Feed Your Retina: Nutrition and Retinal Health

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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?

Are 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!

By 2030

[Map showing obesity rates across different states]
Worldwide Stats

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

Lancet 2016 April; 387(10026):1349-50
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
- BMI > 35  severely obese
- BMI > 40  morbidly obese
- BMI > 45  super obese
- BMI > 50  super morbidly 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)
  - **Hypertension** (RAAS, hyperinsulinemia)
  - **Hypoxia** (Sleep Apnea, $\uparrow$O$_2$ demand)
Fat cells (adipocytes) are endocrine cells, secreting hormones regulating insulin sensitivity & satiety, and are associated with elevated markers of inflammation.
Subcutaneous vs. Visceral Fat

Fat Cells Are Endocrine Cells!!

Reactive Oxygen Species & Inflammation
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 THE 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

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%)
  (J Neuroophthal 2001 21(3):235)

– OSAS is the most frequent disorder in NAION

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

- 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 Feb 10;56(3):1585-92, Ophthalmology. 2005 Apr;112(4):533-9).

- Both conditions are associated with inflammation, smoking, low MPOD and higher intake of added sugars.
“There is a charm about the forbidden that makes it unspeakably desirable” - Mark Twain

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

Read Food Labels*  Year

<table>
<thead>
<tr>
<th>Year</th>
<th>Calories</th>
<th>Carbs</th>
<th>Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>1080 cal</td>
<td>29 gm</td>
<td>57 Gms</td>
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<tr>
<td>1978</td>
<td>320 cal</td>
<td>57 Gms</td>
<td>68 Gms</td>
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<tr>
<td>1995</td>
<td>450 cal</td>
<td>26 Gms</td>
<td>610</td>
</tr>
<tr>
<td>2015</td>
<td>610 cal</td>
<td>26 Gms</td>
<td>77 Gms</td>
</tr>
</tbody>
</table>

210 cal
Macronutrients & Retinal Disease

PROTEIN
FAT
CARBOHYDRATES

MACRONUTRIENTS
Dietary Fat & Eye Disease

- Sat Fat, Trans Fats and Vegetable Oils associated with higher risk of AMD and Diabetic Retinopathy

- EPA + DHA decrease TGs, FFAs, blood glucose & insulin levels, visceral fat mass and many inflammatory markers

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

Arch Ophthalmol. 2009 Nov;127(11):1483-93
Arch Intern Med. 2005;165: 193-7
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

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)*
  - DHA 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?

- Majority of adults need 2000 mg EPA +DHA/d to achieve RBC (Holman) index ≥ 8%
  

- 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)

Relative Risk of Primary Cardiac Arrest vs. RBC Omega-3 Content

Adapted from Siscovick et al. JAMA, 1995
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  
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)

\[
\text{GI} = \frac{\text{AUC Test Food}}{\text{AUC Reference Food}}
\]

\[
\text{GL} = \frac{\text{GI} \times \text{portion size (gms)}}{100}
\]

Criticisms: Many
Are GI and GL Useful?

- Low GI food delay hunger, reduce caloric intake (Lipids. 2003;38(2): 117-21)

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

- 4099 patients
- 55-80 yo


- 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

Autophagy. 2012 Sep 1;8(9).
AGEs block Clearance of lipofuscin and drusen!!


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

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


Take Home

This would also save BILLIONS of dollars and greatly improve quality 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
<table>
<thead>
<tr>
<th>Food</th>
<th>AGEs (μmol/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roasted/BBQ’d chicken thighs with skin</td>
<td>16,000</td>
</tr>
<tr>
<td>Grilled hot dogs</td>
<td>10,000</td>
</tr>
<tr>
<td>Broiled chicken breast</td>
<td>6,000</td>
</tr>
<tr>
<td>Fast food hamburger</td>
<td>4,800</td>
</tr>
<tr>
<td>Microwaved sausage</td>
<td>4,800</td>
</tr>
<tr>
<td>Broiled tofu</td>
<td>3,900</td>
</tr>
<tr>
<td>Feta/American cheese</td>
<td>2,500</td>
</tr>
<tr>
<td>Roasted nuts and nut butters</td>
<td>2,500</td>
</tr>
<tr>
<td>1 cup of whole cow’s milk</td>
<td>1,600</td>
</tr>
<tr>
<td>A fried egg</td>
<td>1,200</td>
</tr>
<tr>
<td>Restaurant French fries</td>
<td>1,500</td>
</tr>
<tr>
<td>Butter</td>
<td>1,300</td>
</tr>
<tr>
<td>Boiled chicken</td>
<td>1,100</td>
</tr>
<tr>
<td>Potato chips</td>
<td>850</td>
</tr>
<tr>
<td>Margarine</td>
<td>850</td>
</tr>
<tr>
<td>Cottage cheese</td>
<td>500</td>
</tr>
<tr>
<td>Life cereal</td>
<td>400</td>
</tr>
<tr>
<td>Canned beans</td>
<td>190</td>
</tr>
<tr>
<td>Corn chips</td>
<td>161</td>
</tr>
<tr>
<td>A slice of whole wheat bread</td>
<td>100</td>
</tr>
<tr>
<td>A roasted yam</td>
<td>75</td>
</tr>
<tr>
<td>Popcorn</td>
<td>40</td>
</tr>
<tr>
<td>A raw tomato</td>
<td>20</td>
</tr>
<tr>
<td>An apple</td>
<td>10</td>
</tr>
<tr>
<td>Oatmeal</td>
<td>4</td>
</tr>
<tr>
<td>1 cup of human milk</td>
<td>2</td>
</tr>
</tbody>
</table>
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

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


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
## Table 3
Multivariate binary logistic regression analysis for late versus no AMD.

