Feed Your Retina: Nutrition and Retinal Health

A. PAUL CHOUS, MA, OD, FAAO TACOMA, WA



Disclosures

 I have been a consultant to, lectured for or had some affiliation with the following:

 Alcon, Baush & Lomb, Cooper Vision, Diabetes In Control, Freedom Meditech, Kemin, Kestrel Health, LifeMed Media, ONS, Optos, Regeneron, Risk Medical Solutions, VSP, ZeaVision

 These affiliations will in no way influence the content of this lecture

What is the goal of "feeding your retina"

- Is it to promote wellness?
- Is it to prevent catastrophic events?
- Is it to improve current health/function?

oAre these all the same??

 I think the goal is all three, and that they are (distinctly) different



Sometimes, though, we feed TOO MUCH!



Rates of obesity are increasing alarmingly!

CURRENT TRACK



Worldwide Stats

640 million people are obese in 2014 Up from 105 million in 1975

Lancet 2016 April; 387(10026):1349-50



Countries With The Most Obese People

- TATATATAT
- **1.** UNITED STATES
- 2. CHINA
- 3. INDIA

How Is Utah Doing Today?

- 25.7% of adults are obese
- 33.8% are overweight
- 7.2% have diabetes

www.cdc.gov



- Utah has the lowest rate of childhood overweight and obesity in the nation (23.1%)
 - National rate is 31.6% http://stateofobesity.org/states/ut/

Obesity - Classic Definition		
• BMI > 25	overweight	
• BMI > 30	obese	nere's an
• BMI > 35	severely obese	app for that "
• BMI > 40	morbidly obese	
• BMI > 45	super obese	
• BMI > 50	super morbid obese	
• BMI > 70	mega-obese	
BMI = Weight (kg)/Height (m) ² or		
Weight (pounds)/Height (inches) ² x 703		

Other Measures: Waist Circumference Waist:Hip Ratio

Why is Obesity Associated With Ocular & Systemic Disease?

An Unholy Triumvirate

 Inflammation (cytokines, endothelial dysfunction)

OHypertension (RAAS, hyperinsulinemia)

OHypoxia (Sleep Apnea, ♠O₂ demand)

Inflammation

Fat cells (adipocytes) are endocrine cells, secreting hormones regulating insulin sensitivity & satiety, and are associated with elevated markers of inflammation

Resistan Adiponectin Leptin

Hormones



Inflammatory Proteins



Reactive Oxygen Species & Inflammation



Fat Cells Are Endocrine Cells!!

Hypertension

- Obesity & BMI are clear and continuous risk factors for HTN
 IR activates the renin-angiotensin system
- Weight loss results in reduced BP in large clinical trials
- HTN is a definitive risk factor for CVD and myriad ocular diseases (RVOs, AION, DR)

Blood Press. 2007;16(1): 13-19 Am J Hyperten. 2006 Nov;19(11): 1103-9

Hypoxia

- Obesity is <u>THE</u> major risk factor for obstructive sleep apnea syndrome (OSAS)
- OSAS causes hypoxic stress and elevates blood pressure
- OSAS is associated with endothelial dysfunction and several eye diseases

J Clin Sleep Med. 2007 Jun 15;3(4): 409-15 Exp Physiol. 2007 Jan;92(1): 51-65

OBSTRUCTIVE SLEEP APNEA

Highest risk if Neck Circumference > 17 inches



Normal Breathing

- Airway is open
- Air flows freely to lungs



Obstructive Sleep Apnea

- Airway collapses
- Blocked air flow to lungs

OSAS in Eye Disease

-Glaucoma prevalence estimated 2-7%

(Eye 2007;22(09): 1105-9)

- Floppy Eyelid Syndrome prevalence - 25% (Ophthalmology. 2006;113(9):1669-74)

– Pseudotumor Cerebri (15-40%)

Neuroophthal 2001 21(3):235)

-OSAS is the most frequent disorder in NAION Curr Eye Res. 2015 Oct 7:1-6.

 Several studies link OSAS to increased risk of severe DR & poor response to anti-VEGF Tx in neovascular AMD

Diabet Med. 2016 Feb;33(2):158-68

Retina. 2016 Apr;36(4):791-7.

./

Inflammation ROS Endothelial Dysfunction

Hypertension

Hypoxia

Major Retinal Diseases Linked to Obesity & Causing Severe Vision Loss and Legal Blindness







AMD

- Increased risk with increasing BMI & waist size (Arch Ophthalmol. 2003;121(6): 785-92)
- 5% increased risk of advanced AMD with every 1 kg/m² increase in BMI (Am J Ophthalmol. 2007;143(3): 473-83)
- In AREDS, BMI > 30 doubled the risk of SRNV (Ophthalmology. 2005;112(4):533-9)

• Greater waist circumference linked to lower macular pigment (Am J Clin Nutr. 2006;84(5): 1107-22)

Diabetic Retinopathy

Obesity & weight gain are the primary risk factors for T2DM Ann Intern Med. 1997;122:481-6

Marked obesity increases the risk of DR Diabetes Care. 1986;9(4): 961-9

6-fold increased risk of PDR when BMI > 30

IOVS 2011 Jun 22;52(7):4416-21



AMD Linked to Diabetes

 Analysis shows diabetes increases risk of AMD (40% to 235% in a UK cohort of 10+ thousand) and advanced AMD (80% in AREDS) Invest Ophthalmol Vis Sci. 2015 Eeb 10:56(3):1585-92

Invest Ophthalmol Vis Sci. 2015 Feb 10;56(3):1585-92 Ophthalmology. 2005 Apr;112(4):533-9.<u>.</u>

 Both conditions are associated with inflammation, smoking, low MPOD and higher intake of added sugars



"My doctor told me to stop having intimate dinners for four..... Unless there are three other people" -Orson Welles



"There is a charm about the forbidden that makes it unspeakably desirable" -Mark Twain

Some General Principles

- Diet is the ideal way to get the nutrition we need for good health
- Nutritional supplements may fill gaps in diet, but don't compensate for unhealthy lifestyle



Healthy eyes belong to healthy people



The Standard American Diet (SAD) IS SAD!!!

