

# Nutrition and the Retina

**Steven Ferrucci, OD, FAAO**

Chief, Optometry, Sepulveda VA  
Professor, SCCO/MBKU

1

## Introduction

- With no effective means of prevention, the prevalence of AMD will only increase as the population ages
- For these reasons, identification of inexpensive, safe strategies to prevent AMD is paramount
- Optometry should be at the forefront of this!

2

## AREDS: The Age Related Eye Disease Study

- Objective: To evaluate the effect of high-dose vitamins C and E, beta carotene, and zinc supplements on AMD progression and visual acuity
  - 11 center, double-masked study
  - 3640 participants, age 55-80
  - Average follow-up of 6.3 years

3

## AREDS

- Patients divided into 4 categories based on level of AMD
  - Category 1: early AMD
    - Less than 5 small drusen (<63um)
  - Category 2: mild AMD
    - Multiple small drusen
    - Single intermediate size druse (63-124 um)
    - RPE changes
  - Category 3: moderate AMD
    - One large druse (125 um)
    - Extensive intermediate drusen
    - GA not centrally
  - Category 4: advanced AMD
    - More than one large drusen
    - GA centrally

4

## AREDS: Results

- 25% decrease risk reduction in developing advanced AMD in categories 3 and 4 with antioxidants plus zinc
  - 500 mg vitamin C
  - 400 IU vitamin E
  - 15 mg vitamin A (25,000 IU beta carotene)
  - 80 mg zinc
  - 2 mg copper
- Due to low progression to advanced AMD in categories 1 and 2, unable to show benefit
- No statistically significant effect on cataracts

5

## AREDS: Shortfalls

- No apparent benefit in category 1 and 2
  - 80% fall into this group
- Unsure how long someone at risk should continue supplements
- Beta carotene associated with increased risk of lung cancer in smokers
  - substitution of other antioxidants (lutein) is unclear
  - how long a non-smoker is debatable

6

### AREDS: Shortfalls

- Did not evaluate the role of lutein/zeaxanthin, or omega 3's
- Benefit is modest, and all groups had progression despite treatment
- **"The supplements are not a cure for ARMD, nor will they restore vision already lost from the disease"**
  - AREDS press release 10/2001

7

### AREDS: Take home

- Reasonable to suggest antioxidant plus zinc in patients with moderate to severe AMD
- No proven benefit in early to mild AMD
- Increased risk of lung cancer with beta carotene should be considered in smokers and past smokers

8

### AREDS 2

- AREDS 2: Enrollment ended June 2008 with =4200 patients followed for six years
  - Effect of lutein, zeaxanthin and omega 3 on AMD
  - Effect of eliminating beta carotene on AMD
  - Effect of reducing zinc on AMD
  - Effect of supplements on cataracts
  - Validate the AMD scale from original AREDS
- Results released at ARVO May 2013

9

### AREDS 2

- Major Conclusions:
  - The addition of lutein and zeaxanthin, DHA and EPA or both to the AREDS formulation did not further reduce the risk of progression to advanced AMD
  - Substituting L/Z (10 mg/2 mg) for beta carotene is an appropriate substitution, because of potential increased incidence of lung cancer in former smokers

10

### Additional findings

- Decreasing zinc from 80 mg to 25 mg had no significant effect
  - No change recommended (?)
  - Deserves further study
- Competitive absorption of carotenoids

11

### Additional findings

- Lutein and zeaxanthin did provide an additional 10% reduced risk over current supplements
- In patients with lowest dietary intake of l/z, additional 26% reduced risk
- VA Outcome: overall no effect
  - However, 18% risk reduction in legal blindness amount patients with lowest l/z intake

12

### Additional findings

- Most positive effect was found on wet AMD patients, not GA patients
- Cataracts: no overall effect except in those patients with lowest l/z intake
- In general, patients were very well educated and well nourished and therefore may not reflect average patient
- Many were on multivitamins

13

### Lutein and Zeaxanthin

- Naturally occurring carotenoids that are found in high concentration in the eye, specifically the macula/retina
- Many feel protective for AMD
  - Absorbing blue light
  - Quenching free radicals
  - Increasing membrane stability

