Blood Glucose, Dietary Sugar Intake & Disease

- Independently of diabetes & its myriad complications, dietary sugars & elevated blood glucose are associated with:
  - Cancer
  - Cardiovascular Disease
  - Dementia
  - Eye Disease

Disclosures – Dr. Reed

- I am or have been a consultant, advisor, speaker, editorial board member, or executive board officer of the following:
  - Alcon
  - Allergan
  - Avenova
  - B&L
  - BioTissue
  - Pfizer
  - MedOp Health
  - Kemin
  - DSM
  - Review of Optometry
  - Optometric Management

- The content of this presentation was developed by the speaker. I thank and acknowledge the generosity of ArcticDx and Emily Chew for providing certain slides and/or images and/or videos contained in the presentation.

- No conflicts of interest exist for the content of this presentation, and it is free from any influence from commercial interest.

Disclosures – Dr. Chous

- I am or have been a consultant, advisor, speaker, editorial board member, or executive board officer of the following:
  - ZeaVision
  - Freedom MediTech
  - Review of Optometry
  - Ocular Nutrition Society
  - Risk Medical Solutions

- The content of this presentation was developed by the speaker.

Carbohydrate

- High intake of simple sugars (glucose, fructose & sucrose) increases serum FFAs and oxidative stress
  

- By a mass effect, post-prandial hyperglycemia increases cellular glucose uptake, production of ROS, pro-inflammatory cytokines, and advanced glycation endproducts (AGEs)

  Nature. 2001;414:813-20
  Circulation. 2002;106: 2067-72
Sugar & Cancer

- Statistically significant increases in colon, pancreatic and breast cancers with increased dietary sugar, per some reports
- Dietary sugar definitely associated with cancer mortality and recurrence
- The Warburg Hypothesis: Cancer cells anaerobically ferment sugar, have more insulin receptors, & perform glycolysis 10-17X the rate of normal cells, even when O\textsubscript{2} is present


Sugar & Cardiovascular Disease

- Meta-analysis of 39 RCCTs shows that higher dietary sugar intake significantly increases triglycerides, LDL-C & BP after all controls


Sugar & Dementia

- Highest quartile of carbohydrate intake increases risk of mild cognitive impairment by 83% (p = 0.004)
  - after all adjustments HR = 3.58 for MCI or frank dementia
  J Alz Dis 2012;22(2):243-266

- High normal fasting glucose (91-100 mg/dl) increases risk of MCI nearly 8-fold
  Alzheimers Dement. 2010 Nov;6(6):440-7

- T2DM QUADRUPLES the risk of Alzheimer’s dementia

Dose Increases Risk

- NHANES data 1988-2010 (n = 31K+) assessing CV mortality
- 71% had > 10% calories from added sugar
- 10% had > 25% calories from added sugar
- After adjustments for age, socio-demographic, behavioral & clinical characteristics
  - HR = 1.3 for those consuming 10-24.9% of calories
  - HR = 2.75 for those consuming > 25% of calories


There is a significant association (p = 0.004) between added sugar consumption and CV death

SPEAKING OF DIABETES......
Myth or Fact: High Sugar Intake Causes Diabetes?

Econometric analysis of 175 countries

Every 150kcal/person/day sugar consumption increases population diabetes prevalence 1.1%

Equivalent to 1 can of soda per day


“Differences in sugar availability statistically explain variations in diabetes prevalence rates at a population level that are not explained by physical activity, overweight or obesity”

National obesity rates are NOT totally synchronous with rates of diabetes

Sugar Availability and Increased Diabetes

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

WHO 2014 Recommendations for Sugar Consumption

- Added sugars, sugar from fruit juices & honey should be less than 5% of total calories
- ≤ 25 grams/day

WHO Guideline: Sugar Intake for adults and children, March 5, 2014

3 gm  24 gm  40 gm

JAMA 1994; 272: 1413 - 1420
Advanced Glycation Endproducts

- More than 6,000 PubMed citations linking AGEs to diabetes risk and complications
- HbA1c is the most commonly performed clinical assay detecting AGEs on RBCs
- Collagenous tissues accumulate long-term AGE deposition (skin, crystalline lens)
- AGEs are analogous to glycosylated hemoglobin over the patient’s lifetime

**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

Significance of AGEs?

