Feed Your Retina: Nutrition and Retinal Health

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Disclosure

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

- Arctic Dx, Alcon, Baush & Lomb, Diabetes In Control, Freedom Meditech, Kemin, Kestrel Health, LifeMed Media, Optos., Risk Medical Solutions, VSP, ZeaVision

I am on the Board of the Ocular Nutrition Society
www.ocularnutritionsociety.org

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.

The rates of obesity are increasing alarmingly!

Etiology of Obesity

- Genetic factors
  - Metabolic imprinting
  - Psychological aspects
  - Cultural and environmental aspects

- Environmental factors
  - Macroeconomic regulations
  - Food intake
  - Physical activity
  - Access to information

- Energy intake
  - Total caloric content
  - Composition of the diet

- Energy expenditure

Obesity Rate
- 60% - 64.9%
- 65% - 69.9%
- 70% - 74.9%
- 75% - 79.9%
- 80% - 89.9%
- 90% - 99.9%

Health outcomes:
- Mortality
- Disability
- Morbidity
**Obesity - Classic Definition**

- BMI > 25  
  overweight
- BMI > 30  
  obese
- BMI > 35  
  severely obese
- BMI > 40  
  morbidly obese
- BMI > 45  
  super obese
- BMI > 50  
  super morbid obese
- BMI > 70  
  mega-obese

\[
\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2} \quad \text{or} \quad \frac{\text{Weight (pounds)}}{\text{Height (inches)}^2} \times 703
\]

It is as easy has plugging into an app on phone to figure out.

**Why is Obesity Associated With Ocular & Systemic Disease?**

- **An Unholy Triumvirate**
  - Inflammation (cytokines, endothelial dysfunction)
  - Hypertension (RAAS, hyperinsulinemia)
  - Hypoxia (Sleep Apnea)

**Links Between Obesity & Eye Disease**

- Cataract
- AMD
- Glaucoma
- Diabetic Retinopathy
- NAION

*Blue Mountains Eye Study. Ophthalmic Epidemiol. 2003;10(4):227-40*
*Am J Clin Nutr 2003;78:400-5*
*Diab Metab Rev. 2005;21(5): 434-40*
*Diabetes Care. 1986;9(4): 961-9*
*Am J Ophthalmol. 2007;143(3): 473-8*

- Floppy Eyelid Syndrome (FES)
- Pseudotumor cerebri (PTC)
- Venous Occlusive Disease

*Ophthalmology. 2006;113(9):1669-74)*
*J Neuroophthal. 2001 21(3):235*
*Ophthalmology. 2005;112(4): 540-7*
*BJO. 2006;90(7):879-82*

**Portion Control: Size Does Matter**

![Calories Graph](Calories.png)

**Read Food Labels**

It's Not Just Food Quantity That Matters…

![Pie Chart](Pie Chart.png)

**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)

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

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

Criticisms: Many

Are GI and GL Useful?
- Low GI food delay hunger, reduce caloric intake (Lipids. 2003;38(2): 117-21)
- Low dGI/dGL diets reduce fasting blood glucose, glycated protein and insulin resistance (Am J Clin Nutr. 2008 Jan;87(1):268S-269S)

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

Take Home
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 qualities of life!

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 associated with 40% higher risk for DR and 224% for STR in Australian and US cohorts Clin Experiment Ophthalmol. 2012 Apr;40(3):288-94
The Importance of Preventing Blood Glucose Spikes

- AKA “Post-prandial Hyperglycemia” or “Glycemic excursions”

DCCT:
Retinopathy developed more often in pts receiving “conventional Tx” at HbA1c Levels equal to those in the “intensive Tx” group

New Evidence

- 1,5-Anhydroglucitol is a serum glucose metabolite reduced by urinary excretion when serum glucose > 180 mg/dl
- Low blood 1,5-AG reflects 1PPG excursions
- Lower levels of serum 1,5-AG increase the risk of DR nearly 3x in T2DM patients, including those with HbA1c levels < 8%

Diabet Med. 2012 Sep;29(9):1184-90

So What Should I Feed My Retina To Lower My Odds of Retinal Disease?

