The Elusive Magic Pill: Supplement Use in FOD’s

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Undiagnosed Diseases program
Epi-743 MitoWorks trial
Congenital Disorders of Glycosylation
July 25, 2014
CDCs Second National Report on Biochemical Indicators of Diet and Nutrition 2013

- Covers 2003-2006
- 80% of American children under 6 years of age were not at risk for Vitamins A, B6, B12, Folate, Vitamin C, or Vitamin D deficiencies
- Women of child-bearing age continue to be at high risk for Iron deficiency
- The darker your skin the more risk of Vitamin D deficiency
- DOES NOT address children with special health needs, formula or TPN based diets or medication-nutrient interactions
Vitamin A (retinol)

- Night and color vision
- Immune regulatory roles and functions
- Maintains cell integrity
- Levels correlate with gestational age and stabilize after the 1st year of life
- Deficiency leads to night-blindness & frequent infections
Vitamin E (\(\alpha\)-tocopherol)

- Anti-oxidant
- Regulates cell proliferation and gene expression
- Transported on lipoproteins LDL & HDL needs interpretation in context of the lipid profile
- Deficiency leads to hemolytic anemia, cardiac rhythm disturbances, peripheral neuropathy
AREDS
(Age-Related Eye Disease Study)

- 30 million people have vision loss with increased risk after age 50 years
- Included single or combination
- Vitamin C 500 mg, Vitamin E 400 IU, Zinc 80 mg, Copper 2 mg & Beta-Carotene 15 mg/Vitamin A 15 mg
- Eliminating both Zinc and Beta-Carotene did not change results
- Has also been studied in premature infants, Cataracts, Glaucoma, Retinitis Pigmentosa and multiple eye infections
AREDS
(Age-Related Eye Disease Study)

- Diabetic retinopathy was not impacted unless blood sugar was well controlled
- Neither Cataracts or Glaucoma was impacted
- Eye Infections were not impacted
- RP from prematurity responded to AREDS with L-carnosine or N-acetylcarnosine drops
- In some studies increasing antioxidants from fruits and vegetables had the same impact
AREDS (Age-Related Eye Disease Study)

- AREDS2 study added Omega-3 Fatty acids, Lutein & Zeaxanthin
- Results were that only patients with deficiency of Lutein or Zeaxanthin benefited with slowed disease progression
- Retinitis Pigmentosa did appear impacted by Vitamin A, Vitamin E (if deficiency was present) and DHA (Omega-3 fatty acid)
CAREDS (Age-Related Eye Disease Study)

CAREDS studied Beta-Carotene, Lutein & Zeaxanthin

Studied only Age-related macular degeneration caused by genes known to be impacted by Lutein & Zeaxanthin

Results were by self-report not objective measures
<table>
<thead>
<tr>
<th>Supplement</th>
<th>β carotene</th>
<th>Vitamin E</th>
<th>Vitamin C</th>
<th>Zinc</th>
<th>Copper</th>
<th>Lutein</th>
<th>Zeaxanthin</th>
<th>Dose/day</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icaps lutein and omega 3</td>
<td>0.6</td>
<td>7</td>
<td>45</td>
<td>7</td>
<td>0.9</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>Also contains omega 3 fatty acids, Vit B and minerals. Preparations with different amounts of various ingredients are also available.</td>
</tr>
<tr>
<td>Macula complete</td>
<td>0.8</td>
<td>20</td>
<td>500</td>
<td>25</td>
<td>0.3</td>
<td>16</td>
<td>4</td>
<td>6</td>
<td>Also contains resveratrol, n-acetyl cysteine, lipoic acid, bilberry, grapeseed extract, green tea leaf, lycopene and coQ10 30 mg</td>
</tr>
<tr>
<td>MDS AREDS1</td>
<td>4.5</td>
<td>400</td>
<td>500</td>
<td>15</td>
<td>1</td>
<td>50</td>
<td>10</td>
<td>2</td>
<td>Also contains bilberry. Preparations with different amounts of the ingredients and fish oils are also available.</td>
</tr>
<tr>
<td>Oculair</td>
<td>0.8</td>
<td>134</td>
<td>250</td>
<td>20</td>
<td>0.3</td>
<td>12</td>
<td>3</td>
<td>3</td>
<td>Also contains bilberry, lipoic acid, lycopene, grapeseed extract and n-acetyl cysteine 100 mg</td>
</tr>
<tr>
<td>Ocuvite</td>
<td>20</td>
<td>60</td>
<td>15</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>Also contains lutein and zeaxanthin. Preparations with different amounts of other ingredients and fish oils are also available.</td>
</tr>
<tr>
<td>Preservision AREDS</td>
<td>4.3</td>
<td>134</td>
<td>226</td>
<td>35</td>
<td>0.8</td>
<td></td>
<td></td>
<td>4</td>
<td>Preparations with different amounts of other ingredients and fish oils are also available.</td>
</tr>
<tr>
<td>Saffron 20/20</td>
<td>85</td>
<td>150</td>
<td>10</td>
<td>0.5</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td></td>
<td>Also contains Vit B2 and resveratol</td>
</tr>
<tr>
<td>VisiVite i –defense gold</td>
<td>7.5</td>
<td>268</td>
<td>500</td>
<td>40</td>
<td>1</td>
<td>15</td>
<td>4.8</td>
<td>2</td>
<td>Also contains bilberry, lipoic acid, grapeseed extract and glutathione</td>
</tr>
<tr>
<td>Vitalux healthy eyes</td>
<td>1.5</td>
<td>33.5</td>
<td>150</td>
<td>20</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>Also contains lycopene, Vit B and minerals. Preparations with fish oils and different amounts of β carotene are also available.</td>
</tr>
<tr>
<td>Viteyes AREDS adv.</td>
<td>7.5</td>
<td>134</td>
<td>250</td>
<td>40</td>
<td>1</td>
<td>5</td>
<td>1.8</td>
<td>2</td>
<td>Also contains selenium, bilberry, grapeseed extract and lipoic acid. Preparations with different amounts of various ingredients are also available.</td>
</tr>
</tbody>
</table>
Vitamin A and fish oils for retinitis pigmentosa (Review)