- Long-term biomarkers of glucose toxicity
- Implicated in virtually ALL diabetes complications, Alz Dis, as well as AMD, glaucoma and cataract
- Inhibit the SIRT1 gene -> shorten lifespan
- Found in foods cooked at high temperatures and low humidity
  - Methylglyoxal found in grilled meats worsens human cognition and insulin sensitivity

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


Autophagy. 2012 Sep 1;8(3).
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!

• Multiple studies show increased AGEs in lamina cribrosa of glaucomatous eyes vs age-matched normals

AGEs in Cataract

Nucleus stained for AGEs in a cataractous vs normal lens

Higher AGE levels in cataracts removed from diabetes vs. non-diabetes patients


AGEs in Common Foods


Benefits of AGE Quantification

• Earlier diagnosis of Pre-diabetes and prevention of conversion to T2DM
  – 86 million Americans with Pre-diabetes

• Earlier diagnosis of diabetes
  – 8 million Americans have undiagnosed diabetes in 2014 (CDC National Diabetes Fact Sheet, 2014)
  – Data show a mean 5 year lag between DM onset and diagnosis
  – Estimate that 50% of pancreatic beta cells are lost by the time of typical diagnosis
More Benefits of AGE Quantification

- Additional risk factor for AMD progression
- Additional risk factor for glaucoma & progression
- Measurable marker for cataract risk and progression
- Gauge and remediate metabolic risk

Practical Strategies to Avoid Chronic Sugar Toxicity

- Keep carbohydrate content of meals ≤ 30 g
- Keep daily added sugars ≤ 25 g
- Substitute whole plant foods & lean protein for processed carbs, packaged foods, sodas
- Avoid cooking foods at high temperature and low humidity, use leaner meats
  - Heterocyclic amines & polycyclic aromatic hydrocarbons
  - Acrylamide
  - AGEs

Avoid NAFLD

- Non-alcoholic fatty liver disease
- 100+ million Americans
- Elevates risk of metabolic syndrome 300%
  

- Directly linked to higher intake of glucose and fructose

Are All Calories Equal?

- NO!!
  - Fructose forms intra-hepatic fat and AGEs at a higher (7X) rate than does glucose
  - Fructose and HFCS raise uric acid & are causally linked to diabetes and Met Syndrome
  - Sucrose is the leading source of fructose

Uric Acid & Metabolic Syndrome

- Fructose & HFCS elevate uric acid that induces fatty liver disease independently of caloric intake
  
Diabetes Care 2010;33:2477–2483

- NAFLD is a definitive risk factor for T2DM
- Uric acid impairs NO necessary for insulin receptor function
- Increased fructose and HFCS consumption is causally linked to Met Synd and type 2 diabetes

Am J Med. 2007 May;120(5):442-7
Hyperuricemia Independently Predicts T2DM in 22 of 24 Studies

<table>
<thead>
<tr>
<th>Location</th>
<th>Population</th>
<th>Follow-up</th>
<th>Independent</th>
<th>Year</th>
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</thead>
<tbody>
<tr>
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<td>10,000 men</td>
<td>diabetes 5 years</td>
<td>Yes</td>
<td>2015</td>
</tr>
<tr>
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<td>diabetes 20 years</td>
<td>Men</td>
<td>2015</td>
</tr>
<tr>
<td>Japan</td>
<td>2,000 men</td>
<td>diabetes 5 years</td>
<td>Yes</td>
<td>2006</td>
</tr>
<tr>
<td>Korea</td>
<td>2,000 men</td>
<td>diabetes 5 years</td>
<td>Yes</td>
<td>2001</td>
</tr>
<tr>
<td>Italy</td>
<td>2,000 men</td>
<td>diabetes 5 years</td>
<td>Yes</td>
<td>2002</td>
</tr>
<tr>
<td>Finland</td>
<td>8,000 men</td>
<td>diabetes 5 years</td>
<td>No</td>
<td>2006</td>
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<td>Sweden</td>
<td>2,000 men</td>
<td>diabetes 5 years</td>
<td>Yes</td>
<td>2008</td>
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<td>10,000 men</td>
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<td>Yes</td>
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<tr>
<td>Brazil</td>
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<td>diabetes 5 years</td>
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<td>2006</td>
</tr>
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<td>China</td>
<td>2,000 men</td>
<td>diabetes 5 years</td>
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<td>2008</td>
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<tr>
<td>U.S.</td>
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<td>diabetes 5 years</td>
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<td>Yes</td>
<td>2011</td>
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<tr>
<td>China</td>
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<td>diabetes 5 years</td>
<td>Yes</td>
<td>2011</td>
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<td>South Africa</td>
<td>2,000 men</td>
<td>diabetes 5 years</td>
<td>Yes</td>
<td>2015</td>
</tr>
<tr>
<td>Italy</td>
<td>2,000 men</td>
<td>diabetes 5 years</td>
<td>Yes</td>
<td>2002</td>
</tr>
</tbody>
</table>

