Fish Oil & Fatty Liver

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SWLA Spring Clinical Update
March 16, 2014
Disclosures

- Speaker’s Bureau: NovoNordisk, AZ Diabetes, Janssen
Case

- 52 y/o WF is referred to you for evaluation of dyslipidemia
- FH: father had an MI at age 53
- SH: no tobacco, social EtOH, sedentary job
- PMH: Metabolic Syndrome x 10 years
Case Labs

- January: TC 205 TG 175 HDL 32 LDL 138
  - Started atorvastatin, 40 mg once daily
- April: TC 144 TG 140 HDL 30 LDL 96
  - ALT 78 AST 85
  - atorvastatin stopped
- May: *presents to your clinic off meds*
  - Lipids back to baseline
  - ALT 44 AST 53
Case
Dyslipidemia with Abnormal LFTs

- What do you do now?
  - Review of medical records finds labs from 2001:
    - ALT 14 AST 18
    - TC 195 TG 125 HDL 41 LDL 129
Asymptomatic Abnormal LFTs

- 1% to 4% of asymptomatic patients on “routine lab tests”
  - primary health care visits
  - routine blood donation
  - insurance screening

- LFTs include:
  - ALT, AST, GGT, LDH, alk phos
  - Bilirubin
  - Albumin
  - Prothrombin time (PT)
Abnormal LFTS

- hepatocellular necrosis
  - ALT, AST, AST/ALT ratio, LDH
- cholestasis
  - Alk phos, GGT, bilirubin
- synthetic function
  - Albumin, PT
Asymptomatic Abnormal LFTs

- Transaminitis
  - < 250 NAFLD†
  - 250-1000 viral hepatitis, hepatotoxic drugs*

* NSAIDs, antiepileptics, antibiotics, statins, anabolic steroids, and recreational drugs of abuse (cocaine, phencyclidine, glues, and solvents)

†NAFLD = nonalcoholic fatty liver disease
Asymptomatic Abnormal LFTs

- Elevated Alkaline Phosphatase
  - chronic cholestasis
    - partial biliary obstruction
    - primary biliary cirrhosis
    - primary sclerosing cholangitis
    - drug-related cholestasis
  - infiltrative disease
    - granulomatous
    - malignancy
Asymptomatic Abnormal LFTs

- Elevated GGT
  - alcohol use
  - anticonvulsant medications
    - carbamazepine
    - valproic acid
  - warfarin
Common Causes of Abnormal LFTS that We Frequently see

- Viral Hepatitis
- Autoimmune Hepatitis
- Fatty Liver
- Valproic acid
- Pregnancy
Common Causes of Abnormal LFTS that We Frequently see

- Viral Hepatitis
- Autoimmune Hepatitis
- Fatty Liver
  - Alcohol
    - An AST/ALT ratio of $\geq 2.0$ and an absolute ALT level less than 300 U/L is suspicious of alcoholic liver disease
  - Obesity
  - Diabetes Mellitus
  - Corticosteroids
  - Hyperlipidemia
  - Idiopathic/familial
Case

- Known Metabolic Syndrome
- Unknown baseline LFTS
- Transaminases increased on a statin
- Transaminases high normal off statin

- What next?
Evaluation of Abnormal LFTS

- Review H&P in detail
- Draw fasting liver panel, hepatitis serologies
  - ALT has a diurnal pattern so always draw at same time of day
  - Elevated fasting alk phos with normal GGT not likely to be hepatic in origin
- Check autoimmune panel, TFTs
  - Not very specific: 10% of fatty liver will have autoantibodies
- Consider liver imaging
  - ultrasound
    - biliary obstruction
    - echogenicity (may be a false negative!)
- Consider liver biopsy?
Evaluation of Abnormal LFTS

- What if these tests are all normal?
- Is fatty liver (NAFLD) the most likely etiology?
  - How do you evaluate this?
  - How do you treat it?
    - weight loss, vitamin E, TZDs, fish oil
    - ?metformin?
NAFLD & NASH

- The morbidity and mortality from liver causes are greatly increased in patients with NASH, they correlate even more strongly with the morbidity and mortality from cardiovascular disease.