Excess Calories Minimal Quantity/Quality Plant Foods Excess Refined Carbohydrates Unhealthy Fats Excess Preservatives Poor Nutrient Density

Portion Control: Size Does Matter





Dietary Fat & Eye Disease

Sat Fat, Trans Fats and Vegetable Oils associated with higher risk of AMD and Diabetic Retinopathy Med Gen Med 2005;7(1):3 Arch Ophthalmol. 2009 Nov;127(11):1483-93

EPA + DHA decrease TGs, FFAs, blood glucose & insulin levels, visceral fat mass and many inflammatory markers Arch Intern Med. 2005;165: 193-7

Despite AREDS2, the preponderance of evidence suggests omega-3s (DHA) and tree nuts lower AMD risk

J Ophthalmol. 2014;2014:901686.

NOT ALL SATURATED FATS ARE "BAD"

Medium chain triglycerides

- Are used for source of fat in malabsorption conditions such as IBS, and ulcerative colitis, and in infant formulas. It is also used to increase the energy intake in cystic fibrosis patients.
- Affects hormone release from intestines differently than LCFA's
- Inhibits bacterial and virus growth
- Reduces LDL and increases HDL
- Reduces abdominal fat
- Increases fat burning
- Not stored in adipose tissue
- Reduces cholesterol synthesis by the liver
- Does not provide essential fatty acids

Curr Opin Clin Nutr Metab Care. 2016 Mar;19(2):81-7.



What About Fish & Fish Oil?

- AREDS2 found no benefit with 650 EPA + 350 DHA
- BUT.....
 - Well-nourished subjects had high baseline O-3 intake
 - Did not measure RBC saturation
 - Used Ethyl Ester form (TG more bioavailable)*
 - ODHA may be more important than EPA
 - Did not measure serum folate (necessary for DHA incorporation into RBC membrane)

*Prostaglandins Leukot Essent Fatty Acids 2010 Sept, 83(3):137-41

Omega 3 FAs to Prevent CNVM?



Am J Clin Nutr. 2006 Jun;83(6 Suppl):1467S-1476S.

 In NAT2 Study (Nutritional AMD Treatment 2 Study), Patients with Wet AMD in one eye and early AMD in the fellow eye who achieved O-3 index > 8% had 68% less CNVM over three years (840mg DHA + 270mg EPA)

Ophthalmology. 2013 Aug;120(8):1619-31.



Dietary Carbs & Eye Disease

- Refined carbs increase risk of AMD
- Refined carbs increase blood glucose and risk of DM/DR
- Increased consumption of whole fruits, vegetables and fiber associated with lower risk of AMD, DR and glaucoma

 JAMA 1994; 272: 1413 -1420
 Arch Ophthalmol. 2004 Jun;122(6):883-92

 Med Gen Med 2005;7(1):3
 Am J Ophthalmol. 2012 Oct;154(4):635-44

 Clin Experiment Ophthalmol. 2012 Apr;40(3):288-94

Good Carb: Bad Carb



Do particular dietary sources of carbohydrate influence glucose homeostasis, inflammation and risk of eye disease?

Glycemic Index (GI) & Glycemic Load (GL)

- GI is the incremental area under the blood glucose response curve of a 50g portion of test food compared to a standard (white bread or glucose)
- GI = <u>AUC Test Food</u> AUC Reference Food
- GL = <u>GI x portion size (gms)</u> 100

Criticisms: Many



Are GI and GL Useful?

- Low GI food delay hunger, reduce caloric intake (Lipids. 2003;38(2): 117-21)
- Low dGI/dGL diets reduce fasting blood glucose, glycated protein and insulin resistance (Am J Clin Nutr. 2008 Jan;87(1):258S-268S)
- High dGL and CHO intake increased mortality risk almost 50% in EPIC (PLoS One. 2012;7(8):e43127. Epub 2012 Aug 23)
- High dGl increases the risk of developing T2DM (Diab Technol Ther 2006;8(1): 45-54) & AMD (large drusen, GA, CNVM) (Am J Clin Nutr. 2007;86(1): 180-8)

Association between dietary glycemic index and age-related macular degeneration in nondiabetic participants in AREDS

- 4099 patients
- 55-80 yo

Am J Clin Nutr. 2007;86(1): 180-8



49% increased risk of advanced AMD (GA + SRNV) if dGI is above the sex median

 20% of prevalent AMD cases would have been eliminated if dGI was < sex median

AGEs, Autophagy and Impaired Ubiquitin

- Advanced glycation endproducts (AGEs):toxic glucose-protein aggregates implicated in DM/DR, AD, PD, AMD
- High GI diet creates AGEs and concomitant basal laminar deposits seen in AMD
- High GI diet impairs lysosomal autophagy and ubiquitin-proteasome system (UPS) activity required for degradation of AGEs & lipofuscin

Aging Cell. 2012 Feb;11(1):1-13

Autophagy. 2012 Sep 1;8(9).