14

### Lutein and Zeaxanthin

- Several smaller studies have shown positive benefit of Lutein and/or Zeaxanthin
  - Seddon Study, 1994: Evaluated dietary carotenoids, vitamins A, C and E
    - 356 pts
    - Pts with highest dietary intake of carotenoids (specifically lutein and zeaxanthin) had a 43% lower risk for ARMD than those with lowest levels
  - LAST Study: Stuart Richer, *Optometry*, April 2004
    - 90 pts, mostly male
    - Increased MPOD, increase VA, glare recovery, contrast sensitivity in pts taking L and L plus antioxidants vs. placebo
  - LUXEA Study: 2006
    - 92 pts taking L, Z, C, or P
    - Small (13%) in MPOD among pts taking L

15

### Lutein and Zeaxanthin

- Cumulative effect of studies indicate a positive effect of Lutein as well as Zeaxanthin on MPOD and AMD
- AREDS 2 results
  - Good substitute for beta carotene
  - May have additional advantage esp. in those patient with lowest dietary intake
- Dosage: 10 mg Lutein, 2 mg Zeaxanthin

16

### Fish Consumption and Omega-3 Fatty Acids

- Conflicting studies in the literature
  - *Seddon et al, Ophth 2004*: 60% reduced risk to advanced ARMD for people who w/ highest fish consumption (> 2 times /wk)
  - *Ophthalmology, July 2006*: issue of protective nature neither clearly supported nor refuted
  - *Arch Ophthalmology, July 2006*: US Twin study showed that fish consumption and omega-3 fatty acids intake reduced the risk of ARMD
  - *Arch Ophthalmology, July 2006*: a diet high in omega 3 fatty acids, especially from fish, suggests protection against early and late in Australian patients

17

### Fish Consumption and Omega-3 Fatty Acids

- Conflicting studies in the literature
  - *AREDS Report No. 20*: 40-50% reduced likelihood of advanced neovascular ARMD in pts with highest levels of omega-3 consumption
  - *AREDS Report No. 23*: 50% decreased likelihood of progression to central GA with highest level of omega 3/FA consumption
  - *The American Journal of Clinical Nutrition, August 2008*: eating oily fish at least once per week reduced risk of neovascular ARMD by half

18

## Fish Consumption and Omega-3 Fatty Acids

- AREDS 2 results
  - Did not show positive results
- Bottom line: unclear, but probably not needed
  - 1000 mg/day
  - At least 2/3 DHA and EPA
- Also now some discussion regarding role in systemic disease
  - Role in GA?
  - Role in dry eye?

19

## Other vitamins

- B Vitamins
  - WAFACS:
    - Folic acid, B6 and B12 decreased risk of AMD by  $\cong$  35%
  - Blue Mountain study:
    - Folate deficiency increased risk of AMD by 75%
    - B12 supplementation decreased risk by 47%

20

## Other vitamins

- Co-Q 10
  - A coenzyme produced by the body and required for basic function of all cells
  - Used in neurology
  - Studies are inconclusive
- Lycopene
  - Another carotenoid found in red fruit and vegetables such as tomatoes, guava, watermelon, pink grapefruit and papaya
  - Helpful for prostate issues in men
  - Unknown effect in ARMD
- Taurine
  - Some studies indicate that due to its high concentration in the eye, may play a protective role in ARMD
  - In cats, taurine deficiency has been shown to cause retinal degeneration
  - Speculative only at this point
- Acetyl-L-carnitine
  - Many have anti-oxidant as well as anti-aging properties
  - Role in ARMD unknown

21

## Cost effectiveness of Vitamin Therapy

- July 2007, *Ophthalmology*
- Computer based model
- Concluded that improves quality of life in AMD patients at a reasonable cost
- Also stated should be a high public health preventive measure
  - As high as breast cancer screening in woman >50 and vision screening in children to detect strabismus and amblyopia at 85% compliance

22

## Vitamins: Take Home

- Use AREDS 2 type formulation in suitable patients
  - Encourage proper dosing
  - Discourage use of similar products that differ from what you want
- Pick one or two products
- Review literature and additional AREDS 2 reports
- Discuss prevention in high risk patients

