Translating Cardiovascular Nutrition from the Laboratory to the Clinic

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Effects of Bioactive Food Components Related to Cardiovascular Disease

- Lipoprotein metabolism
- Blood pressure
- Vascular reactivity
- Oxidative stress
- Inflammation
- Thrombosis
Food components that increase levels of atherogenic lipoproteins

- Cholesterol
- Most saturated fatty acids
- Trans-mono-unsaturated fatty acids
Bases for establishing effects of lipid-altering food components on CVD risk in humans

- Changes in lipoproteins (biomarkers) in animal models and humans
- Induction of atherosclerosis in animals (rodents, nonhuman primates)
- Mechanistic understanding of effects (cells, animals, humans)
- Observational studies of relationships between intake levels and CVD risk in human populations
- Randomized clinical trials of individual food components not feasible
Hyperlipidemic Effects of Dietary Saturated Fats Mediated through PGC-1β Coactivation of SREBP

- Microarray analysis of gene expression in livers of mice fed saturated, polyunsaturated, and trans fatty acids: 
  with sat and trans fat, PGC-1β mRNA increases along with SREBP1c, a major nuclear regulator of lipid synthesis genes
- PCC-1β is recruited to sterol response element of SREBP
- Viral expression of PGC-1β gene in vivo activates lipogenic genes and markedly increases hepatic lipoprotein secretion; the effect is dependent on SREBP and LXR
- Knockdown of PGC-1β by RNAi constructs in cultured cells: PGC-1β is required for full transcriptional activity of SREBP
In vivo knockdown of PGC-1\(\beta\) gene doesn’t quite prove mechanism for saturated and trans fat-induced increases in plasma lipoproteins.

Paradoxical effect due to reduced LDL receptor expression.
Factors limiting direct extrapolation from laboratory studies to clinic

- Differences in lipoprotein metabolism between animals and humans:
  - Mice, rats: HDL >> LDL; genetic manipulation does not reproduce all features of dietary regulation in humans
  - Rabbits: extreme dietary cholesterol responsiveness
  - Non human primates: generally lower triglycerides than humans
- Genetic variation among humans
Distribution of Changes in Major Plasma Lipids with Low-Fat (20%) High-Carbohydrate (55%) Diet

n = 685 men and women

-7 %

-14 %

+27 %

LDL Cholesterol

Triglyceride

HDL Cholesterol

Percent change
Cardiovascular Disease and HDL-C Levels in the Framingham Study

Kannel WB. Am J Cardiol. 52:9B-12B, 1983
Relation of HDL-cholesterol to aortic atherosclerosis in apoE-deficient mice transgenic for human apoAI (model for increased apoAI transport)

$r=0.88, p<0.0001$

Plump et al., PNAS 91:9607, 1994
What are the effects of dietary fatty acids on HDL in humans?

<table>
<thead>
<tr>
<th>Diet component</th>
<th>Effect on HDL</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated fat</td>
<td>Increases apoAI transport</td>
<td>Brinton et al., J Clin Invest 85:144, 1990</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>Increases apoAI catabolism</td>
<td>Brousseau et al., Atherosclerosis 115:107, 1995</td>
</tr>
<tr>
<td>Trans-fat</td>
<td>Increases apoAI catabolism</td>
<td>Matthan et al., ATV 24:1092, 2004</td>
</tr>
</tbody>
</table>

What can we infer from these findings regarding expected effects of dietary fatty acids on CVD risk?
Other experimentally demonstrated bioactive properties of food components

- Polyphenols
  - Lower vascular reactivity, blood pressure, and thrombogenesis
  - Nutritional epidemiology supportive
- Omega-3 fatty acids
  - Improve cardiac electrophysiology, thrombosis, inflammation
  - Epidemiology and clinical trial evidence supportive
Antioxidants - A Case Study

Involvement of oxidative stress in atherosclerosis

- Oxidative modification of atherogenic lipoproteins is critical for arterial macrophage lipid uptake and formation of foam cells and fatty streaks
- Oxidized lipids are proinflammatory and promote endothelial dysfunction, plaque destabilization, and thrombosis
- Oxidation markers are present in atherosclerotic lesions of animal models, e.g., hyperlipidemic apoE knockout
- Vitamin E deficiency induced by knockout of α-tocopherol binding protein in hyperlipemic mice increases atherosclerosis
- Targeted disruption of 12/15 lipoxygenase reduces atherosclerosis
Antioxidants - A Case Study

Dietary antioxidants and atherosclerosis in animal models

- Vitamin E supplementation in vivo reduces lipoprotein oxidation in vitro
- Dietary antioxidants reduce atherosclerosis in some animal models
Antioxidants - A Case Study