What about glucose?

- High glucose ingestion activates the hepatic polyol pathway
- Polyol pathway generates endogenous fructose that is metabolized by ketohexokinase → NAFLD & hyperuricemia
- By mass effect, glucose drives production of methylglyoxal & advanced glycation endproducts
- AGEs kill pancreatic β cells  
  Diabetes Metab. 2012 Jun;38(3):250-7
- AGEs independently predict CV risk in T2DM
- Over-consumption of Glucose is not benign

Summary Statements

- Reduce added dietary sugars
- Avoid HFCS
- Eat a predominantly plant based diet
- Cook foods at low temperature and high humidity
- Don’t get diabetes, pre-diabetes or NAFLD......

Glucose & Vitamin C Antagonism

- Humans, apes, guinea pigs & some fishes/birds/bats are the only animals incapable of producing endogenous vitamin C
- Serum glucose blocks absorption of dietary ascorbic acid (AA - AKA vitamin C)
- AA is necessary for immune function
- Normoglycemia is requisite for maintenance of adequate intracellular levels of AA from normal human diet

Practical Tips To Avoid Diabetes

- Exercise 30 minutes each day (soon after waking)
- Eat a predominantly plant based diet including a variety of fruits and vegetables and more vegetables
- Minimize processed meats
- Drink coffee or tea
- Sleep > 6 hours per night and < 9 hours
- Get your serum vitamin D checked
- Don’t smoke
- Live away from smog
- Breast Feed
- Turn down the thermostat

Source: AP Chous
A few more...

- Enhance endogenous glucagon-like peptide (GLP-1) with oral L-arginine or whey protein
  
  Am J Physiol Regul Integr Comp Physiol. 2014 Feb 1;306(2):R157-63
  Am J Physiol Regul Integr Comp Physiol. 2014 Feb 1;306(1):R157-63

- Metformin and berberine (Oregon grape) block hexokinase linked to hyperuricemia
  
  Int J Endocrinol. 2015;2015:905749

- Reduce light-at-night (LAN)
  - LAN suppresses melatonin and increases risk of obesity, diabetes, cancer, dementia

MELATONIN SUPPRESSION IMPLICATED IN:

- inflammation with excess cortisol production (↑ diabetes/CV risk)
- dementia
- endocrine disruption
- suppression of nitric oxide resulting in elevated blood pressure
- potential activation of oncogenes

Int J Endocrinol. 2015;2015:905749

AMD AND NUTRITION – YOU SAY YOU’RE IN SYNC? DON’T PUT IT DOWN IN INDELIBLE INK!

WHAT’S GOING ON WITH ZINC, DO YOU THINK?

AREDS plus Centrum (67-89% of patients)

AREDS 2 tidbits

- Patients with the lowest dietary intakes of lutein and zeaxanthin (average 0.7 mg per day or less) showed a 26% additional reduced risk of progression to advanced AMD
AREDS 2 Summary

• Thus – L/Z WERE beneficial when added to, or substituted for, the beta-carotene in AREDS and that beneficial effect was most pronounced in patients with low dietary L/Z.
• Most North American adults consume about 1.5 L/Z in the diet daily, as opposed to the AREDS 2 group which was much more well nourished than the general population.

Main Outcomes of AREDS 2

• More patients taking a version of supplement containing beta-carotene died of lung cancer during the study than those not taking beta carotene. Most that died were former smokers.
• Lowering zinc from 80 mg to 25 mg had no significant effect on the risk of advanced AMD.

