Evaluation and Treatment of Hypertriglyceridemia

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John Brunzell, M.D.
Disclosures

• Lars Berglund, MD, PhD: Consultant, Danone; Stockholder, Novo Nordisk, Pfizer

• John Brunzell, MD, No relevant financial relationships

Learning Objectives

Upon completion of this educational activity, learners will be able to:

– Recognize of the extent of hypertriglyceridemia across age, gender and ethnicity
– Define and classify hypertriglyceridemia
– Identify primary and secondary causes of hypertriglyceridemia
– Apply recommended approaches to treatment of hypertriglyceridemia
Triglycerides and disease

- Mild and moderate hypertriglyceridemia – risk factor for cardiovascular disease
- Severe and very severe hypertriglyceridemia – risk factor for pancreatitis
- Expanded classification of hypertriglyceridemia compared to NCEP ATP III – focus attention on triglyceride levels as risk factor for pancreatitis. Little risk at levels from 500 to 999 mg/dl

Classification of hypertriglyceridemia

<table>
<thead>
<tr>
<th>Criteria proposed for clinical diagnosis of elevated triglyceride levels under fasting conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCEP ATP III (mg/dl)</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Borderline-high triglycerides</td>
</tr>
<tr>
<td>High triglycerides</td>
</tr>
<tr>
<td>Very high triglycerides</td>
</tr>
<tr>
<td>Very severe hypertriglyceridemia</td>
</tr>
</tbody>
</table>
Classification of hypertriglyceridemia

Table 1.
Criteria proposed for clinical diagnosis of elevated triglyceride levels under fasting conditions

<table>
<thead>
<tr>
<th>Classification</th>
<th>NCEP ATP III (1)</th>
<th>The Endocrine Society 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;150 mg/dl</td>
<td>&lt;1.7 mmol/liter</td>
</tr>
<tr>
<td>Borderline-high</td>
<td>150-199 mg/dl</td>
<td>1.7-2.3 mmol/liter</td>
</tr>
<tr>
<td>High</td>
<td>200-499 mg/dl</td>
<td>2.3-5.6 mmol/liter</td>
</tr>
<tr>
<td>Very high</td>
<td>≥500 mg/dl</td>
<td>≥5.6 mmol/liter</td>
</tr>
<tr>
<td>Severe hypertriglyceridemia</td>
<td>1000-1999 mg/dl</td>
<td>11.2-22.4 mmol/liter</td>
</tr>
<tr>
<td>Very severe</td>
<td>≥2000 mg/dl</td>
<td>≥22.4 mmol/liter</td>
</tr>
</tbody>
</table>

Christian et al. Am J Cardiol 2011

Hypertriglyceridemia – component in risk factor constellation

- Genetic HTG disorders are common.
- Elevated triglycerides commonly seen with other metabolic abnormalities: untreated diabetes, overweight, certain medications including alcohol
- Often combination of genetic factors and acquired disorders occur together and cause higher triglyceride levels.
### Hypertriglyceridemia across age, gender and ethnicity

#### Meta-analysis of triglycerides as cardiovascular risk factor

- 35 studies with 927,218 participants
- 132,460 deaths and 72,654 cardiac events
- Hypertriglyceridemia significantly associated with:
  - Cardiovascular death – OR 1.80 (1.31-2.49)
  - Cardiovascular events – OR 1.37 (1.23-1.53)
  - Myocardial infarction – OR 1.31 (1.15-1.49)
- Hypertriglyceridemia associated with pancreatitis – OR 3.96 (1.27-12.34)
- No significant association with total mortality

*Murad MH et al, BMC Endocrine Dis 2012; 12: 2*
Study selection process

Potentially relevant studies identified by search (n=765)

- Excluded after abstract screening (n=576)

Articles selected for full text retrieval (n=189)

- Excluded after full-text screening (n=126)
  - Studies with no original data (n=8)
  - Ineligible populations (n=16)
  - No association of varying TG levels (n=46)
  - Irrelevant outcomes (n=41)
  - Unobtainable full text (n=16)

Studies that fulfilled inclusion criteria (n=60)

Studies included in review (n=58)

Studies with insufficient data for analysis (n=58)

