

## 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.ocularnutritionociety.org](http://www.ocularnutritionociety.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

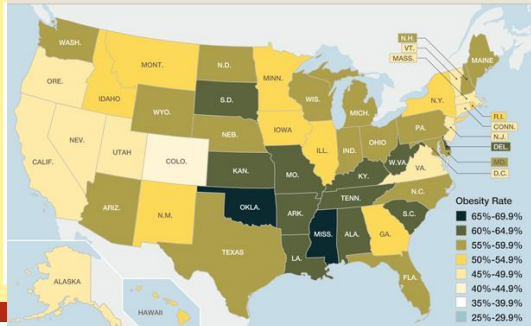


## Sometimes, though, we feed TOO MUCH!

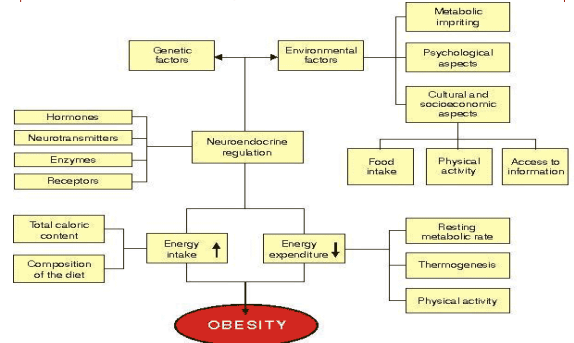


## The rates of obesity are increasing alarmingly!

CURRENT TRACK



## Etiology of Obesity



### 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

**BMI = Weight (kg)/Height (m)<sup>2</sup>    or  
Weight (pounds)/Height (inches)<sup>2</sup> x 703**

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

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

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



### Links Between Obesity & Eye Disease

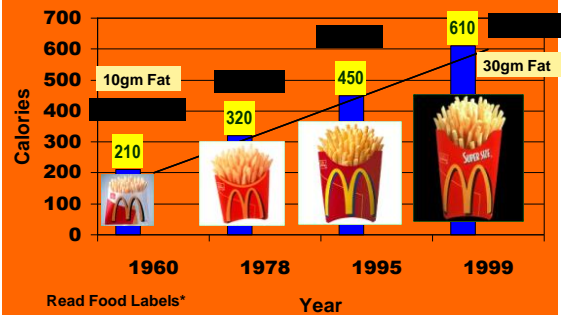
- Cataract
- AMD
- Glaucoma
- Diabetic Retinopathy
- NAION

*Blue Mountains Eye Study, Ophthalmic Epidemiol. 2003;10(4):227-40*  
*Am J Clin Nutr 2003;78:400-5*  
*Diab Metab Res 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

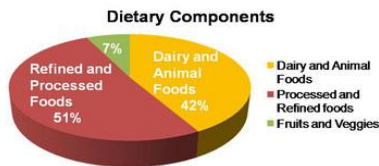
*Ophthalmology. 2006;113(9):1669-74*  
*J Neuroophthal 2001 21(3):235*  
*Ophthalmology. 2005;112(4): 540-7*  
*BJO. 2006;90(7):879-82*

### Portion Control: Size Does Matter



### It's Not Just Food Quantity That Matters...

#### The American Diet: Designed for Disease



Source: USDA Agriculture Fact Book 98: Chapter 1-A

### Good Carb: Bad Carb



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

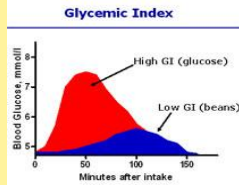
### Glycemic Index (GI) & Glycemic Load (GL)

- 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)

$$GI = \frac{\text{AUC Test Food}}{\text{AUC Reference Food}}$$

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

**Criticisms: Many**



### Are GI and GL Useful?

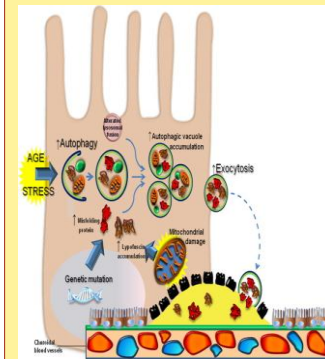
- Low GI food delay hunger, reduce caloric intake (*Lipids*. 2003;38(2): 117-21)
- Low dGI/dGL diets reduce fasting blood glucose, glycated protein and insulin resistance (*Am J Clin Nutr*. 2008 Jan;87(1):258S-268S)
- High dGL and CHO intake increased mortality risk almost 50% in EPIC (PLoS One. 2012;7(8):e43127. Epub 2012 Aug 23)
- High dGI 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



