLA or placebo daily	Sig. objective improvements in EFA group	RCT (n=26)
Vitamins C & E	Oral	1 g vitamin C and 400 IU vitamin E for 10 d	Improvement in several objective parameters	Uncontrolled trial (n=60 diabetics)

Four women (ages 48-72) with sicca syndrome, one of whom had Sjogren's syndrome, were treated with EPO (3 g per day), pyridoxine (25-50 mg per day), and vitamin C (2-3 g per day). The women also suffered from brittle, splitting nails. After 1-3 months, in all

cases the dry eye condition improved and nails became normal.⁶³

Seventeen patients with sicca syndrome, nine of whom had Sjogren's syndrome and three of whom had the condition induced by use of the beta-blocker



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practolol, received 1 g EPO, 50 mg pyridoxine, and 1 g vitamin C three times daily. Thirteen patients (including those with practolol-induced dry eyes) experienced subjective improvement or complete resolution of dry-eye symptoms; in 10 patients, Schirmer's test demonstrated an increase in tear production. Improvement was usually seen after 2-6 weeks of treatment.⁶⁴

Twenty-six patients (mean age, 58.8 years) with aqueous-deficient keratoconjunctivitis sicca (sicca syndrome due to decreased tear production) were randomly assigned to receive placebo or a combination of LA (57 mg per day) and GLA (30 mg per day) orally for 45 days. It was not specified whether the trial was double-blind. All patients used artificial tears four times daily. Compared with placebo, active treatment resulted in significant improvements in symptoms ($p < 0.005$), in an objective measure of dryness ($p < 0.005$), and in ocular surface inflammation ($p < 0.05$).⁶⁵ These results are noteworthy considering the low dose of GLA used (GLA is presumed to be the main active ingredient since the amount of linoleic acid was nutritionally insignificant). The amount of GLA used in this study can be obtained from 333 mg evening primrose oil daily, which is one-tenth or less of the dose of EPO used to treat other health conditions.

Additional research is needed to determine whether the addition of vitamins C and B₆ enhances the effect of LA and GLA and to confirm whether low doses of LA and GLA are effective.

Vitamin C and Vitamin E

Ocular surface changes and tear film abnormalities are common in people with diabetes. In a study of 60 patients with type 2 diabetes, daily supplementation with vitamin C (1 g) and vitamin E (400 IU) for 10 days resulted in significant improvements in tear stability (measured by tear break-up time), tear secretion and volume (measured by Schirmer's test), and health of ocular surface epithelium (demonstrated by an increase in the number of conjunctival goblet cells and a decrease in squamous metaplasia).⁶⁶

It is not known whether vitamins C and E both contributed to these improvements. A therapeutic effect of vitamin C in the study described above is biologically plausible, since vitamin C deficiency is known to cause dry eyes in humans,⁶⁷ and patients with diabetes appear

to have an impaired capacity to take up vitamin C into cells.⁶⁸ If vitamin E is beneficial, it might work by exerting an anti-inflammatory effect.

It is also not known whether the observed benefits of vitamins C and E are specific to patients with diabetes. However, a therapeutic trial would be reasonable for patients at risk of being deficient in one or both of these vitamins, such as smokers, the elderly, and people with various chronic illnesses.

Vitamin B₆

Feeding guinea pigs a vitamin B₆-deficient diet resulted in decreased tear flow.⁶⁹ While severe vitamin B₆ deficiency is rare in otherwise healthy humans, marginal vitamin B₆ status appears to be relatively common.⁷⁰ Supplementation with moderate doses of vitamin B₆ (such as 10-25 mg per day) might therefore be useful as adjunctive treatment.

Multivitamin-Multimineral

In a double-blind trial, patients with marginal dry eye syndrome (i.e., symptoms of dry eyes, but no identifiable objective abnormalities) received a multivitamin-multimineral preparation or placebo. Active treatment possibly improved tear stability and conjunctival health, but subjective symptoms did not improve.