AREDS 2: Their take-home and current standard of care:

• To reduce the risk of advanced AMD, at-risk patients should take a supplement containing:
  • 500 mg vitamin C
  • 400 IU vitamin E
  • 80 mg zinc
  • 2 mg copper as cupric oxide
  • 10 mg lutein
  • 2 mg zeaxanthin

Non-controversial science:

1. Superoxide dismutase is an essential naturally occurring antioxidant

Non-controversial science:

2. There are three SOD’s in the human body
3. SOD(2) is reduced in those carrying the ARMS2 homozygous allele (mitochondria) – binds Manganese
   • Yang et al Hum Molec Genetics 23(13), 2014.
4. Zinc (and copper) binds SOD(1) in cytoplasm and SOD(3) in extracellular spaces making a soluble, powerful antioxidant
Non-controversial science:

4. AMD is at least partially caused by inflammation

5. This inflammation is at least in part mediated by the complement system
   - Part of innate immune system
   - Complex, dozens of enzymes, implicated in more than 30 illnesses
   - Components are made primarily in the liver but also in other locations including the RPE (CFH)

Non-controversial science: Complement

- 3 pathways
  - Ab-Ag complex
  - Lectin pathway – oxidative stress
  - Microbial pathogens and/or debris – in as little as 30 seconds a bacterium can be lysed and ‘tagged’ for elimination by a macrophage

- *Some autoimmune diseases may result from failure to eliminate this type of debris (e.g. lupus)

Non-controversial: Zinc

- Zinc plays a central role in the immune system, in part through interaction with complement
  - (and part through binding of SOD1 & 3)

Non-controversial: Zinc

- The RPE cells can store zinc longer than most/all tissues in the body, and release as needed
- Zinc is secreted from RPE cells under conditions of oxidative stress from light exposure
- Zinc can aggregate / bind / crosslink complement

Complement Factor H

- CFH controls the complement system in fluids and on cellular surfaces
- CFH Inhibits activation of C3 and subsequent, downstream substances
- People with homozygous CFH alleles have a hypofunction or lack of CFH
- Increased inflammation
Complement Factor H
- (Adequate) CFH also binds CRP, reducing inflammation
- Therefore inadequate CRH fails to adequately inhibit inflammation mediated by CRP
- Increased inflammation

Proposed mechanisms of zinc interaction with CFH
- The homozygous CFH gene may also provide a new zinc-binding site
  - Allows more CFH binding
  - → complement factor H inhibition
  - → less blocking of C3 formation
  - → more inflammation

Proposed mechanisms of zinc interaction with CFH
- Zinc also binds CRP on surface of cells
  - CFH is even less able to bind to CRP on cells
  - → more inflammation

CFH and other AMD risk factors
- Smoking decreases CFH levels
  - → increased inflammation
- Smoking causes diminished binding of C3 to CFH
  - → increased inflammation
  - 55% of AREDS pts current or former smokers!!

Makes sense? Not so fast...
- Smalhodzic 2014 November PLoS ONE
- Netherlands
- 72 randomly selected AMD patients in various stages
- 50 mg zinc sulphate + 1 mg cupric sulphate x 3 months
- All genetic subtypes showed = reduction in complement activation
- “May explain part of mechanism by which zinc slows AMD progression”
Drusen

- Drusen are made of more than just ‘waste products’
  - CRP
  - Apolipoprotein E (APOE)
  - Clusterin
  - Serum amyloid P
  - C3a, C5a, C5
  - Vitronectin – protein that inhibits the activity of complement’s membrane attack complex

Putting things together....