<table>
<thead>
<tr>
<th></th>
<th>Liver</th>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>0.2%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Simple Steatosis</td>
<td>0%</td>
<td>8.6%</td>
</tr>
<tr>
<td>NASH</td>
<td>1.6–6.8%</td>
<td>12.6–36%</td>
</tr>
</tbody>
</table>
**Nonalcoholic Fatty Liver Disease and Related Definitions**

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Nonalcoholic Fatty Liver Disease (NAFLD)</td>
<td>Encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis and cirrhosis.</td>
</tr>
<tr>
<td>Nonalcoholic Fatty Liver (NAFL)</td>
<td>Presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes or no evidence of fibrosis. The risk of progression to cirrhosis and liver failure is minimal.</td>
</tr>
<tr>
<td>Nonalcoholic steatohepatitis (NASH)</td>
<td>Presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis. This can progress to cirrhosis, liver failure and rarely liver cancer.</td>
</tr>
<tr>
<td>NASH Cirrhosis</td>
<td>Presence of cirrhosis with current or previous histological evidence of steatosis or steatohepatitis</td>
</tr>
<tr>
<td>Cryptogenic Cirrhosis</td>
<td>Presence of cirrhosis with no obvious etiology. Patients with cryptogenic cirrhosis are heavily enriched with metabolic risk factors such as obesity and metabolic syndrome.</td>
</tr>
<tr>
<td>NAFLD Activity Score (NAS)</td>
<td>An unweighted composite of steatosis, inflammation, and ballooning scores. It is a useful tool to measure changes in liver histology in patients with NAFLD in clinical trials.</td>
</tr>
</tbody>
</table>

![Image showing histological sections of liver: Steatosis (Macro-vesicular), Steatosis Inflammation & ballooning, Inflammation fibrosis.](image-url)
Fatty Liver Disease

Why Fish Oil?
Why Fish Oil for Fatty Liver?

- Fish oil lowers TGs and fatty liver is an accumulation of TGs in the liver
- Fish oil improves hepatic fat accumulation during parenteral nutrition
- Fish oil improves oxidative stress in the liver
- Fish oil may improve insulin sensitivity
The “Multiple Hit” Hypothesis of NAFLD Pathogenesis

Hepatocytes, Kupffer, and Stellate Cells All Contribute to NASH

Marra, F, et al, TRENDS in Molecular Medicine, 2007
Why Fish Oil for Fatty Liver?

√ Omega-3 fatty acids promote fatty acid degradation through increased β-oxidation resulting in reduced substrate for the synthesis of TG

J Clin Endocrinol Metab. 2009;94:3842-8
Fatty Liver Disease

What do we know about using fish oil in liver disease?
### Omega-3 supplementation & non-alcoholic fatty liver disease