Forty patients (median age, 53 years) with marginal dry eye syndrome received, in random order, in double-blind fashion, a multivitamin-multimineral formula, placebo, and no treatment during three separate one-month periods. The nutritional supplement provided daily vitamin E (120 IU), vitamin C (300 mg), vitamin B₆ (30 mg), zinc (15 mg), selenium (200 mcg), and other nutrients typically present in a multivitamin-multimineral. Tear stability and ocular surface status improved compared with baseline following active treatment ($p < 0.05$), whereas no significant changes were seen after placebo or after no-treatment. It was not stated whether active treatment was significantly more effective than placebo. Subjective symptoms did not differ during the active-treatment and placebo periods.⁷¹

Clinical Approach to Dry Eyes

Because of simplicity and relatively high success rate, this author's usual approach is to use Viva-Drops as initial treatment for idiopathic dry eyes. If desired, this treatment may be combined with daily doses of 2-3 g EPO plus nutrients involved in essential fatty acid metabolism (i.e., zinc, vitamin B₆, and vitamin C). For patients with a chronic inflammatory disease (such as Sjogren's syndrome or rheumatoid arthritis), the EPO regimen is usually tried first, with or without Viva-Drops. Vitamins C and E may be helpful for patients with type 2 diabetes and possibly other patients as well. A multivitamin-multimineral preparation may be used as supportive treatment, although evidence for its effectiveness is weak. After improvement occurs the various treatments may be tapered according to patient response.

Uveitis

Uveitis is an acute or chronic inflammation of one or more parts of the uveal tract (i.e., iris, ciliary body, or choroid). The most common form of uveitis is iritis (also called anterior uveitis). Inflammation of the iris and ciliary body is called iridocyclitis. Symptoms of uveitis include ocular pain, redness, and photophobia. Patients with uveitis may develop adhesions between the iris and the lens, which can lead to glaucoma or cataract and subsequent loss of vision or blindness.

While some cases of uveitis are caused by infection or are associated with an autoimmune disease, the condition is frequently idiopathic. The pathogenesis of uveitis is not well understood, but appears to involve autoimmunity. Conventional treatment includes topical glucocorticoids and cycloplegic drugs (which paralyze the ciliary muscle) to relieve symptoms and prevent formation of adhesions.

Food Allergy

According to case reports and clinical observations, food allergy is an important causative factor in some patients with uveitis.^{72,73} In those patients, clear improvement occurred after offending foods were removed from the diet. Cow's milk and other dairy products were common triggering agents; caffeine-containing foods, chicken, chocolate, corn, fish, and shellfish were also involved.

In a case report, a 14-year-old boy showed a resolution of pars planitis (a type of uveitis characterized by inflammation of the vitreous humor) after he stopped drinking a half-gallon of Kool Aid daily.⁷³

It is not known how frequently food allergy is a cause of uveitis. Nevertheless, because of the potential seriousness of the disease, an elimination diet should be considered for any patient with uveitis.

Vitamin C and Vitamin E

Because vitamins C and E have anti-inflammatory activity they might be of value in the treatment of uveitis. In a study in rats, vitamin E supplementation reduced the severity of experimentally induced uveitis.⁷⁴

There is one case report of a "dramatic response" to massive doses of vitamin C in a patient with acute iritis.⁷⁵ Details were not provided, but the practitioner who reported the case typically used bowel-tolerance oral doses of vitamin C, with or without the addition of intravenous vitamin C infusions.

In a double-blind study, supplementation with vitamin C and vitamin E enhanced recovery in patients with acute anterior uveitis. One hundred forty-five patients with acute anterior uveitis were randomly assigned to receive, in double-blind fashion, placebo or 500 mg vitamin C and 100 IU alpha-tocopherol, each twice daily for 30 days. All patients received a conventional therapy of topical prednisolone and scopolamine. Visual acuity did not differ significantly between groups after 30 days; however, eight weeks after the start of the study visual acuity was significantly better in the active-treatment group than in the placebo group ($p=0.01$).⁷⁶

Conclusion

This review presents evidence that dietary modifications and nutritional supplements can be used to aid in the prevention and treatment of various ocular conditions. The evidence presented in this article, combined with that discussed in parts one and two of this series, indicate nutritional therapy has an important role in the practice of ophthalmology.

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