- Genetic risk alleles have a direct, significant impact on development of AMD
- Lifestyle and nutrition can upregulate or downregulate these genetic risks through a variety of proposed mechanisms

2013

- Awh et al, Ophthalmology
- White patients enrolled in AREDS, cat 3 in 1 eye and 1 through 4 in fellow eye
- AREDS formulation
- Not all patients respond the same – about 15% of patients have a genetic profile that may cause more harm than good from taking an AREDS or AREDS2 based formulation containing zinc.
If 2 ARMS2 alleles, no CFH:

Genetic risk and AREDS

- If 1 CFH and 1 ARMS2,
  - AREDS = AO + Z was maximally beneficial
  - This was the only group for which this was true
Table 6. Optimal Treatment for the Study Population as a Function of Measured CFH and ARMS2 Alleles

<table>
<thead>
<tr>
<th>Risk Alleles</th>
<th>Best Age-Related Eye Disease Study Treatment</th>
<th>Study Population Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>5.86</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>5.26</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>22.5</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>1.01</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>22.6</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>13.3</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>6.57</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>16.4</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>6.67</td>
</tr>
</tbody>
</table>

AO = antioxidants; ARMS2 = age-related maculopathy sensitivity 2; CFH = complement factor H.
*The treatment associated with the lowest progression rate for individuals with the indicated genetic risk profile. A dash indicates that there was no best treatment identified.
*The observed frequency of the genetic risk combinations in the study population.

Recommendation*: Zinc
CFH 0, ARMS2 1

Recommendation*: Antioxidants
CFH 1, ARMS2 0

Recommendation*: Zinc
CFH 0, ARMS2 2

How can this be???

- P values determine ‘statistical significance’
- When several statistical tests are being performed simultaneously on a single data set a **Bonferroni correction** is used to modify the P value

**Recommendation**: Antioxidant Vitamins and Zinc: CFH 1, ARMS2 1

![Graph showing zinc, AO & Zinc, Placebo, AO over time](image)


How can this be???

- Bonferroni-corrected P value = P value / # of comparisons being made
- Awh paper used Bonferroni of 4 (4 general treatment groups)

**How significant is that?**

- .05/4 = p value of 0.0125
- .05/27= p value of 0.001
  - No single subgroup showed any positive or treatment effect at this p level

How can this be???

- Chew paper used Bonferroni of 45 (low, medium high risk for CFH and ARMS2, plus CFH+ARMS2 genotypes, each for 3 AREDS treatments vs placebo)
  - Some subgroups had 9 or fewer subjects
Risk of Progression to Late AMD
- Low CFH (0 or 1 risk allele) & Low ARMS2 (0 risk allele)

Risk of Progression to Late AMD
- High CFH (2 risk alleles) & Low ARMS2 (0 risk alleles)

Risk of Progression to Late AMD
- (High CFH (2 risk alleles) & high ARMS2 (1 or 2 risk alleles))

Effect of AREDS supplements (A & Z) for progression to Late AMD - for all 4 GTG*’s

*Genotype Treatment Group 1-4
Where does this leave us?

• Should we be testing every patient for AMD risk alleles?

What About Vitamin D?

• Some studies have suggested higher serum levels of 25-OH-vitamin D lower the risk of disease, whereas others have not

• Some authors propose vitamin D deficiency is a consequence rather than a cause of disease

Lancet Diabetes Endocrinol. 2014 Jan;2(1):76-89

• What’s the deal?

Vitamin D and Retinopathy in T2DM

<table>
<thead>
<tr>
<th>Condition</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 (n=54)</td>
<td>23.2</td>
</tr>
<tr>
<td>DM with NPDR (n=20)</td>
<td>21.5</td>
</tr>
<tr>
<td>DM with PDR (n=49)</td>
<td>18.0</td>
</tr>
</tbody>
</table>

Virtually ALL nutrients display a sigmoid response curve*

American Academy of Ophthalmol:

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

Because Baby Aspirin Doesn’t Relieve a headache……..

Do We Conclude ASA is An Ineffective Analgesic?

Primary Prevention of T2DM

Unpublished data
Average Serum Level
NHANES: 22 ng/ml
US D*action: 53 ng/ml

Equivalent Mean BMI

80% risk reduction
Over 5 yrs after all adjustments

Incidence of Diabetes
NHANES: 8.5/1,000 person-years
US D*action: 0.9/1,000 person-years
Dose Matters!!!