**A systematic review and meta-analysis**

<table>
<thead>
<tr>
<th>Authors, year [Ref]</th>
<th>N (total)</th>
<th>Population (method of diagnosis); Gender; Mean BMI category</th>
<th>Dose n-3/day</th>
<th>Duration</th>
<th>Control</th>
<th>Other instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capponi et al., (2006) [45]</td>
<td>56</td>
<td>NAFLD (ultrasound); M/F; Overweight</td>
<td>1 g</td>
<td>12 mo</td>
<td>No treatment</td>
<td>-</td>
</tr>
<tr>
<td>Chen et al., (2008) [56]</td>
<td>46</td>
<td>NAFLD (elevated LFTs and TGs); M/F; Not specified</td>
<td>5 g</td>
<td>24 wk</td>
<td>Placebo</td>
<td>-</td>
</tr>
<tr>
<td>Cussons et al., (2009) [56]</td>
<td>25</td>
<td>Pre-menopausal women with PCOS; Obese</td>
<td>4 g</td>
<td>8 wk</td>
<td>Placebo</td>
<td>Maintain usual dietary and activity habits</td>
</tr>
<tr>
<td>Hatziililos et al., (2004) [46]</td>
<td>73</td>
<td>Mixed dyslipidemia (&gt;1 of: fasting serum cholesterol &gt;220 mg/dl; serum TG &gt;200 mg/dl; HDL &lt;45 mg/dl); M/F; Overweight</td>
<td>13.7 g</td>
<td>24 wk</td>
<td>Alternative medication (atorvastatin, orlistat)</td>
<td>BMI &gt;25; advised weight reduction</td>
</tr>
<tr>
<td>Sofi et al., (2010) [53]</td>
<td>11</td>
<td>Persistently (&gt;6 mo) elevated serum ALT + ultrasonographic features indicative of fatty liver; M/F; Overweight</td>
<td>0.83 g</td>
<td>12 mo</td>
<td>Placebo</td>
<td>Dietary recommendations (not specified)</td>
</tr>
<tr>
<td>Spadaro et al., (2008) [54]</td>
<td>36</td>
<td>NAFLD (elevated ALT + ultrasound); M/F; Obese</td>
<td>2 g</td>
<td>6 mo</td>
<td>No placebo</td>
<td>Calorie restricted AHA recommended diet</td>
</tr>
<tr>
<td>Tenaka et al., (2008) [47]</td>
<td>23</td>
<td>Biopsy-proven NASH; M/F; Obese</td>
<td>2.7 g</td>
<td>12 mo</td>
<td>-</td>
<td>Maintain usual medications, dietary and activity habits</td>
</tr>
<tr>
<td>Vega et al., (2008) [57]</td>
<td>16</td>
<td>Subset of DHS cohort: elevated HTGC (MRS), + average ALT within reference range; M/F; Obese</td>
<td>9 g</td>
<td>8 wk</td>
<td>Placebo</td>
<td>-</td>
</tr>
<tr>
<td>Zhu et al., (2008) [48]</td>
<td>134</td>
<td>NAFLD associated with mixed dyslipidaemia; M/F; Obese</td>
<td>2 g</td>
<td>24 wk</td>
<td>Placebo</td>
<td>AHA recommended diet; overweight and obese; advised caloric restriction (25-30 kcal/kg BW/day) for weight loss</td>
</tr>
</tbody>
</table>

Parker et al, J Hepatol. 2012 Apr;56(4):944-51
n-3 Polyunsaturated Fatty Acids in NAFLD

- **Treatment**: dietary treatment (n=20) + placebo or 1 gram bid PUFA (n=20) for 6 months
  - diet 50% carb, 20% protein & 30% fat
- **Steatosis eval** by ultrasound using a 4-point scale:
  - **grade 0**: normal echogenicity;
  - **grade 1**: slight, diffuse increase in fine echoes in liver parenchyma with normal visualization of diaphragm and intra-hepatic vessels borders
  - **grade 2**: moderate, diffuse increase in fine echoes with slightly impaired visualization of intra-hepatic vessels and diaphragm
  - **grade 3**: marked increase in fine echoes with poor or non-visualization of intra-hepatic vessel borders, diaphragm and posterior right lobe of the liver

*Spadaro et al, Digestive and Liver Disease 40 (2008) 194–199*
## n-3 Polyunsaturated Fatty Acids in NAFLD

Liver enzymes, γ-glutamyltransferase values, lipid parameters and ultrasound findings before and after treatment in the two study groups