AGEs block Clearance of lipofuscin and drusen!!

Aging Cell. 2012 Feb;11(1):1-13

Autophagy. 2012 Sep 1;8(9).

AGES: Not JUST Diabetes

- Strongly implicated in DM & DR, AMD, glaucoma, cataract, atherosclerosis, kidney/lung disease, neurodegeneration, cancer metastasis
- AGEs form in all humans over time as a function of normal glucose metabolism, age-related mitochondrial derangement, excessive carbohydrate consumption, and consumption of foodstuffs cooked at high temperature & low humidity

 Proc Mol Nutr Food Res 2007;51:1079-1084
 Ageing Res Rev. 2014 May;15:146-60.

 Am J Med Genet A. 2013 Nov;161A(11):2750-5
 Neuroscience. 2013 Oct10;250:140-50

 Proteomics Clin Appl. 2013 Jan;7(1-2):155-70
 Proteomics Clin Appl. 2013 Jan;7(1-2):155-70



100,000 cases of severe AMD would have been prevented if dGI had been < sex

median (Am J Clin Nutr. 2007;86(1): 180-8)



This would also save BILLIONS of dollars and greatly improve qualitiy of life!

How Does This Compare to AREDS Supplements?



LOW SUGAR & LOW DIETARY GLYCEMIC INDEX DIETS ARE AS EFFECTIVE AS AREDS2 SUPPLEMENTS FOR PREVENTING ADVANCED AMD 33% Risk Reduction With Each



ClearPath – Freedom Meditech

Uribarri J, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc 2010;110:911-916

6.000

4,800

4.800

3.900

2,500

2.500

1.600

1,500

1.300

1.100

1,200

AGEs in Common Foods

Roasted/BBQ'd chicken thighs with skin Grilled hot dogs Broiled chicken breast Fast food hamburger Microwaved sausage Broiled tofu Feta/American cheese Roasted nuts and nut butters 1 cup of whole cow's milk A fried egg **Restaurant French fries** Butter **Boiled chicken** Potato chips 850 Margarine 850 Cottage cheese 500 Life cereal 400 Canned beans 190 Corn chips 161 A slice of whole wheat bread 100 75 A roasted yam Popcorn 40 A raw tomato 20 An apple 10 Oatmeal 4 1 cup of human milk 2

Diabetic Retinopathy and GI/GL

 52% DR risk reduction comparing highest to lowest quartiles of dGI after all adjustments

Epidemiology. 2013 Mar;24(2):204-11

 Low dietary fiber/High dGI associated with 40% higher risk for DR and 224% for STR (PDR/DME) in Australian and US cohorts

Clin Experiment Ophthalmol. 2012 Apr;40(3):288-94

Protein & Eye Disease

 Higher red meat consumption is associated with higher risk of early & late AMD, whereas chicken & fish consumption is protective

Am J Epidemiol 2009):867-76

Biomed Res Int. 2014;2014:413150

 Nitrate/nitrite preserved meats, animal protein and Fe⁺² intake significantly increase risk of T2DM

> Diabetes Care. April 1 2014 Am J Clin Nutr. 2011 Aug 10

Red Meat & AMD

Table 3 Multivariate binary logistic regression analysis for late versus no AMD. 95% Cl P value OR **Red meat intake** 1 <Once a week Once a week 1.04 0.82 0.746-1.44 2–6x/week 1.67 1.296-2.16 7.982 × 10-5 2.34 1.610-3.400 8.224 × 10-6 Daily intake

n = 2900 European Genetic Database

Biomed Res Int. 2014;2014:413150

Lose the Nitrates & Nitrites



A daily serving of processed or unprocessed red meat increases the odds of T2DM 35% and 16% (meta-analysis of 442,000 patients) Am J Clin Nutr. 2011 Aug 10



Sodium nitrate & nitrite metabolites are structurally similar to streptozotocin, which kills pancreatic β cells

Dietary Recommendations for Overweight & Obese Patients

 Eat an anti-inflammatory, calorie restricted diet consisting of a variety of low GL fruits & vegetables, nuts, whole grains and plentiful fiber, favoring cold water, fatty fish, chicken minimal red meat and some soy protein

Modify based on clinical history

Mediterranean or Paleolithic-type Diets

 Multiple studies show greater adherence to a Mediterraneantype or Paleolithic-type diet lowers inflammation, insulin resistance, CV events, cancer and mortality

> Am J Clin Nutr. 2005;82:163-73 N Engl J Med. 2003;348: 2599-608

 30% lower risk of mortality in an RCCT versus low fat AHA diet

N Engl J Med. 2013 Feb 25.



One Dietary Change

- Increasing dietary fiber to 30g/d improves markers of Metabolic Syndrome (BP, IR, Iow HDL-C, high triglycerides, body weight) nearly as well as the more complicated & restrictive AHA diet
 - o RCT of 241 with Met Syn
 - o 2.1 kg versus 2.7 kg weight loss at 1 year



Plant Based Diets Increase Photosynthesis in Mammals!

- Chlorophyll metabolites accumulate in mammals and facilitate CoQ10 activity in mitochondria
- When exposed to sunlight (680 nm), mitochondrial ATP production increases significantly
- Worms given light + chlorophyll live 20% longer





Rats given chlorophyll-rich Diet versus controls

J Cell Sci. 2014 Jan 15;127(Pt 2):388-99.