23

## Vitamins: Take Home

- The best intake is through diet/food
  - Not always realistic:
    - Average American gets only 2mg Lutein
    - Leading antioxidants for average American is coffee
    - French fries account for 25% of all vegetable intake in US
    - Vitamin E 13x, A and C 5x recommended daily dose
- Only 3% of Americans follow 4 basic health practices
  - No smoking
  - BMI 18.5 – 25
  - 5 or more FRUITS & VEGABLES daily
  - > 30 minutes physical activity/ 5x times wk

24

### My thoughts...

- Discuss vitamins/nutrition and lifestyle changes with ALL AMD pts
  - Smoking, increased BMI, UV light
- Decide which you feel should start vitamin therapy
- Make SPECIFIC recommendations based on your knowledge
- **DO SOMETHING!!!**

25

### Background

- MPOD is lower in patients with diabetes and lower still in patients with diabetic retinopathy
- Higher serum Zeaxanthin/Lutein is associated with 2/3 lower risk of developing type 2 diabetes and early NPDR
- ECPs should measure and optimize MPOD in our patients with and at-risk for diabetes

Invest Ophthalmol Vis Sci. 2010 Nov;51(11):5840-5

26

### Diabetes Visual Function Supplement Study (DiVFuSS)

- 6 month double-blind placebo-controlled, randomized, controlled clinical trial of adults with type 1 diabetes or type 2 diabetes > 5 years
- No DR (2:1) and mild-moderate NPDR (1:1)
- Daily use of a multi-component nutritional supplement (zeaxanthin, lutein, vitamins D/C/E including tocotrienols, curcumin, benfotiamine, Pycnogenol™, lipolic acid, NAC, resveratrol, green tea & grapeseed extracts, O-3 FAs, CoQ10, Zn)
- Pre- and post- analysis of CSF, MPOD, color vision, macular perimetry, OCT, A1c, lipids, 25(OH) vitamin D3, hsCRP, TNF- $\alpha$ , NFL thickness and diabetic peripheral neuropathy symptom scores (DPNSS)

Br J Ophthalmol 2015 e-published June 18

27

### Subject Characteristics (n = 67)

- 28-79 yo (mean = 56.1 yrs)
- 30 with NPDR & 37 with no DR
- 27 type 1 diabetes & 40 type 2 diabetes
- HbA1c range 5.85 to 10.3% (mean 7.2%)
- Diabetes duration 5-52 years (mean 16.1 yrs)
- Both Placebo and Supplement Groups showed similar and significant deficits in contrast sensitivity, color vision and visual field at baseline

No statistically significant differences at baseline between Supplemented and Placebo groups

28

### Goals

- Improve retinal metabolism, integrity, and visual function without significantly affecting blood glucose or worsening other labs
  - → Avoid hypoglycemia
  - → Don't step on the toes of PCPs and endocrinologists
- 2 capsules per day, at most
- Cost less than \$1.50/day

29

### Who Should Consider Taking DVS Formula?

- Adults with DM  $\geq$  5 years
- Adults with any degree of DR
- Adults with DM and reduced visual function and/or low macular pigment
- Patients with sub-optimal blood glucose control
- Every patient with diabetes???

30

### Summary of Facts

- The DiVFuSS formula significantly improved visual function, diabetic peripheral neuropathy symptoms, blood lipids and hsCRP in patients with established diabetes - without significantly affecting blood sugar control
- The DiVFuSS formula significantly increased MPOD
- The DiVFuSS formula represents a novel & complementary strategy to excellent metabolic control for disrupting the pathobiology of diabetic retinopathy and correcting visual function deficits common in diabetes
- No adverse events occurred during the study
- Available as EyePromise® DVS Formula

31

### Other studies

- DiVFuSS with AniVEGF for pts with CI-DME
  - Looking at CST and number of injections
- DiVFuSS in pts with abnormal fFERG
  - Improvement in fFERG
- Noretin
  - Poitive effect on CST in DME, less so on VA
- Berberine
  - Shown in small studies (n=36) to lower A1c similar to metformin
  - Effect on DR unknown

32

### Others

- Retinitis pigmentosa
- Leber's
- Gyrate atrophy
- Dry Eye
- Optic nerve/glaucoma

33