AMD
9 million Americans

DIABETIC RETINOPATHY
5 million Americans

AMD and why nutrition may affect it

- There are many theories as to why nutrition is helpful in AMD
  - Antioxidants
  - Anti-inflammatory
  - MPOD building
  - Blue light blocking

- It is most likely that it is a combination of all of the above

Nutrition

- The best intake is through diet/food
  - Not always realistic:
    - Average American gets only 2mg Lutein
    - Leading antioxidant source for the average American is coffee
    - French fries account for 25% of all vegetable intake in US
  - Importance of healthy lifestyle
    - But 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%)
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

What did AREDS set out to do?

- Cure AMD?
- Find a way to prevent progression?
  - Prevent progression to advanced dry
  - Prevent progression to wet
  - Prevent vision loss

Vitamins C, E, B-carotene, Zinc, Copper

- Does it truly speak to prevention?

Statistical analysis of AREDS....

- Is some prevention better than none?
  - To what ends? What side affects are you willing to endure?
    - dry to wet 3 lines VA Loss
    - Absolute risk reduction: 8% 6%
    - Relative risk reduction: 25% 19%
    - Number Needed to Treat: 12 17

Now what do you think?

Digging deeper into AREDS

- Higher DHA (64 vs 26mg: .73), EPA (42 vs 12mg: .74), lower dGl (<75.2 vs > or = 81.5: 0.76) lowered risk of advancement to advanced AMD regardless of AREDS supplement


What Happened in AREDS2?

"Comparison with placebo in the primary analyses demonstrated no statistically significant reduction in progression to advanced AMD (hazard ratio [HR], 0.90 [98.7% CI, 0.76-1.07]; p = 0.12 for lutein + zeaxanthin"

- Omega-3 FAs (650 EPA + 350 EPA) also had no effect on progression

Primary Outcome Analysis

Progression to Advanced AMD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Favors Treatment</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutein/Zeaxanthin</td>
<td>p=0.12</td>
<td></td>
</tr>
<tr>
<td>DHA/EPA</td>
<td>p=0.70</td>
<td></td>
</tr>
<tr>
<td>Lutein/Zeaxanthin+DHA/EPA</td>
<td>p=0.10</td>
<td></td>
</tr>
<tr>
<td>Placebo (reference)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hazard Ratio (98.7%CI)

0.7 0.8 0.9 1 1.1 1.2 1.3

JAMA What Happened in AREDS2?

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Key Points About AREDS2

- Baseline serum L/Z levels in subjects far exceeded levels in average Americans
- Subjects were older, had more diabetes and sicker eyes than AREDS
  - Less DM in the L/Z group (10% versus 13%)
- No true placebo group & most on Centrum!!
- L/Z significantly lowered odds of progression when substituted for β-carotene (18% overall and 22% for CNVM, p = 0.02 and 0.01) — ineffective for GA
- Study says nothing about primary prevention

AND……..

Effect of Dietary Intake of L/Z

Progression to Advanced AMD by Quintiles

<table>
<thead>
<tr>
<th>L/Z Dietary Intake Quintile</th>
<th>Favors L/Z HR=0.74 p=0.01</th>
<th>Favors No L/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Quintile amounts: .7/1.1/1.6/2.2/2.9mg

Effect of Lutein + Zeaxanthin on risk of Advanced AMD

MPOD

- Macular Pigment Optical Density
  - The 2 macular pigments are from yellow and orange carotenoids (L&Z)
    - 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.

They Buried the Lead!!!!!

- Comparing the lowest to highest quintile of dietary L/Z intake, adding 10/2 mg supplemental L/Z lowered the risk of progression to advanced AMD by 26% (HR = 0.74, p= 0.01)
- This means that the average American with intermediate AMD consuming the typical American diet would significantly benefit from supplemental L/Z

AREDS & AREDS2 say NOTHING about prevention for the typical patient seen by ODs
Can a healthier retina see better?