Eat Foods that Activate Nrf2

- Nuclear factor (erythroid-derived 2)-like 2 protein
- The master regulator" of the antioxidant response
 → activates genes that code for cytoprotective enzymes and proteins (superoxide dismutase, catalase, glutathione peroxidase)
- Nrf2 activators include:
 - Sulforaphane (cruciferous vegetables)



- Polyphenols (Resveratrol, Curcumin, Green Tea)
- Allicin (garlic)







Michael Pollan's Adage



What We Do







Eat Food-like Products, Far Too Much, **Mostly Refined Carbs with Low** Nutrient Density, **Trans Fats** & Devoid of Fiber So What Else Should I Feed My Retina To Lower My Odds of Retinal Disease?

AMD 9 million Americans

DIABETIC RETINOPATHY

8 million Americans

Micronutrients and Retinal Disease



Assessing Nutritional Status

- Common nutrient deficiencies seen in CVD, obesity, AMD, diabetes/DR include:
 - Zinc
 - Magnesium
 - Vitamin D
 - Vitamin C
 - B vitamins especially B12, folate, thiamin
 - Lutein
 - Zeaxanthin

Am J Clin Nutr. 2013 Jul;98(1):129-35. J Ayub Med Coll Abbottabad. 2003 Jan-Mar;15(1):54-7 Int J Vitam Nutr Res. 1991;61(4):328-33

Nutrition



Average American gets only 2mg lutein/day

- Leading antioxidant source for the average American is coffee
- French fries account for 25% of all vegetable intake in US
- Only 3% of Americans follow 4 basic health practices Nonsmoking (76 %)
 BMI 18.5 – 25 (40%)
 5 or more F &V daily (23%)
 - > 30 minutes physical activity 5 times per week (22%)

Don't Deride Multivitamins

 There is evidence that MVMs improve common nutritional deficiencies, and safeguard animals from chronic marginal deficits that contribute to chromosomal breaks & chronic diseases of aging that occur over years/decades

Low micronutrient intake may accelerate the degenerative diseases of aging through allocation of scarce micronutrients by triage

Proc Natl Acad Sci U S A. Nov 21, 2006; 103(47): 17589–17594



Bruce Ames, PhD – UC Berkeley, National Medal of Science Recipient



Pertinence of AREDS/AREDS2...

To what percentage of YOUR AMD patients do AREDS & AREDS2 apply???



Risk reduction only seen in those with AREDS Category 3 or 4 Dry AMD AREDS & AREDS2 say NOTHING about prevention for the typical patient seen by ODs



 Long-term intake of dietary lutein and zeaxanthin lowered risk of advanced AMD by 40% over 26 yrs (p<0.001)

JAMA Ophthalmol. 2015 Oct 8:1-10. Intakes of Lutein, Zeaxanthin, and Other Carotenoids and Age-Related Macular Degeneration During 2 Decades of Prospective Follow-up.

MPOD

Macular Pigment Optical Density



- The 3 macular pigments are from yellow and orange carotenoids (L, Z) and conversion from L (MZ)
 Unable to be synthesized by humans
 Found in highest concentration in fovea
 Accumulation can protect RPE and photoreceptors
 Lower MPOD associated with lower
- Lower MPOD associated with lower carotenoid intake/serum levels, females, smoking, diabetes, increased BMI, AMD
- Measurable



• May even help with light sensitivity

Reference: Macular pigments, update and measurement. Malinovsky V, Geirhart D.



Effect of Lutein + Zeaxanthin On risk of Advanced AMD



Adapted from Seddon JM et al. JAMA 1994; 272: 1413 -1420

Realistic Dietary Sources of L/Z

Romaine lettuce 2.3 mg

> Spinach 12 mg



L/Z values based on a 100 g serving

U.S. Department of Agriculture, Agricultural Research Service. 2010. USDA National Nutrient Database for Standard Reference, Release 23. Nutrient Data Laboratory Home Page, http://www.ars.usda.gov/ba/bhnrc/ndl

Which is more dangerous: UV or Blue Light??

- Numerous studies show short wavelength Blue light exposure is a risk factor for AMD
- Increased MPOD can help protect from oxidizing effect sof blue light
- 50% of harmful blue light reaches photoreceptors with an MPOD of 0.20
- 18% of blue light reaches photoreceptors with an MPOD of 0.50



Ciulla Ophth 2001 108:730-77. Hammond, Recent research Dev. Nutr 2002.

Visual Performance with Increased MPOD : Filters Blue Light

High MPOD levels enhance

- Visual acuity
- o Glare tolerance
- Glare recovery
- Contrast sensitivity
- Chromatic aberration
- O Photophobia



Bahrami et al. 2006. BMC Ophthalmol 6(1):23. Cangemi et al. 2007. BMC Ophthalmol. 7:3. Kvansakul et al. 2006. Ophthalmic Physiol Opt 26(4):362-71. Massacesi et al. 2001. IOVS. 42(4):S234. Olmedilla et al. 2003. Nutrition. 19(1):21-4. Richer et al. 1999. J Am Opt Assoc 70(1):24-36. Richer et al. 2004. Optometry. 75(4):216-230. Stringham and Hammond. 2008 Opt Vis Sci. 85(2):82-8. Wenzel et al. Vis Res. 46(28):4615-22.