Vitamin D in Type 1 Diabetes Prevention

<table>
<thead>
<tr>
<th>Study and frequency of supplementation</th>
<th>Vitamin D dose (approximate)</th>
<th>Relative risk of type 1 diabetes (vs. no supplement)</th>
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</thead>
<tbody>
<tr>
<td>Stone (+), 1-4 d/wk</td>
<td>&lt;6</td>
<td>0.99</td>
</tr>
<tr>
<td>Stone (+), 5+ d/wk</td>
<td>6-10</td>
<td>0.97</td>
</tr>
<tr>
<td>Hyponen, irregular</td>
<td>1-49</td>
<td>0.16</td>
</tr>
<tr>
<td>Hyponen, regular</td>
<td>50</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Optimal Serum 25(OH)-D Level?

- Observational evidence shows significantly lower risk for multiple diagnoses with ranges from 35 to 54 ng/ml
- Lappe showed a 35% risk reduction in all cancers for every 10 ng/ml increase in 25(OH)-D (mean baseline = 28 ng/ml & mean 12mos = 38 ng/ml)

Summary of Vitamin D

- Recent meta-analyses showing no benefit from vitamin D supplementation primarily used doses barely adequate to prevent Rickets
- Major trials with large numbers but using low-doses obscure critically important dose-response relationships elucidated in small trials with higher doses
  - Weighted averaging

“NERF WHAT?” SAY YOU? DON’T HAVE A CLUE?

WHAT’S THIS I’M HEARING ABOUT NRF 2? IS IT A NEW BREAKTHROUGH?
“Nrf2 Activation”

- Nuclear factor (erythroid-derived 2)-like 2
- “The master regulator” of the antioxidant response
  - Common antioxidant enzymes – SOD, catalase, glutathione peroxidase
  - Other genes controlling other processes
    - Immune / inflammatory responses
    - Carcinogenesis and metastasis

How can we turn on the turner-on?

- Polyphenols
  - Plant based substances, > 8000 variants
  - Includes flavonoids, resveratrol, curcumin, tannins, lignans, and phenolic acids
  - Catechins
    - Green tea:
  - Quercetin
  - Phenolic acids
  - Isoflavones

How can we turn on the turner-on?

- Sulforaphane – an isothiocyanate found in cruciferous vegetables
  - Broccoli
  - Cabbage
  - Kale
  - Brussels sprouts

How can we turn on the turner-on?

- Allicin – in Garlic
- Lycopene – provitamin A
- Cinnamaldehyde – found in bark and leaves of some cinnamon varieties
- Vitamin E
- Coffee

How can we turn on the turner-on?

- Protandim - Patented dietary supplement by LifeVantage
  - “Highly synergistic phytochemical Nrf2 activators”
  - Several papers published using this proprietary supplement
  - Increases SOD, catalase
  - Decreases lipid peroxidation products

How can we turn on the turner-on?

- BARD- Bardoxaolone methyl – from oleanolic acid (olives and olive leaves)
  - Upregulates Nrf2
  - Increased glomerular filtration rate in kidney disease and T2DM
  - Inconsistent results – side effects may limit use
    - Another study suspended due to increased mortality

Nelson et al 2006

Other Nrf2 products in the news

- Other available products
  - Xymogen
  - “me too” products

Macular Pigment Optical Density (MPOD)

WHY WE SHOULD CARE

**Macular Pigment Optical Density (MPOD)**

- **Macular Pigment Optical Density**
  - The 3 macular pigments are from yellow and orange carotenoids (L&Z) & intra-retinal conversion of lutein (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

Which is more dangerous: UV or Blue Light??

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

Visual Performance with Increased MPOD: Filters Blue Light

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

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

MPOD in Glaucoma?

- Mean MPOD in POAG subjects (n=40) was significantly lower than in age-matched normals (n = 54)
  - 0.23 versus 0.36
  - p = 0.03
  - MPOD not correlated with disease severity

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

SW blue light may contribute to RGC death in conditions where RGC health is already compromised, such as glaucoma and diabetes
**MPOD & Cognitive Function**

- MPOD levels were significantly associated with better global cognition, verbal learning and fluency, recall, processing speed and perceptual speed in older adults (n=108, 77.6±2.3 years)


- MPOD is lower in pts with Alzheimer’s Disease, but supplementation with L+Z+MZ did not improve cognitive function


**WHAT’S THE LATEST ABOUT OMEGA-3? IS IT STILL A NUTRITIONAL HONOREE? OR SHOULD IT BECOME A DEPORTEE?**

**Omega-3 in the news**

![Omega-3 in the news](image)

