Vitamin E & Fatty Liver

IS VITAMIN E SAFE TO USE?
### Nonalcoholic Fatty Liver Disease (NAFLD) & Nonalcoholic Steatohepatitis (NASH)

<table>
<thead>
<tr>
<th>Point</th>
<th>Details</th>
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<tbody>
<tr>
<td>Prevalence:</td>
<td>5.7-16.5% in US</td>
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<tr>
<td>Usually diagnosed:</td>
<td>in 40-60 y/o’s</td>
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<tr>
<td>Non-significant alcohol intake:</td>
<td>but biopsies are almost identical to those with <em>alcoholic</em> steatohepatitis</td>
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<tr>
<td>Progression:</td>
<td>15-25% will progress to cirrhosis</td>
</tr>
<tr>
<td>Mortality:</td>
<td>30-40% die within a decade</td>
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<tr>
<td>Symptoms:</td>
<td>none mostly, fatigue, RUQ or abdominal pain in some</td>
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NASH Development

- **NASH develops by the “2 hit theory”:**
  - 1\(^{\text{st}}\) hit: accumulation of excessive hepatocellular fat or steatosis (NAFLD)
  - 2\(^{\text{nd}}\) hit: turns into NASH when there is inflammation, fibrosis or necrosis
  - May be triggered by oxidative stress = Retained lipids in the hepatocytes get digested generating reactive O\(_2\) species leading to cytokine release and oxidative stress! (7)
  - Oxidative stress – treat with antioxidant therapy (vitamin E and C)
Progression from Healthy Liver to NASH

1st Hit: accumulation of excess fat cells
2nd Hit: Inflammation from oxidative stress, lipid peroxidation

Hyperlipidemia, visceral obesity, hypertension, insulin resistance, ethanol, high fat diet

HEALTHY LIVER  NAFLD  NASH

Hematoxylin and eosin stained images by D. McLeod, Westmead Hospital, Sydney, Australia.
NASH: Underlying Cause

- Metabolic Syndrome
  - Hypertension
  - Hyperlipidemia
  - Visceral obesity
  - Diabetes mellitus
  - Fatty Liver

"An Ounce of Prevention is Worth a Pound of Cure"
- Ben Franklin
The aging of the population, along with the increasing prevalence of diabetes and obesity, is expected to contribute to an increase in the prevalence of these conditions and in the overall burden of liver disease in the United States.

Vitamin E

- Fat soluble antioxidant
- Dietary sources: green leafy vegetables, oils, meat, and eggs

- Protects cell membranes from oxidation & destruction
- Helps regulate apoptosis, inflammation and collagen deposition
- Inhibits cell proliferation, platelet aggregation and monocyte adhesion
**PIVENS Trial**

- **PIVENS:** Pioglitazone vs Vitamin E vs Placebo for the Treatment of Nondiabetic Patients with NASH
- Phase 3 RCT
- 247 Non diabetics with biopsy proven NASH and a NAFLD score of ≥4
- 3 arms
  - Pioglitazone 30 mg daily
  - Vitamin E 800 iu daily
  - Placebo
- Liver biopsy before and after treatment
- 96 weeks
PIVENS Trial Endpoints

- **Primary Endpoint – improved liver histology biopsy**
  - Improved hepatocellular ballooning score
  - No worsening of fibrosis
  - Improved NAFLD and either the lobular inflammation or steatosis score

- **Secondary Endpoint –**
  - Reductions in serum alanine & aminotransferase levels
  - Improved Insulin Resistance
## PIVENS Trial Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vitamin E 800 iu/day</th>
<th>Pioglitazone 30 mg /day</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in NASH</td>
<td>43%</td>
<td>34%</td>
<td>19%</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>37%</td>
<td>41%</td>
<td>20%</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>21%</td>
<td>20%</td>
<td>4%</td>
</tr>
<tr>
<td>Reduce hepatic steatosis</td>
<td>54%</td>
<td>69%</td>
<td>31%</td>
</tr>
<tr>
<td>Reduced lobular inflammation</td>
<td>54%</td>
<td>60%</td>
<td>35%</td>
</tr>
<tr>
<td>Improved fibrosis scores</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Improved Insulin Resistance</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Weight gain</td>
<td>No</td>
<td>4.7+kg</td>
<td>No</td>
</tr>
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</table>
American Association for the Study of Liver Disease, the American College of Gastroenterology, and the American Gastroenterological Association recommended:

- Vitamin E 800 iu/daily as 1st line therapy for Nondiabetic adults with biopsy-proven NASH
- Not recommended in the following until more studies to evaluate:
  - NASH with Diabetes
  - NAFLD (without liver biopsy)
  - NASH (without liver biopsy)
  - Cirrhosis
  - Cryptogenic cirrhosis

Chalasani, N et al. 2012. Amer J of Gastroenterology; 107; 811-826.
NAFLD/NASH Treatment

- **TLC**
  - Weight loss – goal 10%
  - Exercise
  - Dietary changes
    - Reduce refined sugars and simple starches
    - Reduce fats

- Treat underlying causes: HTN, DM, Dyslipidemia
- Use insulin sensitizers: Metformin, Pioglitazone
- Antioxidants
  - Vitamin E 400-800 iu daily
  - Vitamin C 500-1000 mg daily
Caution with Vitamin E

