Phytochemicals and Ocular Disease

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Eye Tissues in which Phytochemicals May Play a Role

- Cornea and ocular surface
- Ciliary body and trabecular meshwork
- Iris
- Lens
- Optic nerve
- Retina

Phytochemicals and the Ocular Surface I

- Xerophthalmia
  - A leading cause of blindness in developing countries
  - Caused by vitamin A deficiency
  - Leads to keratinization of the conjunctiva, severe dry eye, ulceration, and scarring
  - Bitot’s Spots
  - Easily treated in early stages with vitamin A or β-carotene supplements

Phytochemicals and the Ocular Surface II

- Chronic dry eye
  - One of the more common complaints encountered in clinical ophthalmology
  - Often is related to a tear film deficiency
  - ω-3 fatty acids may help enhance the wetting properties of the tear film
  - Flax seed oil is the primary consumer source of α-linolenic acid (ALA)
Cyclosporine for Dry Eye

- Cyclosporine (Restasis) was recently approved for severe dry eye
- Immunosuppressive molecule isolated from a fungus *Tolypocladium inflatum Gams*
- Decreases inflammation by inhibiting activation of T-cells permitting more normal tear production

Phytochemicals and Glaucoma

- Glaucoma is an optic neuropathy often associated with high intraocular pressure
- Minimal evidence that nutrient deficiencies contribute to risk
- Interest in ω-3 and ω-6 PUFAs because synthetic prostaglandins are commonly used to lower intraocular pressure

Pilocarpine and Glaucoma

- One of the earliest approved medications for glaucoma is pilocarpine
- Extracted from a South American shrub: *Jaborandi* -- “slobber mouth plant”
- Muscarinic agonist that causes pupil constriction and lowers intraocular pressure
Marijuana and Glaucoma

- Cannabinoids can lower intraocular pressure, but the effect is modest and side effect profile is poor compared to currently available drugs.
- Effect is central—topical THC does not work

Iris Dilation and Phytochemicals

- Atropine has long been known to dilate the pupil
- Muscarinic antagonist extracted from the deadly nightshade Atropa belladonna
- Counteracted by muscarinic agonists such as pilocarpine

Phytochemicals and Cataract

- Leading cause of preventable blindness in developing world
- Cataract surgery is one of the most common surgeries performed in the US
- Reducing the rate of cataract formation would have dramatic impact on Medicare spending and world blindness
- Moderate epidemiological evidence that antioxidant rich foods are associated with decreased risk of cataract
  - Ascorbic acid
  - Vitamin E
  - Carotenoids
- Prospective studies equivocal
Phytochemicals and Optic Neuropathy

- Minimal evidence that phytochemicals play a positive or negative role
- Tobacco/alcohol amblyopia is the best example of a nutritional optic neuropathy
  - Cumulative oxidative stress in nutritionally compromised smokers and drinkers can lead to irreversible optic nerve damage
  - May be related to thiamine or vitamin B12 deficiency
Phytochemicals and Retinal Disease

- Multiple conditions in which phytochemicals play a role
  - Night blindness
  - Retinal degenerations
  - Macular dystrophies
  - Nutritional maculopathies
  - Age-related macular degeneration

Phytochemicals and Night Blindness

- The first described association between diet and ocular disease (ancient Egypt)
- Caused by vitamin A deficiency
  - Common in the developing world
  - Rare in the developed world
- May be associated with malabsorption syndromes
- Night blindness (nyctalopia) generally precedes ocular surface disease
- Lack of retinoids inhibits function of the visual cycle
- Multiple white spots on the retina
- Reversible with prompt supplementation

Phytochemicals and Retinal Degenerations

- Retinitis pigmentosa refers to a wide variety of inherited retinal degenerations affecting over 100,000 people in the US
- Multiple genetic defects responsible
- Night blindness and visual field constriction are prominent clinical symptoms
- Bone spicules and photoreceptor degeneration are prominent clinical signs
Phytochemical Treatment of Retinitis Pigmentosa (RP)

- Vitamin A supplementation (15,000 units per day of retinyl palmitate) can slow the progression of RP, but the effect is modest.
- ω-3 fatty supplementation may also help, but the effect is even weaker.
- Lutein supplementation has been proposed, but there is little evidence there is a deficiency in the first place.