Murad MH et al, BMC Endocrine Dis 2012; 12: 2

Triglycerides and cardiovascular death

Cardiovascular death

<table>
<thead>
<tr>
<th>Statistics for each study</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Lower Upper limit limit p-Value</td>
</tr>
<tr>
<td>Barnett Connex, 1987</td>
<td>0.60 0.99 1.11 1.00</td>
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<tr>
<td>Beck, 1993</td>
<td>0.42 0.91 1.00 0.00</td>
</tr>
<tr>
<td>Chen, 2005</td>
<td>2.67 1.09 8.03 0.05</td>
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<tr>
<td>Ebeling, 2003</td>
<td>1.20 0.59 1.61 0.00</td>
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<tr>
<td>Ellingan, 2003</td>
<td>1.43 0.58 2.31 0.15</td>
</tr>
<tr>
<td>Mazze, 2005</td>
<td>2.49 1.48 4.10 0.00</td>
</tr>
<tr>
<td>Tanko, 2005</td>
<td>3.10 1.40 6.85 0.01</td>
</tr>
<tr>
<td>Tal, 2008</td>
<td>1.65 0.76 1.73 0.44</td>
</tr>
<tr>
<td>Wei, 2003</td>
<td>1.56 1.44 2.10 0.00</td>
</tr>
<tr>
<td></td>
<td>1.80 1.31 2.49 0.00</td>
</tr>
</tbody>
</table>

Meta Analysis

Murad MH et al, BMC Endocrine Dis 2012; 12: 2
Triglycerides and cardiovascular events

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achariya, 2004</td>
<td>1.62</td>
<td>1.02</td>
<td>3.58</td>
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<tr>
<td>Barsal, 2007</td>
<td>1.11</td>
<td>0.92</td>
<td>1.34</td>
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<tr>
<td>Bonanventura, 2010</td>
<td>1.49</td>
<td>1.24</td>
<td>1.79</td>
</tr>
<tr>
<td>Chawer, 1995</td>
<td>2.30</td>
<td>1.68</td>
<td>3.16</td>
</tr>
<tr>
<td>Czernichow, 2007</td>
<td>1.30</td>
<td>1.21</td>
<td>1.19</td>
</tr>
<tr>
<td>Dreyer, 2005</td>
<td>1.17</td>
<td>1.00</td>
<td>1.37</td>
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<tr>
<td>Effer, 2003</td>
<td>1.64</td>
<td>1.20</td>
<td>2.34</td>
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<tr>
<td>Eggen, 1999</td>
<td>1.12</td>
<td>0.88</td>
<td>1.43</td>
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<tr>
<td>Goldberg, 2009</td>
<td>0.66</td>
<td>0.26</td>
<td>2.09</td>
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<tr>
<td>Hoogenraad, 2001</td>
<td>1.07</td>
<td>0.96</td>
<td>1.16</td>
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<tr>
<td>Laranjeira, 1995</td>
<td>0.30</td>
<td>0.54</td>
<td>0.68</td>
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<tr>
<td>Lu, 2003</td>
<td>1.42</td>
<td>1.11</td>
<td>1.81</td>
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<tr>
<td>Men, 2008</td>
<td>1.47</td>
<td>1.00</td>
<td>1.16</td>
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<tr>
<td>Rubens, 1999</td>
<td>1.12</td>
<td>0.86</td>
<td>1.46</td>
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<td>Samuelsson, 1994</td>
<td>1.21</td>
<td>1.03</td>
<td>1.43</td>
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<tr>
<td>Valdivielso, 2009</td>
<td>4.41</td>
<td>1.59</td>
<td>12.22</td>
</tr>
<tr>
<td>1.37</td>
<td>1.23</td>
<td>1.53</td>
<td>0.00</td>
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</tbody>
</table>

Meta Analysis

Triglycerides and myocardial infarction

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Datziano, 1997</td>
<td>2.70</td>
<td>1.36</td>
<td>5.35</td>
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<tr>
<td>Jones et al, 2002 (men)</td>
<td>1.21</td>
<td>1.08</td>
<td>1.38</td>
</tr>
<tr>
<td>Jones et al, 2002 (women)</td>
<td>1.40</td>
<td>1.15</td>
<td>1.70</td>
</tr>
<tr>
<td>Lu, 2003</td>
<td>2.04</td>
<td>1.12</td>
<td>3.72</td>
</tr>
<tr>
<td>Malek, 2009</td>
<td>1.17</td>
<td>1.06</td>
<td>1.27</td>
</tr>
<tr>
<td>Nada, 2010</td>
<td>1.48</td>
<td>0.89</td>
<td>2.33</td>
</tr>
<tr>
<td>1.31</td>
<td>1.15</td>
<td>1.49</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Meta Analysis

Murad MH et al, BMC Endocrine Dis 2012; 12: 2
Triglycerides and total mortality – no significant association