<table>
<thead>
<tr>
<th>Red meat intake</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;Once a week</td>
<td>1.04</td>
<td>0.746–1.44</td>
<td>0.82</td>
</tr>
<tr>
<td>Once a week</td>
<td>1.67</td>
<td>1.296–2.16</td>
<td>7.982 × 10⁻⁵</td>
</tr>
<tr>
<td>2–6x/week</td>
<td>2.34</td>
<td>1.610–3.400</td>
<td>8.224 × 10⁻⁶</td>
</tr>
</tbody>
</table>

\[n = 2900\quad European\ Genetic\ Database\]

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 Mediterranean-type or Paleolithic-type diet lowers inflammation, insulin resistance, CV events, cancer and mortality

  Arch Intern Med. 2007:2461-8
  BMJ 2008, May 29

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

One Dietary Change

- Increasing dietary fiber to 30g/d improves markers of Metabolic Syndrome (BP, IR, low HDL-C, high triglycerides, body weight) nearly as well as the more complicated & restrictive AHA diet

  - RCT of 241 with Met Syn
  - 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.

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

Eat Food—like Products, Far Too Much, Mostly Refined Carbs with Low Nutrient Density, Trans Fats & Devoid of Fiber

What We Do

EAT FOOD, NOT TOO MUCH, MOSTLY PLANTS.
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

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
IT'S EASIER TO STAY WELL THAN TO GET WELL.
Pertinence of AREDS/AREDS2…

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

- A) Some
- B) Most
- C) ALL
- D) VERY FEW *****

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 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

**L/Z values based on a 100 g serving**

Romaine lettuce: 2.3 mg
Spinach: 12 mg
Broccoli: 1.7 mg
Kale: 40 mg

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 of 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.

\[ egin{align*}
\text{Filtered by Cornea \\ & & & & \text{Lens}}
\end{align*} \]

“Blue Light Hazard”

Low Energy Less Damaging

Visual Performance with Increased MPOD: Filters Blue Light

- High MPOD levels enhance:
  - Visual acuity
  - Glare tolerance
  - Glare recovery
  - Contrast sensitivity
  - Chromatic aberration
  - Photophobia

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 with 6mg L over 1yr

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

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

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

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.

Don’t Feed Your Retina Smoke!

- Smoking lowers MPOD

- Smoking increases risk of AMD 2-3X in men and women

- Current smoker & homozygous for CFH Y402H polymorphism: OR = 34x for advanced AMD

- Smoking increases risk of DME in T1DM & T2DM
  Curr Diabetes Rev. 2013 May;9(3):209-17
Vitamin B complex and relationship to AMD

7.3 yrs 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)


n = 400

Metformin depletes B12

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
- Higher 25OH-VitD leads to less AMD
  - OR of .52 in highest vs lowest quintile in <75yo women
  - OR of .64 in highest vs lowest in >7700 over 56yo
- 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
  

- Presence of homozygous complement factor H polymorphism (CFH Y402H) and vit D deficiency → 6.7X increased risk of AMD after all controls
  
Vitamin D and Retinopathy in T2DM

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Serum 25-OH vitamin D (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM (n=123)</td>
<td>22.9</td>
</tr>
<tr>
<td>No DM (n=98)</td>
<td>30.3</td>
</tr>
<tr>
<td>DM without DR</td>
<td>23.2</td>
</tr>
<tr>
<td>DM with NPDR</td>
<td>21.5</td>
</tr>
<tr>
<td>DM with PDR</td>
<td>18.0</td>
</tr>
</tbody>
</table>

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

American Academy of Ophthalmol:
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

More Benefits of Higher Serum 25-hydroxyvitamin D

- Obese women with serum D levels ≥ 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)
- 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
These findings suggest a genuine benefit of genetic testing in patients with Intermediate AMD
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. 

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 high-dose zinc supplementation.
  

- “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
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.
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
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

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?

SERIOUSLY?

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

Diabet Med. 2011 Jul;28(7):865-71
BJO 1996;80: 209-13
IOVS 1997; 38(9): 1819-24
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
The Diabetes Visual Function Supplement Study (DiyFuSS)

A Paul Chous, Stuart P Richer, Jeffry D Gerson, Renu A Kowluru

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 clinical 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 anthocyanins, antioxidants and selected botanical extracts. Measurement of contrast sensitivity, macular pigment optical density, colour discrimination, 5-2 macular threshold perimetry, Diabetic Retinopathy Severity Score, focal and retinal nerve fibre layer thickness, glycohaemoglobin (HbA1c), serum lipids, 25-OH-vitamin D, tumour necrosis factor α (TNF-α) 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 vision-threatening eye disease, age-related macular degeneration. 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-

INTRODUCTION

Diabetic retinopathy (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.

Importantly, serious visual impairment associated with diabetes remains high. Recent estimates show nearly 5% of US adults with diabetes have sight-threatening DR (STR), with significantly higher rates among African, Latino and Native Americans. Although improving blood glucose control lowers
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

Blocks Toxic Glucose Metabolites
benfotiamine

Improve Mitochondrial Health
CoQ10, lipoic acid, vit D, resveratrol, tocotrienols, curcumin
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

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

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

Fisher’s Exact Test
Benefits – Visual Function

- Significant 19% improvement in contrast sensitivity
- Significant 21% improvement 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 significant improvements in blood lipids
- All WITHOUT significantly affecting mean blood glucose (A1c)
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 SOM**E** guidance is better than 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 **can** 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 avocados.
- 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