- 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



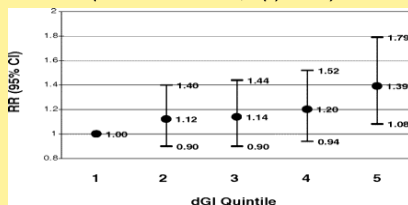
**AGEs block Clearance of lipofuscin and drusen!!**

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

*Autophagy*. 2012 Sep 1;8(9).

### 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)
- Low dGI and dGL results in 37-47% reduction in post-prandial hyperglycemia

*Eur J Clin Nutr*. 2012 Oct;66(10):1146-52  
*Metab Syndr Relat Disord*. 2010 Jun;8(3):255-61  
*Am J Clin Nutr*. 2011 Dec;94(6):1519-24

**RCCT  
 Observational Study  
 Observational Study**

## The Importance of Preventing Blood Glucose Spikes

- AKA "Post-prandial Hyperglycemia" or "Glycemic excursions"

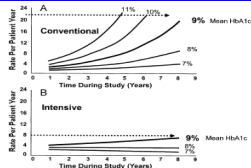


Fig 1. Absolute risk of sustained retinopathy progression as a function of updated mean A1C (percentage) during the DCCT and the time of follow-up during the study (years), estimated from absolute (Poisson) regression models. (A) Conventional treatment group. (B) Intensive treatment group. Reprinted with permission from DCCT Research Group (1995). © American Diabetes Association.

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

## New Evidence

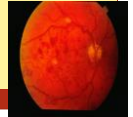


## Matter

- 1,5-Anhydroglucitol is a serum glucose metabolite reduced by urinary excretion when serum glucose > 180 mg/dl
- Low blood 1,5-AG reflects ↑PPG 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%)



IT'S EASIER TO  
STAY WELL  
THAN TO  
GET WELL

### Pertinence of AREDS/AREDS2...

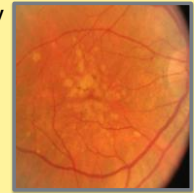
- To what percentage of YOUR AMD patients do AREDS & AREDS2 apply???



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....

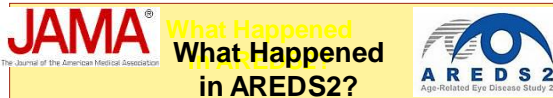
- Is some prevention better than none?
  - To what ends? What side effects are you willing to endure?

	dry to wet	3 lines VA Loss
Absolute risk reduction:	8%	6%
Relative risk reduction:	25%	19%
Number Needed to Treat:	<b>12</b>	<b>17</b>

Now what do you think?

### Digging deeper into AREDS

- Higher DHA (64 vs 26mg: .73), EPA (42 vs 12mg: .74), lower dGI ( <75.2 vs >=81.5: 0.76) lowered risk of advancement to advanced AMD regardless of AREDS supplement
  - Chiu et al. Br J Ophthalmol. 2009 Sep;93(9):1241-6.

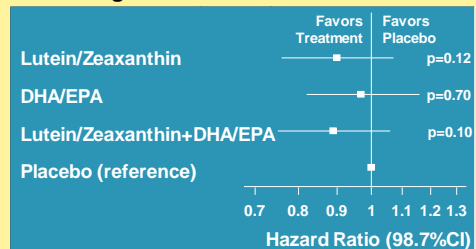


- “Comparison with placebo in the primary analyses demonstrated no statistically significant reduction in progression to advanced AMD (hazard ratio [HR], 0.90 [98.7% CI, 0.76-1.07]; p = 0.12 for lutein + zeaxanthin”
- Omega-3 FAs (650 EPA + 350 EPA) also had no effect on progression

Abstract - JAMA. 2013 May 15;309(19):2005-15.

### Primary Outcome Analysis

#### Progression to Advanced AMD



AREDS2 Research Group. (2013) JAMA, In Press.