Murad MH et al, BMC Endocrine Dis 2012; 12: 2

Non-fasting triglycerides - association with cardiovascular disease

• Non-fasting triglycerides predictive of cardiovascular events in prospective studies in the general population
• MRFIT study: Average fasting (187 mg/dl) and non-fasting (284 mg/dl) triglyceride levels predictive of coronary heart disease (HR .64; 1.46).
• Copenhagen City Heart Study: Trend for increasing non-fasting triglyceride levels significant for MI, IHD and mortality.
• Women’s Health Study: Significant trend for association of higher non-fasting triglyceride levels with cardiovascular events
Non-fasting triglycerides - association with cardiovascular disease

- Non-fasting triglycerides predictive of cardiovascular events in prospective studies in the general population
- MRFIT study: Average fasting (187 mg/dl) and non-fasting (284 mg/dl) triglyceride levels predictive of coronary heart disease (HR .64; 1.46). Times
- Copenhagen City Heart Study: Trend for increasing non-fasting triglyceride levels significant for MI, IHD and mortality. No fasting sample
- Women’s Health Study: Significant trend for association of higher non-fasting triglyceride levels with cardiovascular events. Non-compliance

Non-fasting triglycerides – additional issues to be resolved

- Lack of standardized collection procedures
- Need to establish reference levels
- Impact of variability of postprandial time period
Causes of hypertriglyceridemia (I)

• Primary hypertriglyceridemia
  – FCHL, Familial combined hyperlipidemia
  – FHTG, Familial hypertriglyceridemia
  – Familial dysbetalipoproteinemia
  – FHA, Familial hypoalphalipoproteinemia

• Primary genetic susceptibility
  – Metabolic syndrome
  – Treated diabetes mellitus type 2

Causes of hypertriglyceridemia (II)

• Secondary hypertriglyceridemia
  – Untreated diabetes mellitus
  – Drug-induced conditions, including excess alcohol intake
  – Endocrine diseases
  – Renal disease
  – Liver disease
  – Pregnancy
  – Autoimmune disorders
Familial combined hyperlipidemia (FCHL)

- Population prevalence 1-2%
- Common among patients with cardiovascular disease – frequency about 10%
- Variable phenotype: TG/LDL cholesterol
- ApoB levels increased and small, dense LDL particles present

Familial hypertriglyceridemia (FHTG)

- Population prevalence 1%
- Increased triglyceride synthesis resulting in large VLDL particles
- Triglyceride levels usually in moderate range (<1,000 mg/dl).
- Commonly low LDL and HDL cholesterol levels
- Generally asymptomatic and usually no family history of cardiovascular disease
Familial Hypoalphalipoproteinemia (FHA)

- Described in 1980s by Genest et al.
- Low HDL cholesterol, often with hypertriglyceridemia
- Premature coronary artery disease
- Condition not well characterized
- BG Brown et al. HDL atherosclerosis treatment study (HATS) NEJM 2000. Statin and niacin decreased stenosis and events.
- Lipoproteins pattern similar to FHTG

Chylomicronemia syndrome

- Severe and very severe hypertriglyceridemia
- Associated with pancreatitis – reduced risk if triglyceride levels maintained <1,000 mg/dl
- Genetic defect usually combined with acquired lipoprotein disorder (e.g. untreated diabetes mellitus type 2).
Dysbetalipoproteinemia (type III)

- Associated with apoE genetic variant (usually apoE2 homozygosity)
- Second genetic or acquired defect needed to precipitate syndrome
- Accumulation of triglyceride-rich lipoprotein remnants – hypertriglyceridemia (and hypercholesterolemia) in moderate range (<1,000 mg/dl). Palmar xanthomas.
- Frequency about 1/10,000

Metabolic syndrome

- Hypertriglyceridemia a component of the syndrome
- Important to consider FCHL among subjects with metabolic syndrome, glucose disorders and polycystic ovary syndrome
- Increase in long-chain unesterified fatty acid hepatic delivery suggested as contributory
Management of hypertriglyceridemia

- Lifestyle therapy
  - Diet composition
  - Physical activity
  - Weight reduction
- Drug therapy: use statins
  - Fibrates
  - N-3 fatty acids
  - Niacin

Association between BMI and hypertriglyceridemia

<table>
<thead>
<tr>
<th>BMI</th>
<th>TG ≥ 150 mg/dl (n=1,744)</th>
<th>TG ≥ 200 mg/dl (n=937)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>20.1 %</td>
<td>17.5 %</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>39.9 %</td>
<td>39.6 %</td>
</tr>
<tr>
<td>≥ 30</td>
<td>39.9 %</td>
<td>42.9 %</td>
</tr>
</tbody>
</table>

Miller M et al, Circulation (2011) 123, 2292
Diet and hypertriglyceridemia: efficiency of approaches