Phytochemicals May Make Some Forms of RP Worse

- Refsum disease
  - Inability to metabolize phytanic acid (a branched chain fatty acid)
  - Treated with a diet low in phytol and phytanic acid (no green leafy vegetables, animal fats, or milk products)
- Gyrate atrophy
  - Defect in ornithine metabolism
  - Treated with a low protein, low arginine diet

Phytochemicals and Macular Dystrophies

- Stargardt disease is the most common cause of early onset inherited macular degeneration (~25,000 affected in US).
- Recessive form (STGD1) accounts for 95% of cases and is caused by a defect in the ABCA4 gene.
- Dominant form (STGD3) accounts for <5% of cases and is caused by a defect in the ELOVL4 gene.
Nutritional Interventions Against STGD1

- The ABCA4 protein transports excess vitamin A aldehyde out of the photoreceptor outer segments
- Excess vitamin A aldehyde can react with phosphatidylethanolamine to form toxic metabolites such as A2E, a component of lipofuscin
- Vitamin A restriction might be therapeutic

Nutritional Interventions Against STGD3

- The ELOVL4 protein is homologous to yeast enzymes that elongate very long chain fatty acids
- A defect in ELOVL4 may inhibit production of EPA, DHA, and their metabolites in the human retina
- The most affected family members who consume the least EPA and DHA (fish, algae, etc.) are the least affected
- A clinical trial of EPA and DHA supplementation is in progress at the Moran Eye Center

Some Phytochemicals Can Induce Maculopathies

- Canthaxanthin is a xanthophyll carotenoid derived from microorganisms and fungi that has been used as a skin tanning agent
- At high cumulative doses, it can crystallize in the macula, although visual loss is rare
- Oxalic acid found in many green vegetables can form retinal crystals, especially in susceptible individuals
- Niacin (nicotinic acid, vitamin B6) can cause cystoid macular edema when taken at high doses (>1.5 g/day) to lower cholesterol
**AMD Prevalence**

- Leading cause of irreversible visual loss in developed countries.
- 1.7-20 million Americans have AMD, ~200,000 have advanced forms.
- ~2% of 50-60 year olds have AMD
- ~30% of individuals over age 75 have some form of AMD.
- Wet AMD accounts for 10-15% of AMD, but 90% of blindness.

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**Estimated Specific Prevalence Rates for AMD**

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**AMD Clinical Features**
More AMD Pictures

Choroidal Neovascularization

AMD Diagnostic Studies

- Visual acuity
- Amsler grid
- Dilated eye examination
- Fluorescein angiography
- ICG angiography
- Optical coherence tomography
Laser AMD Treatments
- Laser photocoagulation
- Transpupillary thermotherapy
- External beam irradiation
- Visudyne Photodynamic therapy +/- Kenalog

Surgical AMD Treatments
- CNVM removal
- Macular translocation
- RPE or retinal transplantation
- Gene therapy
- Prosthetic vision
- Focal radiation delivery
- Encapsulated cell technology (CNTF)

Nonsurgical AMD Treatments
- Low vision services
- Plasmapheresis
- “Alternative” medicine
- Angiogenesis inhibitors
  - Macugen
  - Lucentis
  - Avastin
  - Bevasiranib
  - VEGF Trap
  - Anecortave acetate
  - Squalamine
AMD Risk factors

- Nonmodifiable
  - Age
  - Heredity
  - Gender
  - Pigmentation
  - Race
  - Iris color

- Modifiable
  - Smoking
  - Cardiovascular disease, blood lipid status, and hypertension
  - Alcohol consumption
  - Light exposure
  - Nutrition

Nutrition and AMD

- Retina/RPE have highly unsaturated lipids susceptible to oxidative damage in a region of high oxygen and light.
- AMD is in part a disease of oxidative stress, so antioxidant nutrients may play a role in protection against AMD.
- Difficult studies to perform since many interacting factors are involved.

Approaches to Identifying Nutritional Factors for AMD

- Epidemiology
- Animal Studies
- Physiology
  - Nutrient should be found in appropriate quantities in the retina.
  - Physiological mechanisms should be plausible.
  - Deficiency states should be associated with higher risk of AMD.
- Prospective Trials
Nutrients Epidemiologically Linked to Decreased AMD Risk

- Antioxidant minerals
  - Zinc
  - Selenium
- Antioxidant vitamins
  - Vitamin C
  - Vitamin E
  - Vitamin A
- Polyunsaturated fats
  - DHA and its precursors
- Carotenoids
  - Lutein
  - Zeaxanthin
- β-Carotene
- Lycopene
- Herbals
  - Bilberry
  - Polyphenols
  - Other “herbals”

Age-Related Eye Disease Study (AREDS)

- National Eye Institute
- 4757 subjects, 55-80 years old
- Followed for at least 5 years
- Randomized antioxidant supplementation—neither lutein nor zeaxanthin in supplement
- Incidence of cataracts, severe vision loss, and AMD progression monitored

AREDS Grading Scale

- 1) No drusen or a few small drusen. Good acuity (better than or equal to 20/32).
- 2) Pigment abnormalities or non-extensive small or intermediate drusen. Good acuity.
- 3) Extensive intermediate drusen or any large drusen or non-central atrophy. Good acuity.
- 4) Good acuity and no advanced AMD in the study eye. Advanced AMD in the fellow eye (choroidal neovascularization or geographic atrophy) or acuity worse than 20/32 due to AMD in the fellow eye.
The AREDS Formulation

- 80 milligrams of zinc oxide
- 2 milligrams of cupric oxide
- 500 milligrams of vitamin C
- 400 international units (IU) of vitamin E
- 15 milligrams (25,000 IU) of beta-carotene
AREDS Results

- Significant reduction in progression for AMD patients supplemented with high-dose zinc, vitamin C, vitamin E, and beta-carotene for categories 3 and 4.
- No significant reduction in cataract progression.
- Role of lutein and zeaxanthin and other antioxidants remain to be determined.
- Formulation not optimized.