### 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.....**

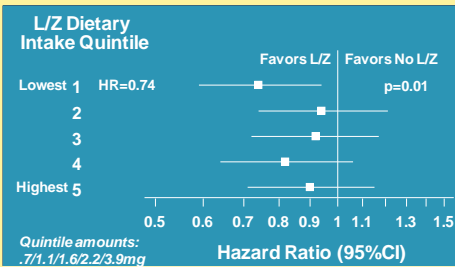
### They Buried the Lead!!!!

- 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**



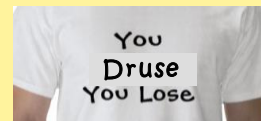
### Effect of Dietary Intake of L/Z

#### Progression to Advanced AMD by Quintiles



AREDS2 Research Group. (2013). *JAMA*, In Press

- AREDS & AREDS2 say NOTHING about prevention for the typical patient seen by ODs



### 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.

### Effect of Lutein + Zeaxanthin On risk of Advanced AMD



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



## Can a healthier retina see better?

- Visual function improved through diet and/or supplementation
- ZVF (Zeaxanthin Visual Function Study) – Stuart Richer, OD, PhD
  - 1 yr study w 60 participants w mild-mod AMD in 3 groups: 8mgZ vs 8mg Z + 9mgL vs 9mg L (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



Bahrami et al. 2006. BMC Ophthalmol 6(1):23. Cangemi et al. 2007. BMC Ophthalmol. 7:3. Kivansakul et al. 2006. Ophthalmic Physiol Opt 26(4):362-71. Massacesi et al. 2001. IOVS. 42(4):5234. 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.

## 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



## 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

**Lutein & Zeaxanthin Improve Visual Function**

## 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 1<sup>st</sup> 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 3<sup>rd</sup> macular carotenoid

- Mesozeaxanthin is the 3<sup>rd</sup> 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
  - Egg a day and L, Z and HDL/LDL and Cholest. J Nutr. 2006 Oct;136(10):2519-24.
- 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
    - Egg yolks and MPOD. Am J Clin Nutr. 2009 Nov;90(5):1272-9.

### 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
      - F&V affecting MPOD: Br J Ophthalmol. 1998 Aug;82(8):907-10.
- Note; For all intensive purposes, Mesozeaxanthin is NOT found in food sources

### Realistic Dietary Sources of L/Z

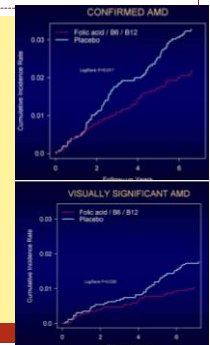
Romaine lettuce 2.3 mg		Broccoli 1.7 mg	
Spinach 12 mg		Kale 40 mg	

L/Z values based on a 100 g serving

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>

### 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
    - 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

## 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%
  - Golan et al. *Eye (Lond)*. 2011 Sep;25(9):1122-9. doi: 10.1038/eye.2011.174

## 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
    - Christen et al. *Ophthalmology*. 2012 Aug;119(8):1642-9
- Over 39k women health professionals without AMD
  - Given 600 IU Vit E alternate days
  - No difference seen after 10 years
    - Christen et al. *Ophthalmology*. 2010 Jun;117(6):1163-8

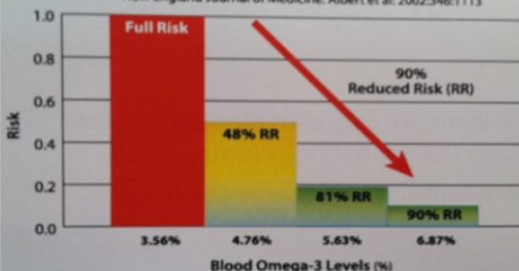
## What About Fish & Fish Oil?

- 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

## Risk of Sudden Cardiac Death and Omega-3 Blood Levels

<sup>7</sup> New England Journal of Medicine: Albert et al; 2002;346:1113



Albert et al NEJM 2002;346:1113

## Omega 3 FAs to Prevent CNVM?

- Majority of adults need 2000 mg EPA +DHA/d to achieve RBC (Holman) index  $\geq 8\%$ 
  - 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  $\geq 8\%$  had 68% less CNVM over three years (840mg DHA + 270mg EPA)
  - Ophthalmology. 2013 Aug;120(8):1619-31.