Miller M et al, Circulation (2011) 123, 2292

Simple sugars and triglycerides – dietary sources

Johnson RK et al, Circulation (2009), 120: 1011
Hypertriglyceridemic diet – key points

- Decrease in saturated fat intake, replace calories with PUFA, MUFA or complex carbohydrates.
- Decrease in simple sugars
- Attempt to normalize weight

Triglyceride-lowering drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Triglyceride Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrates</td>
<td>30-50</td>
</tr>
<tr>
<td>Immediate-release niacin</td>
<td>20-50</td>
</tr>
<tr>
<td>Omega-3</td>
<td>20-50</td>
</tr>
<tr>
<td>Extended-release niacin</td>
<td>10-30</td>
</tr>
<tr>
<td>Statins</td>
<td>10-30</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>5-10</td>
</tr>
</tbody>
</table>

Miller M et al, Circulation (2011) 123, 2292
Fibrates and cardiovascular disease: Gemfibrozil reduces cardiac events in VA-HIT study

Rubins H et al, NEJM 1999; 341: 410

VA-HIT study: Gemfibrozil reduced triglycerides and increased HDL-cholesterol

Rubins H et al, NEJM 1999; 341: 410
Combination therapy statins/fenofibrate reduced TG levels in D2M

Combination therapy fenofibrate/statins: No impact on cardiovascular events or mortality

ACCORD Study Group, NEJM 2010; 362: 1563
Fibrates & CVD Meta-analysis

2870/45,058

• Events: 10% major CVE  \( p = .048 \)
  13% coronary events  \( p < .001 \)

• Mortality: 0% all cause  \( p = .92 \)
  3% CV  \( p = .59 \)

• Baseline: TG  \( p = .030 \)
  HDL cholesterol  \( p = .474 \)

Jun et al. Lancet 2010; 375:1875

N-3 fatty acids and reduction of triglycerides

Adjusted for Placebo Effect

Musa-Veloso et al, Nutr Rev 2010; 68: 155
Metaanalysis Fish Oil

- N=68,680 patients in 20 large RCT studies
- “Overall, omega-3PUFA supplementation was not associated with a lower risk of all-cause mortality, cardiac death, myocardial infarction, or stroke based on relative and absolute measures of association.”

Rizos et al. JAMA 2012; 308:1024-1033

Elevated TG is marker for:

- Increased small-dense LDL particles
- Increase IDL (or remnant lipoproteins)
- Decreased HDL₂ cholesterol
- Little evidence TG is direct cause of CAD

Brunzell NEJM 2007; 357:1009
In Hypertriglyceridemia: Combination Therapy

**GOAL**
- ↓ LDL Cholesterol
- ↓ small, dense LDL
- HDL<sub>2</sub> Cholesterol
- All of above

**DRUG**
- Statin
- Nicotinic acid
- Nicotinic acid?
- Both

Niacin Therapy in HTG

- Old studies consistent benefit, but too small CDP, FATS, HATS, etc.
- Aim High: Raising HDLc not of benefit in patients with low LDLc and TG
- HPS 2 Thrive pending, analysis started
Rx of Moderate HT

- Goal: to decrease triglyceride: fibrate/fish oil

- Goal: to use triglyceride as marker for LDL heterogeneity: use niacin.

- Not clear which is best.

Recommendations (1)

- Screening adults for hypertriglyceridemia every 5 yrs
- Diagnosis of hypertriglyceridemia based on fasting triglyceride levels
- Recommend against routine measurement of lipoprotein particle heterogeneity in hypertriglyceridemic patients, use Non-HDLc
- Measurement of apoB and Lp(a) can be of value
Recommendations (II)

- Subjects with elevated fasting triglyceride should be evaluated for and receive appropriate treatment for secondary causes of hyperlipidemia
- Patients with primary hypertriglyceridemia should be assessed for other cardiovascular risk factors
- Patients with primary hypertriglyceridemia should be evaluated for family history of dyslipidemia and cardiovascular disease

Recommendations (III)

- Lifestyle therapy as initial treatment for mild-moderate hypertriglyceridemia
- Combine reduction of dietary fat and simple carbohydrate intake with drug therapy in patients with severe and very severe hypertriglyceridemia
- Treatment goal should be non-HDL cholesterol in agreement with NCEP ATP guidelines
- Fibrate used as first line therapy in patients at risk for triglyceride-induced pancreatitis
Recommendations (IV)

• Statins not used as monotherapy for severe or very severe hypertriglyceridemia.
• Consider three drug classes (fibrates, n-3 fatty acids, niacin) alone or in combination for treatment of moderate-severe hypertriglyceridemia

Acknowledgments

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European Society of Endocrinology