CS, photophobia & glare may be altered by Carotenoids: VISUAL ENHANCEMENT BY FEEDING OUR RETINA



LAST & ZVF study (Dr. Richer)

Beyond just MPOD

 We may even see improvement in function before/without improvement in MPOD
 Significant improvement in CS without

improvement in MPOD w 6mg L over 1yr

Sasamoto et al. Graefes Arch Clin Exp Ophthalmol

L/Z increase neural processing speed and make you smarter!!

Renzi LM *et al.* FASEB J 22 (abstract 877.5), 2008 Miller LS *et al.* Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 17:575-90, 2010. Arch Ophth. 2006 124(4):537-43, 2006 Kang, et al. Ann Neurol 57:713-720, 2005



Feed your Retina..even when it is gasping Supplementation can improve treatment efficacy

- Feeding your macula Zeaxanthin can help treatment outcome in Neovascular AMD
- Study by Peralta et al showed:
 - Triple therapy w/ laser/Avastin/Dex inj can be improved w 20mg Zeaxanthin / day
 - Total treatment cycles in 2yrs with add-on Z averaged 2.1 versus 2.8 without Z (25% reduction)
 - Fellow eye involvement at 2 years only 6.25% versus 12.5% (50% reduction p = 0.03) and saved \$6K per year

MZ: The 3rd macular carotenoid

- Mesozeaxanthin is the 3rd macular carotenoid
- Naturally converted from lutein (likely in most people)
- Although MZ is not found at meaningful levels in the food chain, it can be synthesized and supplemented
- It does improve MPOD & visual function
- It has not been tested on its own in humans to show increase in plasma or macula
- It is not found in the brain, where L/Z comprise 70% of all carotenoid levels

J Ophthalmol. 2015; 2015: 865179

Low MPOD: Not Just in AMD

- Evidence shows that low macular pigment is associated with:
 - -AMD
 - Diabetes and diabetic retinopathy
 - -Glaucoma
 - –Cognitive decline
 - -Alzheimer's Disease Br J Ophthalmol. 2013 Aug;97(8):994-8.

Age Ageing. 2014 Mar;43(2):271-5.

J Alzheimers Dis. 2014;42(4):1191-202.

Non-provitamin A Carotenoids

- Lutein
- Zeaxanthin
- Lycopene
- Highest serum ratio of non-PVA: PVA carotenoids associated with a 66% lower risk of DR in pts with T2DM

Br J Nutr 2009 Jan;101(2):270-7.




Diabetes and DR are Associated with Low Macular Pigment

- MPOD is lower in T2DM than age-matched controls
- MPOD is lower in pts with DR than in DM pts without DR.
- As HbA1c goes up, MPOD goes down
- L/Z supplementation increased MPOD and improved VA ,contrast and foveal thickness in NPDR patients

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

Int J Ophthalmol 2011;4(3):303-6.

Don't Feed Your Retina Smoke!

Smoking lowers MPOD

. . . .

- Smoking increases risk of AMD 2-3X in men and women Ophthalmology. 2007 Jun;114(6):1157-63.
- Current smoker & homozygous for CFH Y402H polymorphism: OR = 34x for advanced AMD Hum Hered. 2006;61(3):157-65.
- Smoking increases risk of DME in T1DM & T2DM
 Curr Diabetes Rev. 2013 May;9(3):209-17 J Diabetes Complications. 2008 Nov-Dec;22(6):430.

Vitamin B complex and relationship to AMD

7.3yrs f/u w 5205 women

OR to develop AMD: .66 OR for Advanced AMD .59

Treatment group consisted of: folic acid (2.5 mg/d) vitamin B6 (50 mg/d) vitamin B12 (1 mg/d)

B-Complex and incident AMD in women. WAxFACS: Arch Intern Med. 2009 Feb



Vitamin B12 and diabetic retinopathy

B12 levels were significantly higher in controls vs DM (p < 0.01), and significantly higher comparing DNR vs DR (p < 0.05)



B12 deficiency was independently associated with hyperhomocysteinemia and DR after all adjustments

Vitamin D

- Increased Vit D consumption leads to less (severe) AMD
- Monozygotic twin study: those w less severe AMD had more Vit D intake: 200 vs 170 IU/d
 - Seddon et al. Ophthalmology . 2011;118:1386–1394
- Higher 25OH-VitD leads to less AMD
 - OR of .52 in highest vs lowest quintile in <75yo women
 Millen et al, Arch Ophthalmol . 2011;129:481–489
 - OR of .64 in highest vs lowest in >7700 over 56yo
 × Parekh et al. Arch Ophthalmol . 2007;125:661–669

Neither of these studies showed significance w advanced AMD

Au contraire: D & AMD

- Israeli study found conflicting results:
- 1045 diagnosed w AMD & 8124 non-AMD
- The mean±SD level of 25-OH vitamin D was 24.1±9.41 ng/ml for the AMD patients and 24.13±9.50 ng/ml for the controls Eye (Lond). 2011 Sep;25(9):1122-9. doi: 10.1038/eye.2011.174

 Presence of homozygous complement factor H polymorphism (CFH Y402H) and vit D deficiency → 6.7X increased risk of AMD after all controls

JAMA Ophthalmol. 2015 Oct;133(10):1171-9

Vitamin D and Retinopathy in T2DM

Mean Serum 25-OH vitamin D (ng/ml)

DM (n=123)	22.9	
No DM (n=98)	30.3	
DM without DR	23.2	
DM with NPDR	21.5	
DM with PDR	18.0	

44% of pts taking a multivitamin were vit D insufficient 83% of pts not taking a multivitamin were insufficient

American Academy of Ophthalmol: Abstract PO223. Presented October 17, 2010.