## 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

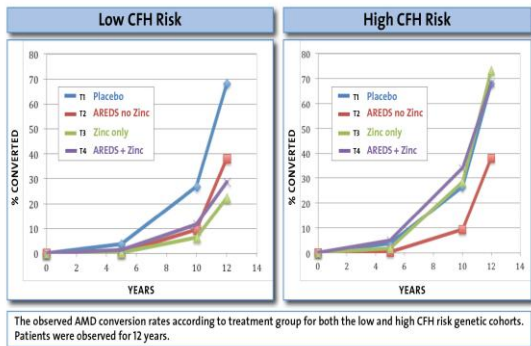
Ophthalmology. 2013 Aug 20. [Epub ahead of print]

ARTICLE IN PRESS

### CFH and ARMS2 Genetic Polymorphisms Predict Response to Antioxidants and Zinc in Degeneration

Carl C. Aurb, MD,<sup>1</sup> Anne-Marie Lane, MPH,<sup>2</sup> Steven Hawken, MS,<sup>3</sup> Brent Zarke, MD, PhD,<sup>4,5</sup> Inna K. Kim, MD<sup>2</sup>

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



CFH ALLELES	ARMS2 ALLELES	Optimal Treatment	Population Frequency
0	0	AREDS	0.18
0	1		0.10
0	2		0.01
1	0	Antioxidants Alone	0.31
1	1		0.16
2	0		0.13
2	1		0.07
1	2	None	0.02
2	2		0.01



LET'S TALK ABOUT DIABETES

## 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

National Diabetes Fact Sheet 2011, ADA

## Risk Factors for Diabetes in the US

### Established

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

Diabetes Care. 2011 Jun;34(6):1400-2  
J Clin Endocrinol Metab. 2011 Dec;96(12):3822-6

### Emerging

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

Environ Health Perspect. 2010 Sep;118(9):1273-9  
Food Nutr Res. 2012;56.  
Diabetes Care. 2010;33(10): 2196-2201  
Diabetes Care. 2009 Dec;32(12):2230-5

## 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**
- Lifestyle and risk of DM. Reis et al. Ann Intern Med. 2011 Sep 6;155(5):292-9.

## 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%

Eur J Clin Nutr. 2012 Aug 1



- 2+ servings of blueberries per week or 5+ servings of apples/pears lowered T2DM risk by 27% compared with  $\leq 1$  serving/month
- 205,000 pts followed over 20 yrs (NHS & NHS II)

Am J Clin Nutr. 2012 Apr;95(4):925-33. Epub 2012 Feb 22.

## 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%

Arch Int Med 2009;169(22): 2053-63



## 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, epub

## 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.



## 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

Diabetes Care. 2011 Jan;34(1):14-19



## 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

Diabetes Res Clin Pract. 2010 Aug;89(2):97-102  
Diabetes Res Clin Pract. 2009 Dec;86 Suppl 1:S41-8.  
Nutr Metab Cardiovasc Dis. 2011 Sep;21(9):740-7.



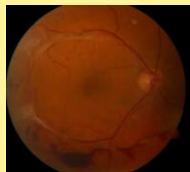
## Diet for DR Prevention?

- 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

## Relevance To Eye Disease

- DCCT data shows worsening retinopathy directly associated with total fatty acid & sat fat intake & smoking, and indirectly associated with fiber intake

MedGenMed 2005;7(1): 3



## Can We Do Better?

### RCCTs of Med & Paleo Diets in T2DM

- 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 ↑ 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

	Hunter-gatherer	Traditional Mediterranean
Protein (%)	High (19-35)	Moderate (16-23)
Carbohydrates (%)	Moderate (22-40)	Moderate (50)
Total fat (%)	Moderate (28-47)	Moderate (30)
Saturated fat	Moderate	Low
Monounsaturated fat	High	High
Polyunsaturated fat	Moderate	Moderate
Omega-3 fat	High	High
Total fiber	High	High
Fruits and vegetables	High	High
Nuts and seeds	Moderate	Moderate
Salt	Low	Moderate
Refined sugars	Low	Low
Glycemic load	Low	Low

### 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

Invest Ophthalmol Vis Sci. 2011 Jun 22;52(7):4416-21  
 Endocr Pract. 2012 Mar-Apr;18(2):185-93  
 Diabet Med. 2010 Apr;27(4):423-30  
 PLoS One. 2011;6(11):e26747