- Visual function improved through diet and/or supplementation
- VZF (Zeaxanthin Visual Function Study) — Stuart Richer, OD, PhD
  - 1 yr study w 60 participants w mild-mod AMD in 3 groups: 8mgZ vs 8mgZ + 9mgL vs 9mgL (placebo/control group)
  - On avg, all pts improved MPOD
  - Functional benefit as follows:
    - Z: High contrast, shape discrimination and scotoma resolution on Kinetic Visual Fields
    - L: low-contrast visual acuity, CSF, and glare recovery (Zx showed a trend toward significance)
    - L&Z group: did not fare as well
  - Base for improvements in biologic locations of L & Z

“Enhancing Vision” (with the carotenoids Lutein & Zeaxanthin)

- Falsini Study — 2003
- LAST — April 2004
- TOZAL — Feb 2007
- LUXEA — April 2006 & Feb 2007
- LUNA — April 2007
- LAST II — May 2007
- CARMIS — Feb 2008
- Lutein in normal subjects July 09 British J. Nut
- ZVF study: Richer Nov 2011

Visual Performance with Increased MPOD: Filters Blue Light

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

Recent publication in AJO 10/12

- Pts randomized to 10L, 20L or 10L/10Z
- mFERG and MPOD measured at 24 and 48wks
- Significant increases in both MPOD and mFERG in central central ring with the 20L and L/Z group
- Le et al. Improved retinal function w L/Z. AJO 10/12

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
  - 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
  - Study by Peralta et al showed:
    - Triple therapy w/ laser/Avastin/Dex inj can be improved w 20mg Zeaxanthin / day
    - Total treatment cycles in 1yr avg. 1.42 (improved from previous studies by authors not using Zeaxanthin) by 14.5%
    - Fellow eye involvement at 1 yr only 4%
    - So... improve outcome of 1st eye, and preventing the second eye from developing CNVM
  - TAKE AWAY MESSAGE: IT IS NEVER TOO LATE TO FEED YOUR RETINA THE RIGHT DIET!

Peralta et al. PO Zeaxanthin in CNVM ARVO 2012 poster
The 3rd macular carotenoid

- Mesozeaxanthin is the 3rd macular carotenoid
- Naturally converted from lutein (likely in most people)
- Although it is not found naturally in food chain, can be synthesized and supplemented
- It has not been tested on its own to show increase in plasma or macula
- Some fear that its intake will compete with L/Z
- Go to ORS website for well written white paper by Dr. Larry Alexander
- The rest is a discussion all of its own...

H.M. Rasmussen et al. / Journal of Food Composition and Analysis,

Smoking

A Bad Habit……

- Smoking increases risk of AMD 3X in men and women.
- Smokers develop AMD 6 to 10 years earlier than non smokers.
- In MPS laser trials, risk for recurrent CNV was 50% at 5 years but 85% for current smokers!
- Smoking lowers MPOD
- Current smoker & homozygous for CFH Y402H polymorphism: OR = 34x for advanced AMD

An egg a day???

- Increasing diet to 1 egg/d in older adults can increase serum L & Z without affect on serum total cholesterol, HDL, LDL or triglycerides
- Increases in MPOD egg consumption: 31% increase w 2 yolks/d. Serum L and Z increased 16% and 36% at 5wks
- Serum HDL increased 5% and no change in LDL
  - NOTE: These were elderly pts on lipid lowering meds

Which fruits/veggies should I eat?

- Historically, recommendations are made for green leafy veggies
- Maize has highest % of lutein, and Orange pepper/Goji Berries has highest % of Zeaxanthin
- High amounts were also found in: kiwi fruit, grapes, spinach, orange juice, zucchini and different kinds of squash
  - Note: different colors of f/v involved
  - Note: For all intensive purposes, Mesozeaxanthin is NOT found in food sources

Realistic Dietary Sources of L/Z

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

L/Z values based on a 100 g serving


Vitamin B complex and relationship to AMD

7.3yrs f/u w 5205 women
55/82 incident cases of AMD
OR to develop AMD: .66
OR to devel VSAMD .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 D

- Increased Vit D consumption leads to less (severe) AMD
  - NOTE: majority of Vit D comes from environmental exposure
    - Monozygotic twin study w asym. AMD: 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

Not so fast with Vit D…

- Study done in Israel found conflicting results to previously mentioned studies:
  - 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 (P=ns).
  - 33.6% of AMD patients and 32.86% of controls had a 25-OH vitamin D level <16 ng/ml
  - 25-OH vitamin D level was >74 ng/ml 0.19% and 0.14%

Not all good w Vitamins C & E either

- Over 14,000 male US physicians without AMD
  - Followed for 8yrs on 400IU vit E every other day or 500mg C vs placebo
  - OR for Vit C was .99 and for Vit E was 1.03
  - Over 39k women health professionals without AMD
    - Given 600 IU Vit E alternate days
    - No difference seen after 10 years

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 (rTG 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)
Do No Harm

- New evidence presented at ASRS shows that benefit or harm realized from supplemental zinc and AREDS antioxidants (C, E, B-carotene) depends on specific genetic profile for each patient.
- The majority of 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.