<table>
<thead>
<tr>
<th></th>
<th>Diet alone</th>
<th></th>
<th>Diet + PUFA</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>59.7 ± 31.0</td>
<td>55.5 ± 31</td>
<td>56.6 ± 24.1</td>
<td>39.5 ± 14$\text{a}$</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>26.7 ± 8.8</td>
<td>27.8 ± 8.4</td>
<td>31.5 ± 13.2</td>
<td>28 ± 8.8</td>
</tr>
<tr>
<td>γ-GT (U/l)</td>
<td>41.5 ± 23</td>
<td>42.4 ± 21</td>
<td>39.3 ± 25.5</td>
<td>28.0 ± 17.1$\text{a}$</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>189.8 ± 43.2</td>
<td>191.7 ± 44.7</td>
<td>194.4 ± 26.8</td>
<td>189.4 ± 15.9</td>
</tr>
<tr>
<td>HDL–cholesterol (mg/dl)</td>
<td>47.6 ± 10</td>
<td>48 ± 8.7</td>
<td>43.5 ± 14.7</td>
<td>46.8 ± 12.9$\text{a}$</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>139.8 ± 47</td>
<td>135 ± 52</td>
<td>147.4 ± 41.1</td>
<td>110 ± 39.1$\text{a}$</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>3.08 ± 0.39</td>
<td>3.02 ± 0.67</td>
<td>3.34 ± 0.47</td>
<td>2.70 ± 0.52$\text{a}$</td>
</tr>
<tr>
<td>Steatosis degree 0/1/2/3 (%)</td>
<td>0/0/44/56</td>
<td>0/11.1/50/38.9</td>
<td>0/0/39/61</td>
<td>33.4/22.2/44.4/0</td>
</tr>
</tbody>
</table>

$\text{a}$ p value < 0.05.

$\text{a}$ p value < 0.01.

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**Fig. 1.** Effects of 6 months of diet (●) and diet + PUFA (□) treatment on HOMA-IR; *p < 0.05 for before vs. after treatment.
Effects of n-3 PUFAs from seal oils on NAFLD associated with hyperlipidemia

- Group A (n = 72) received recommended diet and 2 g n-3 PUFA from seal oils TID
- Group B (n = 72) received recommended diet and 2 g placebo TID
- Primary endpoints:
  - symptom scores, ALT and serum lipid levels after 8, 12, 16, and 24 wk.
  - Hepatic fat infiltration detected by ultrasonography at weeks 12 and 24

At week 24

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total symptom scores</td>
<td>0.42 ± 0.72&lt;sup&gt;a&lt;/sup&gt;&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.53 ± 0.97&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum ALT (U/L)</td>
<td>39.27 ± 18.94&lt;sup&gt;d&lt;/sup&gt;</td>
<td>42.32 ± 22.23&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum AST (U/L)</td>
<td>30.45 ± 12.67&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30.25 ± 14.21&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum GGT (U/L)</td>
<td>42.47 ± 26.84&lt;sup&gt;b&lt;/sup&gt;</td>
<td>58.43 ± 36.21&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum TCHO (mmol/L)</td>
<td>5.08 ± 0.76&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.21 ± 1.22&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum TG (mmol/L)</td>
<td>2.08 ± 1.03&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.38 ± 1.42&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum HDL-C (mmol/L)</td>
<td>1.25 ± 0.25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.20 ± 0.21&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum LDL-C (mmol/L)</td>
<td>3.12 ± 0.84&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.11 ± 0.78</td>
</tr>
<tr>
<td>Steatosis degree 0/1/2/3 (%)</td>
<td>20/64/12/4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>7/51/36/6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*World J Gastro 2008;14: 6395-6400*
Liver Fat content (HTGC) by MR Spectroscopy after Fish Oil Therapy x 8 weeks

- **sequential design:**
  - 4 weeks of placebo followed by 8 weeks of treatment with 9 g/d of fish oil

- **evaluation:**
  - Changes in HTGC (by MRS), body weight, vital signs, plasma lipoprotein and apo B levels

<table>
<thead>
<tr>
<th>TABLE 1. Patient Demography and Clinical Characteristics</th>
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<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
</tr>
<tr>
<td>Liver triglyceride</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
</tr>
<tr>
<td>VLDL + IDL cholesterol (mg/dL)</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
</tr>
<tr>
<td>Total Apo B (mg/dL)</td>
</tr>
</tbody>
</table>

ALT indicates alanine transaminase; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

**FIGURE 2.** Concomitant changes in plasma triglyceride levels and liver triglyceride content during treatment with fish oil.