**Omega-3 in the news:**

- “Why Fish Oil Fails: A Comprehensive 21st Century Lipids-Based Physiologic Analysis”  
  *Peskin, 2014, J Lipids*

- Cites 3 major failures of O-3  
  – Brasky et al – Prostate Cancer Risk  
  – AREDS 2 – fails to halt AMD  
  – Risk and Prevention Study Collaborative Group (Italy) – no benefit to prevent MI, stroke, death

**Risk and Prevention Study Collaborative Group**

- NEJM 2013  
- 860 general practitioners in Italy  
- Men and women with multiple CV risk factors but not MI  
- 1 g n-3 (ethyl ester, EPA+DHA not less than 85%) or placebo (olive oil) daily  
- Evaluated cumulative rate of death, nonfatal MI, nonfatal stroke – 5 year study

**Aimed to complement other studies showing benefit**

- Italy – GISSI and GISSI-HF  
  – Significant benefit of O-3 in patients in reducing risk of sudden cardiac death  
- Japan – JELIS  
  – Decrease in nonfatal coronary events in patients with hypercholesterolemia  
- Many other smaller studies
Baseline characteristics

<table>
<thead>
<tr>
<th>Fish consumption — no/tot no. (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Never or very seldom</td>
<td>144/6066 (23.1)</td>
</tr>
<tr>
<td>1 time/wk</td>
<td>2025/6066 (66.3)</td>
</tr>
<tr>
<td>2 times/wk</td>
<td>1651/6066 (27.3)</td>
</tr>
<tr>
<td>≥3 times/wk</td>
<td>362/6066 (6.0)</td>
</tr>
</tbody>
</table>

How should we interpret this?

- Controlled for fish intake
  - Does this imply O-3 intake?
- Controlled for dose of fish oil
  - Compliance?
  - Serum levels?
  - RBC membrane levels?

Bottom line?

- The literature overall has not shown harm from O-3 supplements
- Many studies have found significant benefit in reducing MI, death, stroke using high doses of O-3
- Some studies have found no benefit, no harm

Prostate cancer and O-3

- Brouwer et al, Dec 13: Effect of ALA Supplementation of Serum PSA: Alpha Omega Trial
  - No increase in PSA using 2g/day ALA over placebo
  - 40 months of supplementation

How should we interpret this?

- Other lifestyle factors?
- Incidence of events of all types was much lower than in the GISSI trials — study not powered to detect reduction in risk?
- Disclosures: Supported by
  - Pfizer
  - Societa Prodottii Antibiotici
  - Sigma Tau Pharmaceuticals
Then this happened.

- Brasky et al, July 2013: Higher plasma O-3 levels associated with overall 43% increased prostate cancer risk
- Used subset of SELECT participants
  - Black men 50+, other men 55+, n=35,533
  - 2013 paper used n=834 cases, 1393 controls

Breaking it down

- Serum analysis used
  - Designed to measure short-term fluctuations in omega-3 levels
  - Represents previous few days' intake, not a sustained intake
  - One-time measure at baseline of study (2001-2004)
  - Looked at diagnosis of cancer before July 31, 2009

 Let’s look at the numbers

<table>
<thead>
<tr>
<th>Fatty acid (% of total)</th>
<th>Mean (95% CI)</th>
<th>P</th>
<th>Mean (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cancer (n = 684)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a-3 fatty acids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPA + DPA + DHA</td>
<td>0.46 (0.56 to 0.77)</td>
<td>0.002</td>
<td>0.47 (0.63 to 0.78)</td>
<td>0.03</td>
</tr>
<tr>
<td>EPA (20:5ω3)</td>
<td>0.66 (0.63 to 0.68)</td>
<td>0.02</td>
<td>0.65 (0.70 to 0.74)</td>
<td>0.01</td>
</tr>
<tr>
<td>DPA (22:5ω3)</td>
<td>0.99 (0.99 to 0.99)</td>
<td>&lt;0.01</td>
<td>0.89 (0.96 to 0.95)</td>
<td>0.16</td>
</tr>
<tr>
<td>DHA (22:6ω3)</td>
<td>3.01 (2.54 to 3.63)</td>
<td>0.002</td>
<td>3.08 (2.59 to 3.61)</td>
<td>0.009</td>
</tr>
<tr>
<td>o-6 fatty acids</td>
<td>18.91 (18.71 to 19.31)</td>
<td>0.11</td>
<td>19.09 (18.66 to 19.54)</td>
<td>0.81</td>
</tr>
<tr>
<td>Linoleic acid (18:2ω6)</td>
<td>11.22 (11.06 to 11.39)</td>
<td>0.026</td>
<td>11.33 (11.01 to 11.67)</td>
<td>0.54</td>
</tr>
<tr>
<td>Arachidonic acid (20:4ω6)</td>
<td>1.12 (1.10 to 1.14)</td>
<td>0.12</td>
<td>1.14 (1.12 to 1.16)</td>
<td>0.07</td>
</tr>
<tr>
<td>Total fatty acids</td>
<td>1.41 (1.02 to 1.91)</td>
<td>0.20</td>
<td>0.21 (0.17 to 0.25)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