### Obesity and PDR

- Australian cohort study (n= 492)
- BMI  $\geq 30$  km/m<sup>2</sup> 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%

Invest Ophthalmol Vis Sci. 2011 Jun 22;52(7):4416-21

#### Feed Your Retina Less & Let It Breathe

Caloric restriction and aggressive Tx of OSAS

logMAR acuity improved 0.11 in OSAS with  $\geq 2.5$  hrs CPAP in a pilot study of CSME Respiration. 2011 Dec 20



### 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.

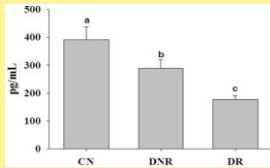
### Confirmation in youth with T1DM

- 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  $\leq 20$ ng/ml
  - 9% prevalence for 25(OH)-vit D  $> 20$ ng/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.

### Vitamin B12 and diabetic retinopathy

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



PLoS One. 2011;6(11):e26747

n= 400

**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

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



### Mechanisms?

- Z normalizes oxidative stress and prevents diabetes-induced increases in VEGF and ICAM-1 in animal models
- L prevents increased ROS/NF- $\kappa$ B and increases the neuroprotective cytokine BDNF in animals
- L and Z restore protective cytokines (AMPK), mitochondrial antioxidant defense (MnSOD) and nuclear transcription factors (FOXO3 $\alpha$ ) in animal models

Exp Biol Med 2011 Sep 1;236(9):1051-63. J Renin Angiotensin Aldosterone Syst. 2012 May 15. Invest Ophthalmol Vis Sci 2008 Apr;49(4):1645-51. Diabetologia 2010 May;53(5):971-9

### Diabetes and DR are Associated with Low Macular Pigment

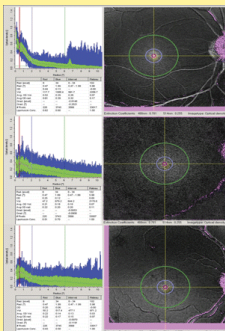
- MPOD is lower in T2DM than age-matched controls
- MPOD is lower in pts with DR than in DM pts without DR.
- As HbA1c goes up, MPOD goes down
- L/Z supplementation increased MPOD and improved VA, contrast and foveal thickness in NPDR patients

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

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

### Mean MPOD within 2° of Fovea

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



Lima VC, Rosen RB. Invest Ophthalmol Vis Sci 2010 Nov;51(11):5840-5.

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



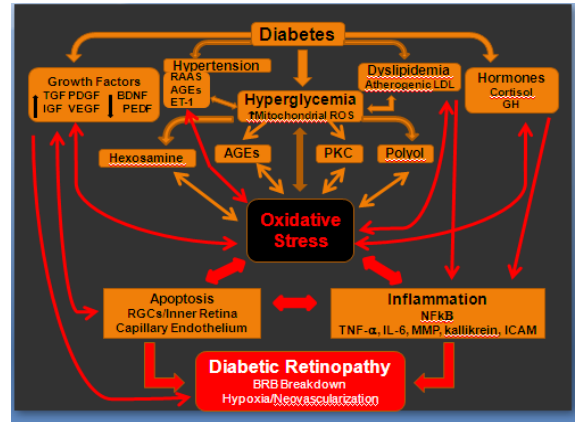
**My Top 5 Supplements for Diabetic Retinopathy**



## 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



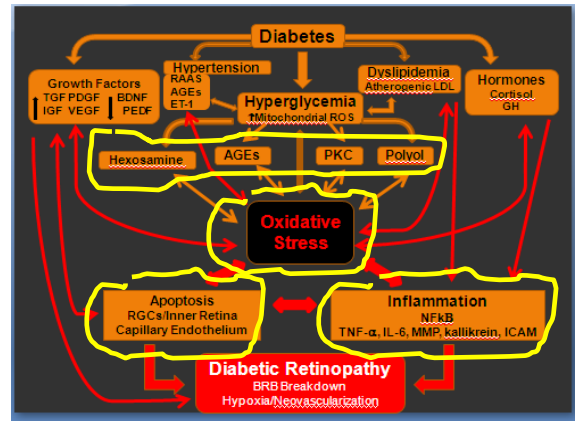
## A Summary Preview

- 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

Nat Med. 2003 Mar;9(3): 294-9  
Diabetologia. 2008 Oct;51(10): 1930-2

Nutr Res 2008;28(5):315-2  
J Ocu Pharmacol Ther. 2009;25(6):537-40

Lab Invest. 2012 Jun;92(6):827-4  
Nutr Metab 2007 Apr 16:4:8



## 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

Eur J Ophthalmol. 2011 Sep-Oct;21(5):637-43



**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  $\geq$  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 6.70% in those with no DR
  - mean 7.74% in T1DM
  - 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