Highly Purified EPA Treatment Improves NASH

- Biopsy confirmed NASH (14 men/9 women)
- Treatment x 12 months:
  - Highly (>98%) purified EPA ethyl ester (ethyl all-cis-5, 8, 11, 14, 17-icosapentaenoate)
  - 2700 mg/day, maximum dose certified by Japanese medical insurance system
- 7/23 underwent posttreatment liver biopsy
  - 6/7 biopsies showed improvement of
    - steatosis
    - fibrosis
    - hepatocyte ballooning
    - lobular inflammation

Tanaka et al, J Clin Gastroenterol 2008;42:413–418
Omega-3 FA supplementation decreases liver fat content in PCOS: an RCT employing proton MRS

- 25 women with PCOS
- double-blinded with a randomized crossover design
- 8 weeks of 4 g daily of omega-3 fatty acids (56% DHA/27% EPA) or control (capsules of olive oil containing 67% oleic acid)
- followed by an 8-wk washout period then the alternate supplement capsules for another 8 wk

| TABLE 2. Comparison of the effects of omega-3 fatty acids and placebo on biochemistry, liver fat, and blood pressure in 25 subjects with PCOS |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | Placebo         | Omega-3 fatty acids | Group difference | P value         |
| BWT (kg/m²)                   | 35.1 (7.0)      | 34.8 (6.6)        | 0.3 (0.7)        | 0.157           |
| Waist-hip ratio               | 0.91 (0.09)     | 0.90 (0.06)       | 0.01 (0.09)      | 0.506           |
| Liver fat (%)                 | 10.2 (1.1)      | 8.4 (0.9)         | 1.8 (3.6)        | 0.022           |
| ALT (U/liter)                 | 25.52 (23.08)   | 27.36 (10.52)     | -1.84 (21.04)    | 0.911           |
| SBP (mm Hg)                   | 124.1 (12.1)    | 122.3 (14.5)      | 1.8 (13.8)       | 0.018           |
| DBP (mm Hg)                   | 73.2 (8.4)      | 69.7 (6.3)        | 3.6 (7.0)        | 0.005           |
| Cholesterol (mmol/liter)      | 4.71 (0.99)     | 4.70 (1.07)       | 0.01 (0.54)      | 0.918           |
| Triglycerides (mmol/liter)    | 1.19 (1.03–1.47) | 1.02 (0.93–1.18)  | 0.85 (0.73–0.99) | 0.002           |
| LDL (mmol/liter)              | 2.76 (0.90)     | 2.82 (0.83)       | -0.06 (0.53)     | 0.723           |
| HDL (mmol/liter)              | 1.34 (0.30)     | 1.39 (0.33)       | -0.05 (0.20)     | 0.454           |
| NEFA (mmol/liter)             | 0.44 (0.18)     | 0.40 (0.18)       | 0.04 (0.14)      | 0.345           |
| Glucose (mmol/liter)          | 4.94 (0.82)     | 5.05 (0.82)       | -0.11 (0.30)     | 0.140           |
| Insulin (mU/liter)            | 13.13 (8.68)    | 12.02 (6.87)      | 1.11 (3.62)      | 0.235           |
| HOMA-IR                       | 3.01 (2.33)     | 2.78 (2.01)       | 0.23 (0.96)      | 0.243           |
| hs-CRP (mg/liter)             | 7.47 (8.00)     | 7.15 (8.47)       | 0.31 (4.90)      | 0.942           |
| Testosterone (nmol/liter)     | 1.28 (0.88)     | 1.37 (0.73)       | -0.09 (0.46)     | 0.551           |
| SHBG (nmol/liter)             | 72.77 (77.20)   | 73.06 (83.45)     | -0.29 (20.00)    | 0.296           |
| Free androgen index           | 3.76 (3.47)     | 4.43 (3.59)       | -0.67 (2.96)     | 0.242           |