Rayapudi S, Schwartz SG, Wang X, Chavis P
We did not find evidence for the benefit of treatment with vitamin A or DHA, or both, for people with RP with the exception of one subgroup in Berson 1993, in which participants with high cone amplitude at baseline appear to have had a reduced rate of loss of remaining cone function compared to non-supplemented controls.
Needed to keep the toxic acylcarnitine levels down and the DHA levels up to preserve vision

Both the cell biology of chorioretinitis and the real mechanism of action of DHA remain unknown
Essential polyunsaturated fatty acids in plasma and erythrocytes of children with inborn errors of amino acid metabolism

H. Vlaardingerbroek a, G. Hornstra b, T.J. de Koning c, J.A.M. Smeitink d, H.D. Bakker e, H.B.C. de Klerk f, M.E. Rubio-Gozalbo g,*

• Studies 33 children (1-18 years) with Maple Syrup Urine disease, Propionic acidemia, Tyrosinemia I, Classical Homocysteinemia, Urea cycle disorders (not PKU or FOD’s)
• Had 38 age-matched controls
• DHA was low in all
• Similar studies have been done in PKU patients

Molecular Genetics and Metabolism 88 (2006) 159–165
Epi-743

- Vitamin E analogue chemically altered to cross the blood-barrier and formulated to be many fold more powerful than CoQ
- It has been used successfully to treat vision in a 5 patients with LHON
- Visual restoration in 1 of 5 and arrest of further visual loss in 4 of 5
- Would it be useful in LCAHD patients??
Resveratrol

- Plant generated polyphenol that acts a powerful anti-oxidant
- Found naturally in wine, red grapes and peanut-butter
- Has been shown to promote mitochondrial biogenesis, improve aerobic capacity and be neuro-protective particularly to basal ganglia and hippocampus

Human Molecular Genetics, 2011, Vol. 20, No. 10
Resveratrol

- French study published in 2011
- Used fibroblasts of patients with CPT-2 and VLCAD – not patients
- Demonstrated improved FAO flux and improved protein levels

Human Molecular Genetics, 2011, Vol. 20, No. 10
Beta Hydroxybutyrate in GAII

- Provides synthetic ketones to provide energy to brain and heart
- Reported in 4 patients with GAII (2003)
  - Restores energy deficit
  - Reduces disease specific toxic acylcarnitine
  - Improvement continued for several years
- Reported in 1 patient with GSDIII (2013)
  - Used with Ketogenic, high-protein diet
  - Improvement continued to for several years
Creatine

- Creatine produced in the liver, kidney, and pancreas
- Creatine can be taken up by the brain, heart, and skeletal muscle
- Two randomized studies of creatine monohydrate supplementation +/- lactulose demonstrated no clinical significance in treatment outcomes
Carnitine

- Carnitine requires combination of dietary intake, biosynthesis from lysine and methionine, and renal reabsorption
- Skeletal and heart muscle use carnitine to import of long-chain fatty-acids into the mitochondrial matrix for fatty acid oxidation
- Carnitine supplementation is FDA-approved, considered safe and effective for patients with chronic kidney disease on dialysis and patients with inborn errors of organic acid metabolism and mitochondrial disorders, there have not been randomized, controlled studies demonstrating clear clinical improvement in patients
Acknowledgements
William A. Gahl, MD, PhD

Cynthia Tifft, MD, PhD
David Adams, MD, PhD
Camilo Toro, MD
Andrea Gropman, MD
Paul Lee, MD
Ariane Soldatos, MD
Fred Gill, MD
Gretchen Golas, MS, CRNP
Lynne Wolfe, MS, CRNP
Catherine Groden, MS, CRNP
Michele Nehrebecky, MS, CRNP
Colleen Wahl, DNP, CRNP
Rena Godfrey, PA
David Draper, RN
Jean Johnston, RN
Casey Hadsall, RN

Neil Boerkoel, MD, PhD
Tom Markello, MD
Roxanne Fischer
Valerie Maduro
Yan Huang
Numerous IRTA’s & Fellows

Support Staff
Anabella Roman
Jose Salas
Iris Goode
Quentin Whitley
Lisa Gardner