Confirmation in youth with T1DM

- 517 Australian pts (8-20 yo) with T1DM
- VDD associated with DR prevalence but not DKD nor DN
 - 18% prevalence for 25(OH)-vit D < 20ng/ml
 - 9% prevalence for 25(OH)-vit D > 20ng/ml

VDD more predictive of DR than duration or HbA1c!

• HR 2.13 vs 1.13 and 1.24

Diabetes Care. 2011 Jun;34(6):1400-2.

More Benefits of Higher Serum 25-hydroxyvitamin D



- Obese women with serum D levels
 <u>></u> 32 ng/ml lost 19 lbs versus 12 lbs over 12 months (CR + exercise)
- Higher D levels also yielded a 20% greater reduction in IL-6 and C-reactive protein (↓ inflammation)

Cancer Prev Res (Phila). 2015 Jul;8(7):628-35. Am J Clin Nutr. 2014 May;99(5):1015-25

- A 20 ng/ml increase in serum D reduced risk of MI/Stroke/CABG by 28% in the FIELD trial
- The same increase lowered microvascular risk (DR, DKD, DPN, amputation) by 18%

Diabetes Care. 2015 Mar;38(3):521-8

What About Zinc?

ARTICLE IN PRESS

CFH and ARMS2 Genetic Polymorphisms Predict Response to Antioxidants and Zinc in Patients with Age-related Macular Degeneration

Carl C. Awh, MD,¹ Anne-Marie Lane, MPH,² Steven Hawken, MSc,³ Brent Zanke, MD, PhD,^{4,5} Ivana K. Kim, MD²

These findings suggest a genuine benefit of genetic testing in patients with Intermediate AMD

Do No Harm

 Evidence presented by Awh et al shows that benefit or harm realized from supplemental zinc and AREDS antioxidants (C, E, B-carotene) depends on specific genetic profile for each patient

 1 in 6 AREDS patients with intermediate AMD were more likely to progress to advanced AMD when given high-dose supplemental zinc based on their specific complement factor H (CFH) and age-related maculopathy susceptibility (ARMS2) gene profiles <u>Ophthalmology. 2013 Nov;120(11):2317-23.</u>

Zn Controversy Abounds

 Chew et al (NEI) ran a similar statistical analysis on an overlapping (not identical) subset of AREDS participants and found no differential response to hidose zinc supplementation

Ophthalmology. 2014 Nov;121(11):2173-80.

"Awh's analysis is insufficiently powered"

Emily Chew - Retina Today, January 2015

 There are lawyers looking for cases where intermediate AMD progressed on the AREDS formula without genetic testing

Paraphrased - Jerome Sherman

Dueling Statisticians



My Take...

- There may be some patients who are harmed by high-dose zinc
- AREDS2 showed no statistically significant difference in efficacy comparing 25 mg to 80 mg zinc oxide
- It may be prudent to use lower dose zinc in patients with AREDS Cat 3 or 4 dry AMD, OR do genetic testing for risk alleles and pharmacogenomics
 Macula Risk[®]

Predict and Protect

What About AMD Treatment Failures?

 15% of patients with neovascular AMD do not respond to anti-VEGF therapies

Treating the untreatable patient: current options for the management of treatment-resistant neovascular age-related macular degeneration

Acta Ophthalmologica 2014; 92(8):713-723

Now What 711





Micronized Resveratrol Longevinex.com Images courtesy of Stuart P. Richer, OD, PhD

76 yo with occult CNVM After 5d resveratrol+





86 yo with CNVM unresponsive to VEGF Tx gained 7 lines VA @ 21 d



88 yo with CNVM & refusing Lucentis - 14 days

Nutrients. 2013 Jun; 5(6): 1989–2005.

Prevention Beats Cure

 The best way to prevent vision loss from AMD or diabetic retinopathy is to prevent them from occurring in the first place



We can't always accomplish this, but we can try

Current Algorithm For Preventing Diabetic Retinopathy

- Keep blood glucose, blood pressure and blood lipids as close to normal as possible
- Get annual dilated retinal examinations
- Get treatment if/when you develop STR







Is There Anything More We Can Do? SERIOUSLYP

THAT'S ALL YOU GOT?

Diabetes & DR Affect Visual Function



Snellen visual acuity is a 150+ yr old test that does not always reflect real world visual function

DM/DR also impair: color perception, contrast sensitivity, visual field sensitivity

Graefes Arch Clin Exp Ophthalmol. 2012 Dec;250(12): Diabet Med. 2011 Jul;28(7):865-71 Acta Opthalmol 2005; 82(5):574-80 Graefes Arch Clin Exp Ophthalmol. 2001 Sep;239(9):643-8 BJO 1996;80: 209-13 IOVS 1997; 38(9): 1819-24 Diabetes Care 1992; 15(5):620-25 Graefes Arch Clin Exp Ophthalmol.1996 May;234(5):300-5 It may be time to develop, test and educate ECPs about an AREDS type multi-component supplement specifically developed for patients with diabetes and diabetic retinopathy

Beyond AREDS: is there a place for antioxidant therapy in the prevention/treatment of eye disease? Kowluru RA, Zhong Q. Invest Ophthalmol Vis Sci. 2011 Nov 7;52(12):8665-71

AMD Supplementation as a Working Model

- Numerous studies show beneficial effects of micro-nutrient supplementation in Age-related Macular Degeneration
- Reduced risk of progression to advanced AMD
 - e.g. AREDS, AREDS2
- Improvements in Visual Function with xanthophyll supplementation
 - e.g. LAST, LUNA, CARMIS, ZVF Study

Key Question

 Can a nutritional supplement help patients with diabetes prevent or minimize loss of visual function and progression of retinopathy?