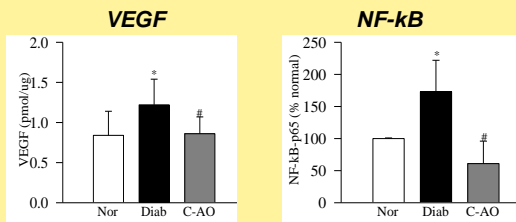
- Mean serum 25(OH)-vitamin D = 42.8 ng/ml
  - 38.5 DR
  - 48.7 no DR
- Mean MPOD = 0.44 DU
  - 0.21 DR
  - 0.48 no DR

## 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)

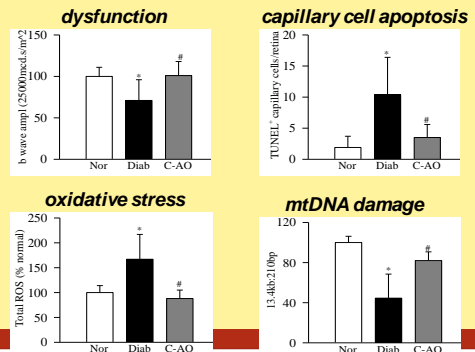
Presented at ARVO 2013, Seattle

### Supplementation with DVFuSS Formula Prevents diabetes-induced increase in



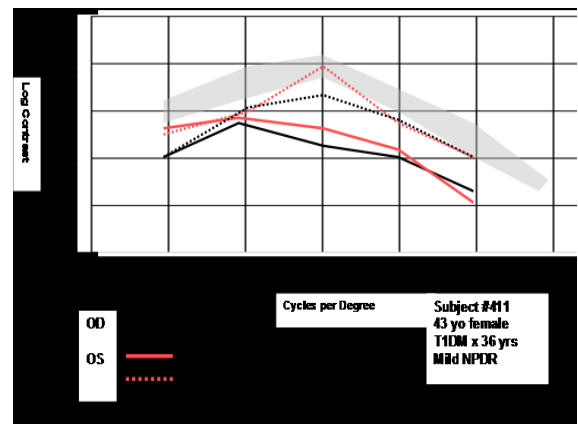
Kowluru RA – Kresge Eye Institute  
Presented at ARVO 2013, Seattle

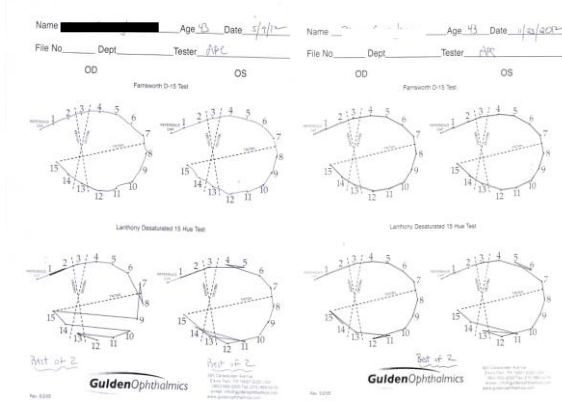
### Supplementation with DVFuSS Formula Prevents diabetes-induced retinal



### 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  $\geq 3$  decibels
- 2/42 test points worsened  $\geq 3$  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



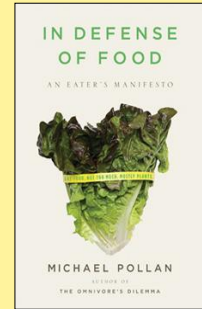
### Goal Setting – be an advocate & be specific

- 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](http://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

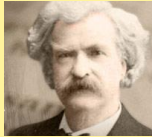
### ◉ Eat (Real) Food

### ◉ 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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