"Mean percentages of each TFA (18:1, 18:2, and 16:1) were statistically significantly higher among total and low-grade prostate cancer case subjects compared with the subcohort, although differences were small."

Let’s look at the numbers

- These are very low levels and would be unlikely for patients supplementing with O-3
- “Japanese living in Japan have higher blood omega-3 fatty acid levels than whites living in Pennsylvania and Japanese Americans living in Honolulu.
- The lower 5th percentile of blood omega-3 fatty acids in the Japanese living in Japan is higher than the mean levels in whites and Japanese Americans even though total fat is comparable.”

Sekikawa et al, J Am Coll Cardiol 2008
More about prostate cancer

• Extensive literature demonstrates
  – a lower incidence of prostate cancer and death
  – better survival among men who already had prostate cancer
  – reduced risk of aggressive cancer

• So what gives?

Finally -- Fatty acid metabolism is complex

• Is the higher O-3 a consequence of disease, or coincidental, or causative?

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

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, 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, hsCRP


ClinicalTrials.gov Identifier: NCT01646047
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 affect on blood glucose

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

DiVFuSS Unmasked

Analysis of 67 subjects to complete the trial

British Journal of Ophthalmology 2015, in review

DiVFuSS Unmasked Data

<table>
<thead>
<tr>
<th></th>
<th>Suppl versus Plac</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast</td>
<td>+28%</td>
<td>-15%</td>
</tr>
<tr>
<td>Color Error Score</td>
<td>-42%</td>
<td>-4%</td>
</tr>
<tr>
<td>5-2 MD</td>
<td>+1.3 dB</td>
<td>+0.11 dB</td>
</tr>
<tr>
<td>hsCRP</td>
<td>-60%</td>
<td>-11%</td>
</tr>
<tr>
<td>HbA1c</td>
<td>-1.7%</td>
<td>+1.7%</td>
</tr>
<tr>
<td>NFL &amp; RT</td>
<td>unchanged in both groups</td>
<td>0.79</td>
</tr>
<tr>
<td>DPNSS</td>
<td>-46%</td>
<td>+8%</td>
</tr>
</tbody>
</table>

C-Reactive Protein & DME

- Blood samples from 1441 DCCT subjects
- Analyzed for ICAM, TNF-α and hsCRP
- Highest quartile of hsCRP linked to 83% increased risk of CSME vs lowest quartile


Subject Characteristics (n = 67)

- 28-79 yo (mean = 56.1 yrs)
- 30 with NPD & 37 with no DR
- 27 T1DM & 40 T2DM
- HbA1c range 5.8 to 10.3% (mean 7.2%)
- Mean A1c in those with DR = 7.8%
- Mean A1c in those with no DR = 7.1%
- Diabetes duration 5-52 years (mean 16.1 yrs)
- Mean 23.4 years in those with DR
- Mean 14.7 years in those with no DR

No statistically significant differences at baseline between S and P groups
Subject # 38  retinal images OS

Good Control Does NOT Eliminate Risk of Severe DR

• 10 year risk of PDR and/or CSME in a newly Dx patient with A1c = 6.5% and BP = 120/80 is nearly 4%

• With mild NPDR the 10 yr risk is 8.4%

Diabetologia. 2011 Oct;54(10):2525-32