- Conflicting studies on vitamin E and NASH
- May blunt statin effects (may be the reason that some studies have shown increase in CHD mortality)
- Increased risk of hemorrhagic CVA on 400 iu every other day
- Increased risk of prostate cancer in the Selenium and Vitamin E Cancer Prevention Trial (SELECT)

Vitamin E & C Treatment for NASH

- Retrospective, single center study
- Goal: Determine whether Vitamin E 400-800 iu and Vitamin C 500-1000 mg daily would reduce serum aminotransferases in subjects with NASH
- 68 patients – 38 in treatment group
- LDL and Triglycerides were significantly higher in the treatment group
- 12 month follow up

Vitamin C & E vs Placebo and LFTs

VITAMIN E & C

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<tr>
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<th>AST</th>
<th>ALP</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>99.6</td>
<td>63.7</td>
<td>63.7</td>
</tr>
<tr>
<td>Follow up</td>
<td>101.3</td>
<td>68.5</td>
<td>41.2</td>
</tr>
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CONTROL

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<tbody>
<tr>
<td>Baseline</td>
<td>84.1</td>
<td>94</td>
<td>84.1</td>
</tr>
<tr>
<td>Follow up</td>
<td>63.9</td>
<td>52.7</td>
<td>89.9</td>
</tr>
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</table>

(P<0.001)

Patient Case with NASH
Omega 3 Oil

IS IT SAFE TO USE?
Favorable Omega 3 Results

- (GISSI)-Prevenzione Trial with 11,324 MI patients
- First large randomized trial to produce evidence that a pharmaceutical grade of omega-3s at 1 g/day, had a favorable effect on hard clinical end-points in post-myocardial infarction patients
  - 20% all-cause mortality benefit
  - 45% reduction in sudden cardiac death
- Used for MI prophylaxis
Plasma Phospholipid Fatty Acids and Prostate Cancer Risk in the SELECT Trial


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SELECT – Selenium & Vitamin E Cancer Prevention Trial

- Goal: Determine whether Vitamin E or Selenium alone or in combination reduced the risk of prostate cancer
- Later: Determine whether Omega 3 fatty acids reduced the risk of prostate cancer
- Analyzed ONE blood sample from the study group:
  - 834 men with prostate cancer
  - 1,393 healthy men

- Claimed a link between increased blood levels of omega-3 fatty acids and increased incidence of prostate cancer
Omega 3 Levels and Prostate Cancer

- Men with the highest concentrations of Omega 3 fatty acids in their blood vs those with the lowest:
  - 43% higher risk of developing prostate
  - 71% higher risk of aggressive, possibly fatal prostate cancer

- Problem with analyzing 1 blood sample:
  - Blood levels of these fatty acids will rise and stay high for 4-12 hours after a single dose of fish oil or a meal containing fish
  - Blood levels wash out in 48 hours unless more fish or another supplement is consumed
SELECT STUDY FLAWS

- Retrospective case controlled cohort design the SELECT that was designed to determine whether Vitamin E or Selenium led to prostate cancer – not Omega 3s

- Missing information: Where did they get their omega-3 fatty acids - eating fatty fish or from supplements?

- Prior health status was unknown –
  - Did they start using fish oil once they were diagnosed with prostate cancer?
  - Were they taking fish oil all along?
SELECT STUDY FLAWS

- Other known causes of cancer were not considered:
  - Smoking, nutrition, exercise, environmental toxicity, stress

- Analysis of *one* single sample of blood plasma instead of *red blood cells* is not an accurate measurement

- The tumor grading system that was used overestimated the severity of prostate cancer
Cultures with High Omega 3 Consumption

- **Japanese**
  - Japanese males have some of the highest levels of EPA and DHA **but** some of the lowest rates of prostate cancer

- **Native Alaskan Indian**
  - Alaska Native men have a significantly lower incidence of prostate cancer vs US Caucasian men

- **Multiple studies have shown:**
  - Salted or smoked fish may increase risk of advanced prostate cancer
  - Fish oil consumption may be protective against progression of prostate cancer in elderly men
  - In a setting with very high fish consumption, no association was found with prostate cancer

“Bottom line: this appears to be an unfortunate combination of questionable science, unwarranted conclusions, and dreadful media coverage. The well documented evidence for myriad benefits of high dietary intake of omega-3 fatty acids on both physical and mental health is very strong.”

Andrew Weil, M.D.

www.drweil.com, Does Fish Oil Cause Prostate Cancer - 7/26/13
Recent Analysis of Omega 3s

- Multiple trials since GISSI have shown benefits with reduction in:
  - Coronary heart disease events, cardiovascular death, sudden cardiac death, prevention of restenosis after revascularization
  - All-cause mortality
  - Stroke
- Recent trials testing omega-3s have generally failed to confirm these benefits
- There is more of a challenge for Omega 3’s to show additional benefit with the use of statins, aspirin, and antihypertensive medications

Uses for Omega 3 PUFAs

- **Hypertriglyceridemia** –
  - Triglycerides > 500 mg/dL - Expect a 40% reduction with 4 grams daily
  - Triglycerides 200-499 mg/dL – Expect a 20-30% reduction

- **MI prophylaxis:**
  - Especially helpful in early months after MI
  - Exceptionally helpful with the lowest ejection fraction patients
  - Enhanced effects with healthy diet
Thank You!

ANY QUESTIONS?