Diabetes Visual FUnction Supplement Study (DiVFuSS)

- 6 month placebo-controlled RCCT of adults with T1DM or T2DM > 5 years
- With and without retinopathy
- Daily use of a novel, multi-component nutritional supplement

CSF, MPOD, color vis., macular perimetry, OCT, A1c, lipids, 25(OH) vit. D, TNF-a, hsCRP, DPNS score Brit J Ophthalmol. Feb;100(2):227-34 BJO Online First, published on June 18, 2015 as 10.1136/bjophthalmol-2014-306534



The Diabetes Visual Function Supplement Study (DiVFuSS)

A Paul Chous,¹ Stuart P Richer,² Jeffry D Gerson,³ Renu A Kowluru⁴

¹Private Practice, Tacoma, Washington, USA ²Captain James A Lovel Federal Heath Care Center, North Chicago, Illinois, USA ³Private Practice, Olathe, Kansas, USA ⁴Kresge Eye Institute, Wayne State University, Detroit, Michigan, USA

Correspondence to Dr A Paul Chous, FAAD, 6720 Regents Blvd, Tacoma, WA 98466, USA; dr.chous@dabeticeyes.com

Received 18 December 2014 Revised 8 April 2015 Accepted 26 May 2015

ABSTRACT

Background Diabetes is known to affect visual function before onset of retinopathy (diabetic retinopathy (DR)). Protection of visual function may signal disruption of mechanisms underlying DR.

Methods This was a 6-month randomised, controlled dinical trial of patients with type 1 and type 2 diabetes with no retinopathy or mild to moderate non-proliferative retinopathy assigned to twice daily consumption of placebo or a novel, multi-component formula containing xanthophyll pigments, antioxidants and selected botanical extracts. Measurement of contrast sensitivity, macular pigment optical density, colour discrimination, 5-2 macular threshold perimetry, Diabetic Peripheral Neuropathy Symptoms, foveal and retinal nerve fibre layer thickness, glycohaemoglobin (HbA1d), serum lipids, 25-OH-vitamin D, tumour nervosis factor α (TNF-a) and high-sensitivity C reactive protein (hsCRP) were taken at baseline and 6 months. Outcomes were assessed by

the risk of DR and its progression, evidence shows that there is no level of average blood glucose (as reflected by glycosylated haemoglobin) that is totally protective against DR. The current clinical algorithm for delaying DR and preventing STR is earlier diagnosis of diabetes, tighter metabolic control, routine dilated retinal examinations and treatment (laser photocoagulation, intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents and corticosteroids) if/when DR progresses to a level that threatens vision.

The Age-Related Eye Disease Study (AREDS) demonstrated that a nutritional supplement could positively influence progression of a visionthreatening eye disease, age-related macular degeneration.³ This begs the question as to whether nutritional supplements may benefit other eye diseases, including DR. Vitamins, minerals and other micronutrients have a variety of biological func-



The Diabetes Visual Function Supplement Study (DiVFuSS)

A Paul Chous,¹ Stuart P Richer,² Jeffry D Gerson,³ Renu A Kowluru⁴

Identifier: NCT01646047

INTRODUCTION

Diabetic retin opathy (DR) remains a leading cause of visual impairment and blindness worldwide. Despite clinical trials showing that tighter control of blood glucose and blood pressure reduces the risk of microvascular diabetes complications, and despite tremendous advances in the clinical management of diabetic eye disease, rates of DR in the USA have increased by 89% over the last decade.²

Importantly, serious visual impairment associated with diabetes remains high.² Recent estimates show nearly 5% of US adults with diabetes have sightthreatening DR (STR), with significantly higher rates among African, Latino and Native Americans. Although improving blood glucose control lowers tion effects of a novel, multi-component nutritional supplement designed to disrupt established biological pathways in the genesis of DR (www. ClinicalFrials.gov Identifier: NCT01646047).

SUBJECTS

A total of n=67 adult subjects, 42 women/25 men, mean age 56.1 years (\pm 13.2 years) with either type 1 or type 2 diabetes, were recruited following informed consent under the Declarations of Helsinki. Sample size was based on previous published trials and differences in key visual function variables. Subjects were primarily pre-existing patients from a single optometric practice emphasising diabetes eye care, with n=12 referred from either a local retinal specialty or endocrinology practice.