Data are expressed as mean (SD), except for triglycerides and group difference scores for transformed variables, which are expressed as geometric mean (95% CI).
Omega-3 FA supplementation decreases liver fat content in PCOS: an RCT employing proton MRS

- 25 women with PCOS
- double-blinded with a randomized crossover design

| TABLE 3. Comparison of the effects of omega-3 fatty acids and placebo on biochemistry, blood pressure, and liver fat in NLF and HLF subgroups |
|---------------------------------|----------------|----------|----------------|----------------|
|                                | NLF (≤5%) (n = 13) | HLF (>5%) (n = 12) |                 |                 |
|                                | Placebo          | Omega-3 fatty acids | P value | Placebo          | Omega-3 fatty acids | P value |
| BMI (kg/m^2)                   | 32.0 (5.1)       | 31.8 (4.5)         | 0.681   | 38.5 (7.5)       | 38.1 (7.1)         | 0.147   |
| Waist hip ratio                | 0.90 (0.05)      | 0.90 (0.05)        | 0.185   | 0.94 (0.1)       | 0.91 (0.1)        | 0.293   |
| Liver fat (%)                  | 2.7 (1.5)        | 2.4 (1.8)          | 0.303   | 18.2 (11.1)      | 14.8 (9.3)        | 0.03    |
| ALT (IU/liter)                 | 17.77 (5.85)     | 22.31 (9.18)       | 0.260   | 33.9 (31.3)      | 32.8 (9.3)        | 0.389   |
| SBP (mm Hg)                    | 120.6 (10.8)     | 117.4 (9.6)        | 0.002   | 127.9 (12.8)     | 127.6 (17.4)      | 0.691   |
| DBP (mm Hg)                    | 72.1 (7.0)       | 68.5 (6.8)         | 0.06    | 74.4 (9.9)       | 70.9 (9.8)        | 0.095   |
| Cholesterol (mmol/liter)       | 4.50 (0.66)      | 4.52 (0.69)        | 0.994   | 4.93 (1.24)      | 4.91 (1.38)       | 0.882   |
| Triglycerides (mmol/liter)     | 1.03 (0.74–1.42) | 0.88 (0.74–1.06)   | 0.142   | 1.41 (1.20–1.62) | 1.18 (1.00–1.39)  | 0.012   |
| LDL (mmol/liter)               | 2.58 (0.62)      | 2.66 (0.59)        | 0.888   | 2.97 (1.11)      | 3.00 (1.03)       | 0.580   |
| HDL (mmol/liter)               | 1.34 (0.34)      | 1.43 (0.30)        | 0.089   | 1.32 (0.25)      | 1.35 (0.38)       | 0.820   |
| NEFA (mmol/liter)              | 0.35 (0.11)      | 0.31 (0.12)        | 0.282   | 0.53 (0.21)      | 0.49 (0.19)       | 0.774   |
| Glucose (mmol/liter)           | 4.66 (0.28)      | 4.85 (0.33)        | 0.143   | 5.24 (1.1)       | 5.27 (1.1)        | 0.765   |
| Insulin (mU/liter)             | 8.05 (4.91)      | 8.29 (2.85)        | 0.804   | 18.63 (8.63)     | 16.06 (7.74)      | 0.038   |
| HOMA-IR                        | 1.67 (1.02)      | 1.78 (0.57)        | 0.631   | 4.47 (2.51)      | 3.87 (2.44)       | 0.021   |
| hs-CRP (mg/liter)              | 5.34 (6.57)      | 4.32 (7.51)        | 0.231   | 9.75 (9.04)      | 10.21 (8.68)      | 0.926   |
| Testosterone (nmol/liter)      | 1.25 (0.72)      | 1.38 (0.81)        | 0.379   | 1.33 (1.06)      | 1.36 (0.68)       | 0.981   |
| SHBG (nmol/liter)              | 87.78 (94.12)    | 87.45 (106.14)     | 0.218   | 56.5 (52.7)      | 57.5 (49.0)       | 0.482   |
| Free androgen index            | 3.47 (3.46)      | 4.56 (4.39)        | 0.345   | 4.08 (3.6)       | 4.28 (3.45)       | 0.560   |