Ophthalmology. 2013 Aug 20. [Epub ahead of print]

ARTICLE IN PRESS

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

These findings make a strong case for genetic testing in patients with Intermediate AMD.

Diabetes and Diabetic Retinopathy

- 27.7 million Americans have DM (2012 estimate)
- 79 million American have pre-diabetes
- 1.9 million new cases of DM/year
- 4.2 million Americans > 40 yrs had DR in 2008
- 700K had sight-threatening DR

LET’S TALK ABOUT DIABETES

National Diabetes Fact Sheet 2011, ADA
**Risk Factors for Diabetes in the US**

**Established**
- Older age
- Fam Hx
- Obesity
- Sedentary
- HTN
- Non-European Ancestry

**Emerging**
- Sleep disturbances
- Malnutrition
- Air pollution
- Workplace stress
- Vitamin D deficiency
- Bisphenol A exposure

**Risk for diabetes cut dramatically w lifestyle**
- Both men and women can cut incident DM by altering lifestyle
- Can cut by up to 39%/31% per lifestyle factor
  - Physical activity, non-smoking, appropriate diet and appropriate alcohol
  - If all 4, then cut risk to .43/.61 for men/women
- **If add in absence of overweight or obesity, then OR down to .28/.16**

**EPIC Variety**
- Higher quantity of vegetable (but not fruit) consumption lowers T2DM risk by 24%
- Increased variety of fruit and vegetable consumption lowers T2DM risk by 39%

**Coffee, Tea or Diabetes?**
- Meta-analysis of 18 studies involving 457,000 persons
- Four or more cups of tea (green or black) or coffee (caffeinated or decaffeinated) was associated with a 25% lower risk of T2DM diagnosis compared with 2 cups/day
- Each additional cup reduces excess risk an additional 7%

**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)

**Environ Health Perspect. 2010 Sep;118(9):1273-9**
**Food Nutr Rev. 2012;35(1): 2196-2301**
**J Clin Endocrinol Metab. 2011 Dec;96(12):3822-6**
**Diabetes Care 2010;33(10): 2196-2201**
**Diabetes Care. 2009 Dec;32(12):2230-5**
**Diabetes Care. 2011 Jun;34(6):1400-2**
**Diabetes Care 2012;56.**
**Environ Health Perspect. 2010 Sep;118(9):1273-9**
**Food Nutr Rev. 2012;35(1): 2196-2301**
**J Clin Endocrinol Metab. 2011 Dec;96(12):3822-6**
**Diabetes Care 2010;33(10): 2196-2201**
**Diabetes Care. 2009 Dec;32(12):2230-5**
**Kick the (plastic) Bottle & the Can**
- Bisphenol A (BPA): a polymer additive commonly lining bottles (#7), cans and food containers
- Higher urinary BPA concentrations associated with a 68% increased risk of T2DM in NHANES
- Early BPA exposure may trigger fat cell growth (*Diabesity*)
  
  J Clin Endocrinol Metab. 2011 Dec;96(12):3822-6.

**Benefits of Mediterranean Diet**
- Meta-analysis shows lower risk of T2DM and improved FBS, HbA1c and CV risk with greater adherence to Med Diet
- Comparison of Med vs Low Fat vs Low Carb energy equivalent diets showed Med Diet achieves better FBS & Lipid profiles & Low Carb decreases HbA1c the most
  

**Diet to Prevent Diabetes**
- High adherence to a Mediterranean-type diet reduced the risk for Dx of T2DM by 83% over 53 months compared to low adherence, after adjusting for other risk factors in healthy 23-55 yo
  
  BMJ. 2008 Jun 14;336(7657):1348-51
- Ad libitum Med Diet in older pts (55-80 yo) at high CV risk reduced diabetes risk by 52% at 4 years vs ad libitum low fat diet
  

**Diet for DR Prevention?**
- Medical Nutrition Therapy (MNT) refers to “the application of evidenced based nutritional recommendations using an individualized, coordinated team effort including the person with DM”
- Energy-restricted low-fat or low-carb diet (45-55% CHO)
- Increased dietary fiber (>20g/d)
- Eliminate trans fats; reduce saturated fat to <7% of calories
- 150 minutes exercise/week
- 5-7% weight loss in obese pts
- Smoking avoidance