To cite: Chous AP, Richer SP, Genson JD, et al. Br J Ophthalmol Published Online Fist: [please include Day Month Year] doi:10.1136/bjophthalmol-2014-306534







The Strategy



 Choose ingredients that have been shown to interfere with the biology of diabetic retinopathy in animal models and human trials

DiVFuSS Formula

- Zeaxanthin & Lutein
- Benfotiamine
- Alpha Lipoic Acid
- Vitamin D3
- Vitamins C & E
- Mixed Tocopherols/Tocotrienols
- Resveratrol
- Green Tea

- Curcuminoids
- N-Acetyl Cysteine
- Grape Seed Extract
- CoQ10
- Zinc Oxide
- EPA/DHA
- Pycnogenol



Mechanisms of Action

Reduce Free Radicals and Inflammation

zeaxanthin, lutein, curcumin, green tea ,grapeseed, resveratrol, lipoic acid, zinc, NAC, vit C & E, tocotrienols

Reduce VEGF

zeaxanthin, curcumin, Pycnogenol

Seals leaky retinal capillaries Pycnogenol

Neuroprotection of RGCs

Lutein, EPA/DHA, lipoic acid, curcumin, resveratrol

Improve Mitochondrial Health

CoQ10, lipoic acid, vit D, resveratrol, tocotrienols, curcumin

Blocks Toxic Glucose Metabolites benfotiamine

Animal Model of DR

- DiVFuSS formula blocked early mitochondrial damage in rats
- DiVFuSS formula blocked retinal capillary apoptosis underlying DR
- DiVFuSS formula improved b-wave ERG (retinal function)

No Difference in Blood Glucose Levels

Nutr Metab (Lond). 2014 Jan 30;11(1):8.

So Did This Formula Work in Humans with Diabetes Mellitus?



Mean Change/SD in visual function measures, serum lipids, hsCRP, TNF- α , glycohemoglobin, foveal thickness and symptoms of diabetic peripheral neuropathy with 95% p-Values

Δ from baseli	ne Suppl v	v. Plac	<u>p-Value</u>
Contrast Sens (%)	+19.1 <u>+</u> 8.9	-6.2 <u>+</u> 5.1	<0.0001
Color Error Score	-20.55 <u>+</u> 24.37	+7.5 <u>+</u> 22.01	<0.0002
5-2 MD (db)	+2.78 <u>+</u> 9.83	-0.75 <u>+</u> 0.98	<0.0001
MPOD (du)	+0.09 <u>+</u> 0.05	-0.01 <u>+</u> 0.03	< 0.0001
LDL-C (mg/dl)	-7.61 <u>+</u> 16.08	+0.82 <u>+</u> 10.15	0.01
HDL-C (mg/dl)	+3.82 <u>+</u> 6.24	-1.61 <u>+</u> 5.31	0.0004
TGs (mg/dl)	-10.46 <u>+</u> 28.48	+2.39 <u>+</u> 11.56	0.01
hsCRP (mg/L)	-2.14 <u>+</u> 3	-0.28 <u>+</u> 1.83	0.01
HbA1c (%)	-0.1 <u>+</u> 0.4	+0.1 <u>+</u> 0.4	0.06
Foveal Thickness	2.66<u>+</u>11.25 μm	0.34 <u>+</u> 3.48 μm	0.35
DPNSS	-30.7%	+10.7%	0.0024 Fisher' s Exact Test

Benefits – Visual Function

- Significant 19% improvement in contrast sensitivity
- Significant 21% impovement in color vision
- Significant 31% increase in MPOD
- Significant 3 dB (14%) increase in visual field mean sensitivity

Other Benefits

- Significant 50% reduction in hsCRP, a risk factor for CVD & DME
- Significant 31% reduction in diabetic neuropathy symptoms (DPNSS)
- Small but signiicant improvements in blood lipids

All WITHOUT significantly affecting mean blood glucose (A1c)

Subject # 38 - retinal images OS



We CAN Do More than Counsel, Watch & Wait to Treat


WHAT IS YOUR ROLE AS THE OPTOMETRIST?

My Basic Principles for Nutritional Counseling

 Giving patients patients SOME guidance is better then giving them NO guidance

It doesn't have to take a lot of time

 You know far more about nutrition and eye disease than any of your patients



Counseling Patients

- Talk about nutrition with your patients who have or are at risk for/from DM & AMD
- Discuss Prevention with everyone
- Ask for permission to discuss weight status as it relates to risk of retinal disease
- Measure & Improve Visual Function
- Criticize behaviors, not the patient

 Make specific recommendations, set goals and use handouts



Discussing Epigenetics With Patients

- We can't change the genes we inherit from our parents
- We <u>can</u> often change whether or not the good and bad genes are 'turned on' by leading a healthy lifestyle



Simple Steps

- Counsel on link between adiposity and eye disease
- Recommend sensible dietary and lifestyle choices based on evidence
- Assess macro- and micronutrient status by asking about diet, supplements, measuring macular pigment, lab analysis (e.g. 25-OH-D)
- Motivate and follow up

Sensible Lifestyle Advice

- Ensure plant foods fill at least 2/3 of your plate
- Reduce added sugars (packaged/boxed foods, soda, fruit juice) to less than 40 grams per day
- Eat less red meat and eliminate preserved meat products
- Exercise at least 30 minutes each day buy a pedometer and try to get 10K steps/day
- Eliminate trans fats (hydrogenated oils) and consume healthy fats in nuts and avocadoes
- Do not smoke ANYTHING

A Simple Strategy for Motivational Interviewing

- Ask patients to write down your recommendations (more likely to remember)
- Ask patients the one thing they would like to improve upon – enter that in the chart (get 'buy-in')
- Ask patients about that one thing at follow-up (a big or small step is better than no step at all)

"The only way to keep your health is to eat what you don't want, drink what you don't like, and do what you'd rather not."



"Get your facts first, then you can distort them as you please"

Thank You!!

PAUL CHOUS DR.CHOUS@DIABETICEYES.COM