Data are expressed as mean (SD), except for triglycerides and group difference scores for transformed variables, which are expressed as geometric mean (95% CI).
Omega-3 PUFAs & NAFLD

- Improvement in multiple parameters has been demonstrated from a variety of sources
  - Seal oil
  - Sigma-Tau Pharmaceutical Company, Rome, Italy
  - Fish rich in omega-3
  - Local drug store
- Purified EPA currently being tested in several large multicenter trials in adult & pediatric populations
34 trials of fatty liver + fish oil
– 11 open/recruiting

WELCOME Trial

DHA/EPA vs Olive oil in NAFLD
Double-Blind, Placebo-Controlled Study of Two Doses of EPA-E in Patients With Non Alcoholic Steatohepatitis (NASH)

This study has been completed.

Sponsor:
Mochida Pharmaceutical Company, Ltd.

Information provided by (Responsible Party):
Mochida Pharmaceutical Company, Ltd.

ClinicalTrials.gov identifier:
NCT01154985

First received: June 29, 2010
Last updated: January 8, 2014
Last verified: October 2013

Purpose

This is a controlled study to determine the effectiveness and safety of ethyl icosapentate (EPA-E) in the treatment of adult patients with non-alcoholic steatohepatitis (NASH).
AASLD PRACTICE GUIDELINE

The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

Naga Chalasani, MD, FACG, Zobair Younossi, MD, FACG, Joel E. Lavine, MD, PhD, Anna Mae Diehl, MD, Elizabeth M. Brunt, MD, Kenneth Cusi, MD, Michael Charlton, MD, and Arun J. Sanyal, MD
Management Strategy for NAFLD

Fig. 3  Management algorithm for NAFLD. Based on Rafiq and Younossi [10].

- Persistent elevation of liver enzymes
  - Exclude other liver disease
  - Risk factors? E.g., metabolic syndrome, insulin resistance, etc.
    - Yes
      - Diet/exercise
      - Treat metabolic syndrome
    - No
      - Potential signs of cirrhosis
        - Hard edge, AST > ALT, low albumin or platelets
        - Abnormal ALT after 6 months
        - Consider liver biopsy

Liver biopsy

- Simple steatosis
  - Liver prognosis good
  - Treat cardiac risks
- NASH
  - Treat associated conditions

BMI < 35 or overweight
- Diet and exercise
- Behavior modification
- Medical treatment
- Protocol treatment

BMI > 40 or > 35 + risk factor
- Diet/exercise
- Behavior modification
- Bariatric surgery?
Research Questions

- Metabolic Liver Evaluation
  - OGTT with glucose, insulin & proinsulin levels
  - Stimulated c-peptide
  - MRI and/or ultrasound
  - NASH FibroSURE™
  - BMI, waist circumference, waist-height ratio
Summary
NAFLD, NASH, Cirrhosis

- The natural history of FLD is to progress to cirrhosis and/or hepatocellular carcinoma over 20 years
- Hepatocellular carcinoma may develop in the presence or absence of cirrhosis
- Abnormal LFTs should be rechecked and not ignored
- While awaiting randomized controlled clinical trials (RCTs) treatment with omega-3 fish oil should be part of our armamentarium
Questions?
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