AREDS II

- New generation formulation
  - Add fish oil (EPA/DHA) 1000 mg
  - Add lutein 10 mg and zeaxanthin 2 mg
  - Decrease zinc and β-carotene
- 4000 patients for 5 years at 100 sites
- Age 50-80 with high risk dry AMD
- Moran Eye Center participates
- Recruitment is in progress
Why Fish Oil?

- Multiple epidemiological studies have shown protection against AMD
- Major constituent of photoreceptor membranes
- Shown to be protective against an inherited macular dystrophy (STGD3)
- Safe and well tolerated

Dietary Carotenoid Groups

- **Group 1**: Kale, spinach green leafy vegetables (6 mg lutein)
- **Group 2**: Tomato products (10 mg lycopene)
- **Group 3**: Corn, mandarin oranges, orange peppers (0.4 mg zeaxanthin)
- **Group 4**: Carrots, winter squash, cantaloupe, apricots (8 mg beta carotene)

Xanthophylls and AMD

- Lutein and zeaxanthin form the macular pigment
- Dietary sources include green leafy vegetables and orange-yellow fruits
- Act as antioxidants or light screening compounds
Eye Disease Case-Control Study (1993-1994)

- Inverse correlation between serum carotenoid levels and risk of exudative AMD.
- Dietary consumption of green leafy vegetables high in lutein and zeaxanthin (spinach and collard greens) associated with lower risk of AMD compared to diets high in β-carotene such as carrots.
- BUT...it is probably more important to know ocular carotenoid levels.

Carotenoids as Light Screening Compounds

- The macular carotenoids absorb phototoxic blue light strongly.
- The anatomical localization of macular carotenoids is ideal for them to act as an optical filter.
- Animals raised on carotenoid-free diets appear to be more susceptible to light damage.
- Limited studies in humans indicate that long-term supplementation can change macular pigment levels in humans.

Carotenoids are Antioxidants

- The retina is exposed to high levels of light and oxygen that can generate free radicals.
- Photoreceptor membranes are very unsaturated and are thus susceptible to free radical damage.
- Carotenoids are efficient quenchers of singlet oxygen and related free radicals.
- It is debatable whether carotenoids are located close enough to the photoreceptors to allow for direct chemical quenching.
Dietary Carotenoid Intake and Macular Pigment Density

- Human autopsies and Raman studies have shown ~30% less MP in those with AMD than without AMD.
- Limited studies indicate that diet or supplementation can increase macular pigment levels.
- Macaque monkeys deficient in carotenoids exhibit drusen and pigment changes reminiscent of human ARM.

Herbals and AMD

- Traditional medicine has provided a wealth of herbal medicines for eye disorders
- Objective evidence is generally lacking
- May provide leads for further interventions
- Popular AMD herbals:
  - Bilberry
  - Red wine
  - Eyebright
  - Goji berries

Bilberry and AMD

- Promoted to enhance dark adaptation and to treat AMD
- Rich in anthocyanidin flavonoids
- High levels of antioxidant activity
- Anecdotal reports (RAF pilots)
- No prospective studies
Red Wine and AMD

- Some epidemiological studies indicate lower levels of AMD in red wine drinkers
- Similar findings for cardiovascular disease
- Rich in polyphenols such as resveratrol

Eyebright and AMD

- Herbal medicine promoted for many eye ailments including conjunctivitis, blepharitis, eyestrain, and AMD
- May be used topically, in compresses, as an extract, or in tea
- No objective mechanism or data

Goji Berries and AMD

- Ancient Chinese herbal medicine for eye disorders
- Also known as wolfberry
- Usually consumed as dried fruit or in tea
- Extraordinarily rich in zeaxanthin
General Recommendations for AMD Patients

- Eat a "healthy" diet with lots of fruits and vegetables and fish, but no excessive fat
- Consider AREDS supplement + ~6 mg lutein in high risk individuals
- Wait on other single nutrient supplements and herbals until more data is available.
- Alcohol in moderation
- Don’t smoke
- Avoid excessive light exposure
- Support and participate in clinical studies (AREDS II)