Evidence for reduction of CVD risk in humans

- Observational studies
  - Relative risk reduction associated with high vitamin E intake ~30-65%
  - Reduced plasma antioxidant levels associated with CHD
  - Dietary antioxidant-disease relationships confounded by other health-related behaviors

- Randomized clinical trials
### Summary of Randomized Controlled Trials of Antioxidant Vitamin Supplementation in CVD

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Dose (daily)</th>
<th>Follow up (yrs)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1° CVD Outcome</td>
</tr>
<tr>
<td>CHAOS</td>
<td>2,002</td>
<td>E-800/400</td>
<td>1.4</td>
<td>0.53 (0.34-0.83)*</td>
</tr>
<tr>
<td>GISSI</td>
<td>11,324</td>
<td>E-300 IU</td>
<td>3.5</td>
<td>0.95 (0.86-1.05)</td>
</tr>
<tr>
<td>HOPE</td>
<td>9,541</td>
<td>E-400 IU</td>
<td>4.5</td>
<td>1.05 (0.95-1.15)</td>
</tr>
<tr>
<td>SPACE</td>
<td>196</td>
<td>E-800 IU</td>
<td>1.4</td>
<td>0.54 (0.33-0.89)*</td>
</tr>
<tr>
<td>PPP</td>
<td>4,495</td>
<td>E-300 IU</td>
<td>3.6</td>
<td>1.07 (0.74-1.56)</td>
</tr>
<tr>
<td>HPS</td>
<td>20,536</td>
<td>E-600 IU+ C-250 mg+ β-carotene-20 mg</td>
<td>5</td>
<td>1.02 (0.94-1.11)</td>
</tr>
</tbody>
</table>

*Significant
HOPE Trial: Increased risk for heart failure in patients with CVD or diabetes treated with 400 IU vitamin E

![Graphs showing heart failure rates for vitamin E and Placebo groups over time.](image)

*JAMA 293:1338, 2005*
WAVE Trial: Probability of death or nonfatal MI with vitamin E 400 IU bid and vitamin C 500 mg bid in postmenopausal women

Probability of death or MI

<table>
<thead>
<tr>
<th>Time (d)</th>
<th>Placebo</th>
<th>Vitamin</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>211</td>
<td>212</td>
</tr>
<tr>
<td>200</td>
<td>205</td>
<td>201</td>
</tr>
<tr>
<td>400</td>
<td>204</td>
<td>194</td>
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<td>600</td>
<td>201</td>
<td>187</td>
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<td>800</td>
<td>185</td>
<td>178</td>
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<tr>
<td>1000</td>
<td>134</td>
<td>124</td>
</tr>
<tr>
<td>1200</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>1400</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

$p=0.049$

Waters et al., JAMA 288:2432, 2002
HATS: Percent change in coronary artery stenosis with lipid lowering drugs and/or antioxidants

- Placebo
- Antioxidant vitamins (*p=0.16 for comparison with placebo)
- Simvastatin/niacin (†p<0.001)
- Simvastatin/niacin/antioxidants (‡p=0.004)

*HATS=HDL-Atherosclerosis Treatment Study.
HATS: Clinical events with lipid lowering and/or antioxidants


*P<0.01
**VEAPS: Effects of vitamin E on early carotid artery atherosclerosis (intimal-medial thickness)**

<table>
<thead>
<tr>
<th>IMT progression rate, mm/y</th>
<th>Placebo (n=170)</th>
<th>Vitamin E (n=162)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All evaluable subjects</td>
<td>0.0023±0.0007</td>
<td>0.0040±0.0007</td>
<td>0.08</td>
</tr>
<tr>
<td>Adjusted for baseline LDL</td>
<td>0.0024±0.0007</td>
<td>0.0039±0.0007</td>
<td>0.13</td>
</tr>
<tr>
<td>Females (n=87/85)</td>
<td>0.0026±0.0009</td>
<td>0.0036±0.0009</td>
<td>0.40</td>
</tr>
<tr>
<td>Males (n=83/77)</td>
<td>0.0020±0.0010</td>
<td>0.0044±0.0011</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*Hodis et al. Circulation 106:1453, 2002*
Antioxidants - A Case Study

• Despite strong evidence supporting benefits of antioxidants in cellular and animal studies, trials of dietary antioxidants in humans have largely failed to confirm benefits on CVD, and in some cases have suggested harm.

• If dietary antioxidants have potential for CVD prevention, more studies are needed to determine optimal levels and combinations, appropriate subgroups for treatment, and suitable model systems that better predict outcomes in humans.
Conclusions

While basic research in model systems will continue to be of critical importance in understanding nutritional effects on CVD, increasing efforts should be made to promote the development and application of improved molecular and clinical approaches for directly assessing relevance of these effects in humans.