**Can We Do Better?**
- Cretan Med Diet significantly lowered HbA1c, trans and SFA, increased lutein/zeaxanthin over 12 weeks
- Low carb Med Diet reduced HbA1c & weight > traditional Med Diet > ADA diet (LCM 1 LDL 1.8 mg/dl) over 1 year
  
  Diabetes Obes Metab. 2010 Mar;12(3):204
- Reduced need for new DM meds 40% vs low fat diet over 4 yrs
  
  Nutr Metab Cardiovasc Dis. 2011 Sep;21(9):740-7
- Paleolithic diet lowered HbA1c (-.4%), weight (-3 kg), waist (-4 cm) more than an ADA-type diet over 3 mos
  
  Cardiovasc Diabetol. 2009 Jul 16;8:35.
Paleo vs Mediterranean Diet

- Higher protein & less salt content in the Paleo Diet

<table>
<thead>
<tr>
<th>Protein (%)</th>
<th>Paleo (14.5)</th>
<th>Mediterranean (10.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate (%)</td>
<td>Paleo (22.4)</td>
<td>Mediterranean (25.6)</td>
</tr>
<tr>
<td>Total Fat (%)</td>
<td>Paleo (26.4)</td>
<td>Mediterranean (26.9)</td>
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<tr>
<td>Sodium</td>
<td>Paleo</td>
<td>Mediterranean</td>
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<tr>
<td>Cholesterol</td>
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<td>Mediterranean</td>
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<td>Omega 3 Fat</td>
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<tr>
<td>Folic Acid</td>
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<tr>
<td>Omega 3</td>
<td>Paleo</td>
<td>Mediterranean</td>
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</tbody>
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Key Question

WILL THE METABOLIC BENEFITS OF LOW GLYCEMIC INDEX MEDITERRANEAN-TYPE OR PALEOLITHIC-TYPE DIETS FOR DIABETES TRANSLATE INTO LESS DIABETIC RETINOPATHY?

Risk Factors For Diabetic Retinopathy

Established
- Disease duration
- HbA1c
- Disease sub-type
- HTN
- Microalbuminuria

Emerging
- Obesity
- Sleep apnea
- Vitamin D insufficiency
- Vit B12 deficiency
- Carotenoid imbalance

Vitamin D and Retinopathy in T2DM

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

<table>
<thead>
<tr>
<th>Category</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 vitamin D insufficient
83% of pts not taking a multivitamin were insufficient

American Academy of Ophthalmol:

Obesity and PDR

- Australian cohort study (n= 492)
- BMI ≥ 30 km/m² mildly associated with any DR (OR = 1.06) but dramatically associated with PDR (OR = 6.52) after controlling for conventional risk factors
- Each 1 cm increase in neck circumference increased the risk of STR by 5%

Feed Your Retina Less & Let It Breathe
Caloric restriction and aggressive Tx of OSAS

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

American Academy of Ophthalmol:
Vitamin B12 and diabetic retinopathy

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

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


Mechanisms?

- Z normalizes oxidative stress and prevents diabetes-induced increases in VEGF and ICAM-1 in animal models
- L prevents increased ROS/NF-κB and increases the neuroprotective cytokine BDNF in animals
- L and Z restore protective cytokines (AMPK), mitochondrial antioxidant defense (MnSOD) and nuclear transcription factors (FOXO3α) in animal models

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


Might Other Targeted Micronutrients Play a Role in DR Prevention/Mitigation?

My Top 5 Supplements for Diabetic Retinopathy

Mean MPOD within 2° of Fovea

- Non-diabetic: 0.29 DU
- Diabetes sans retinopathy: 0.22 DU
- Diabetes with mild NPDR: 0.14 DU

What Causes Diabetic Retinopathy?

• A number of complex and inter-related biochemical and hemodynamic factors
  – Hyperglycemia
  – Hypertension
  – Inflammatory Dyslipidemia
  – Oxidative Stress
  – Release and Suppression of Growth Factors
  – Hormonal influences
  – Apoptosis
  – Up-regulation of inflammatory cytokines
  – BRB breakdown and hypoxia

A Summary Preview

• The lipophilic vitamin B1 analog, benfotiamine, normalizes harmful glucose metabolites implicated in DR (AGEs, PKC, hexosamine, sorbitol)
• Curcumin normalizes retinal oxidative stress and VEGF, improves clearance of AGEs
• A patented extract of French Maritime Pine bark (Pycnogenol) lowers HbA1c, inhibits MMP implicated in BRB breakdown and may reduce RT in DME

Pycnogenol + Benfotiamine

• 22 yo male T1DM x 11 years
• Notes fuzzy spot in Vision OD x 1 mo
• LEE 1 year  HbA1c = 7.2%
• “New” exudate OD  BCVA 20/25
• No CSME but retinology offered focal laser → pt declined
• Started 150mg benfotiamine TID + 125mg Pycnogenol QD
• F/U in 3 mos
“It’s a pain in the neck to take a whole bunch of different supplements…..
Can’t I just take a multi-vitamin?”

Combo Anti-oxidants for DR?
- RCCT of 105 T2DM pts with NPDR
- 5-year follow-up of oral anti-oxidant supplement vs. placebo (C, E, Zn, Cu, Se, Mn, lutein, niacin, b-carotene)
- No change in BCVA for either group
- DR progression was retarded in the supplement group only


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

Diabetes Visual Function Supplement Study (DiVFuSS)
- 6 month placebo-controlled RCCT of adults with T1DM or T2DM ≥ 5 years
- No DR (2:1) and mild-moderate NPDR (1:1)
- Daily use of a multi-component nutritional supplement (non-provit. A carotenoids, D, C, E, curcumin, benfotiamine, Pycnogenol, lipoic acid, NAC, resveratrol, green tea, O-3 FAs, CoQ10)
- Pre- and post- analysis of CSF, MPOD, color vis., macular perimetry, OCT, A1c, lipids, 25(OH) vit. D, TNF-a

ClinicalTrials.gov Identifier: NCT01646047

Preliminary DiVFuSS Subject Characteristics (n = 32)
- 31-74 yo (mean = 53 yrs)
- 22 with DR (8 T1DM/14 T2DM) 10 with no DR (5 T1DM/5 T2DM)
- HbA1c 6.0% - 9.1% (mean = 7.25%)
  - mean 7.64% in those with DR
  - mean 7.74% in T1DM
  - mean 6.70% in those with no DR
  - mean 7.0% in T2DM
- Diabetes duration 5-34 yrs (mean = 17.2 yrs)
  - mean 23.3 yrs in those with DR
  - mean 10.8 yrs in those with no DR
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)

Supplementation with DVfuSS Formula Prevents diabetes-induced increase in

- VEGF
- NF-kB

Kowluru RA – Kresge Eye Institute
Presented at ARVO 2013, Seattle

First Subject to Complete DiVFuSS

- 43 yo female with T1DM x 36 yrs
- Mild NPDR
- MPOD improved from 0.18 to 0.48
- HDL & 25(OH)-vitamin D increased 20%
- HbA1c, LDL, TGs, TNF-alpha worsened
- Improved CSF, color vision and visual fields
- Resolution of longstanding retinal microaneurysm
- "I see better"
Macular Perimetry

- 46% of points improved – 16% worsened
- 7/42 test points improved ≥ 3 decibels
- 2/42 test points worsened ≥ 3 decibels
- Mean Deviation improved from -2.14/-1.88 to -0.88/-0.12

Counseling Patients

- Talk about nutrition with your patients who have or are at risk for DM & AMD
- Ask for permission to discuss weight status as it relates to risk of retinal disease
- Measure macular pigment and prescribe appropriate intervention – re-measure to assess efficacy and motivate pts
- Criticize behaviors, not the patient
- Make specific recommendations, set goals and use handouts
Goal Setting — be an advocate & be specific

- Take these supplements and bring back the empty bottles next time for 30% off your next eyeglass purchase
- Let's get you a pedometer and walk 10,000 steps/day every day until your next appointment (www.fitbit.com)
- Let's increase your MPOD to 0.40
- Let's get your A1c under 7% by next visit
- Let's work on losing 5% of your current weight for next visit
- If you want to quit smoking, I will help you

Eat (Real) Food

- Not Too Much
- Mostly Plants

“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!!

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