Role of Triglyceride-enriched Lipoproteins in Atherogenesis

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Triglycerides and Remnant Lipoproteins

- Severe hypertriglyceridemia is an established risk factor for pancreatitis.
- Elevated triglycerides also correlate with increased risk for acute cardiovascular events.
- Triglycerides are hydrophobic and do not circulate freely. They are carried in plasma by lipoproteins.
- Hypertriglyceridemia is associated with elevated remnant lipoproteins.
- A remnant lipoprotein is a lipoprotein whose triglyceride content is incompletely hydrolyzed, thereby preventing its progressive conversion to smaller lipoproteins (i.e., VLDL to IDL to LDL).
- Though definitions may vary, in the nonfasting state, remnants include chylomicron remnants, VLDL remnants, and IDL; in the fasting state VLDL remnants (principally small VLDL3 and IDL).
- Remnants could be atherogenic because of both cholesterol and triglyceride components are carried into subendothelial space. Triglycerides are a source of diacylglycerol and free fatty acids, both of which can participate in augmenting the inflammatory response.
Remnant Lipoprotein Cholesterol

- Lipoprotein cholesterol as a function of increasing levels of nonfasting triglycerides
  - Increased levels of plasma triglycerides were associated with increased levels of remnant cholesterol and with reduced levels of HDL cholesterol, while association with LDL cholesterol was less pronounced.


Remnant Lipoproteins (RLPs)

- Serum lipids are measured typically after 8-12 hours of fasting.
- In Western societies, during routine daily living, the majority of people are persistently post-prandial. In fact, meals tend to be consumed before the lipids and lipoproteins from the preceding meal are fully metabolized and cleared from the circulation.
- Consequently, we are exposed to much higher levels of RLPs and in a more persistent manner than what is suggested by the results of studies using fasting lipid samples.
- This would be especially true of patients afflicted with genetic variants of hypertriglyceridemia (familial combined hyperlipidemia, familial hypertriglyceridemia, a variety of lipoprotein lipase deficiency states), insulin resistance, or established diabetes mellitus. As found in adults, RLPs are elevated in obese or diabetic children and adolescents.
The half-life of VLDL is about 30-60 minutes; the half-life of IDL is even shorter.
The LDL particles have a much longer half-life in circulation (~2-3 days) compared to chylomicrons, VLDLs and IDLs, and account for the bulk of the plasma apoB-containing lipoproteins.

Directly measured apoB is considered roughly equivalent to the "LDL particle number," as generally 90%-95% of the apoB-containing particles in circulation are actually LDLs.

Multiple proteins are at play in regulating lipolytic pathways.
- ApoE, C-II, and apoA-V are activators of lipolysis
- C-III and Angptl3 and 4 are inhibitors.


Commonly used LPL inhibitors include: 
- LPL-specific inhibitors (e.g., Lipostat®)
- Non-LPL inhibitors (e.g., fibrates, statins)

It is important to further delineate how HTG is diagnosed and treated in the US and try to further establish the relationship between HTG and risk of pancreatitis.
Triglyceride (TG)–rich lipoproteins (LPs) containing a single molecule of apolipoprotein B are released into the circulation by the liver or intestine and bind the LPL on the surface of endothelial cells. CETP activity and lipolysis of TG–rich LPs by LPL yields a TG–depleted but cholesterol–rich remnant LP (RLP) which can cross the endothelial barrier. Unlike native LDL, RLPs do not have to be oxidatively modified and can be taken up in an unregulated fashion by scavenger receptors expressed by resident macrophages in the subendothelial space, facilitating foam cell formation and atherosclerosis.

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Postprandial Change in Lipids and Flow Mediated Dilation after Oral Fat Load

15 moderately overweight & dyslipidemic men with baseline TG of 210 and HDL of 39 given an oral fat load.

TG & RLP-C increased significantly and continuously up to 4 & 6 hours respectively.

FMD revealed decreased vasodilation at 4-6 hours.

RLP contribute significantly to impair endothelial dilation.

Oral Triglyceride Tolerance Test

Triglycerides (mg/dL)

Nondiabetics

Diabetics

Time After Oral Fat Load (hours)
Postprandial Triglyceride Levels in Subjects With and Without Coronary Artery Disease

- Time elapsed between ingestion of the test meal and the triglyceride peak also distinguished cases from controls.
  - A majority of cases (57.4%) displayed peak triglyceride concentrations at 6 hours after the test meal and the majority of control subjects (67.5%) at 4 hours.
  - Shape of average postprandial triglyceride curves differed conspicuously in that curve was still rising between 4 and 6 hours in cases while in control subjects it was already falling.


Women's Health Study: Fasting versus Nonfasting Triglycerides

<table>
<thead>
<tr>
<th>Time from Last Meal (hrs)</th>
<th># patients</th>
<th># Events</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - &lt;4</td>
<td>2257</td>
<td>68</td>
<td>4.48 (1.26-15.15)</td>
</tr>
<tr>
<td>4 - 8</td>
<td>4644</td>
<td>127</td>
<td>1.05 (0.73-1.52)</td>
</tr>
<tr>
<td>8 - 12</td>
<td>10372</td>
<td>686</td>
<td>1.96 (1.36-2.82)</td>
</tr>
<tr>
<td>≥ 12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Association of TG with Future CV Events Stratified by Time from Last Meal

- Fully adjusted HR (95% CI)

Association of TG with Individual CV Endpoints according to fasting status

Association of High vs Low TG levels with future CV events stratified by HDL-C level

Women's Ischemia Syndrome Evaluation (WISE): The TG/HDL-C Ratio

Kaplan-Meier curves for freedom from cardiovascular events by TG/HDL-C quartile. Quartile 1 (Q1) through Q4 correspond to the quintiles of TG/HDL-C.

Excess risk of cardiovascular events is limited to individuals in Q4 of the TG/HDL-C distribution.

Mean follow-up time for surviving women was 5.6 ± 2.2 years (median 6.0 years; range 3.7 - 7.3 years).

Remnant Lipoproteins

- The suggestion that RLPs contribute to atherogenesis was first made by Zilversmit in 1979. (Zilversmit DB. Circulation 1979;60:473-485.)
- Remnants correlate significantly with risk for CV events.
- In the Framingham Offspring Study, serum levels of RLPs correlate with risk for CV events in women with established coronary artery disease (CAD). (Makelmura JR, et al. Atherosclerosis. 2001;154:229-236.)
- Similarly in the Honolulu Heart Study, serum levels of RLPs were significantly associated with risk for CV events among men of Asian descent. (Imke C, et al. Atheroscler Thromb Vasc Biol. 2005;25:1718-1722.)
- Among patients with Fredrickson type III dyslipoproteinemia (familial dysbetalipoproteinemia, due to defective apoE), serum remnants are increased leading to the development of xanthomas and elevated risk for CV events. (Vermeer BJ, et al. J Invest Dermatol. 1992;98:57S-60S.)

Remnant Cholesterol as a Causal Risk Factor for Ischemic Heart Disease

- As remnants progressively increase from first to fifth quintile, there is a rising gradient of risk for future CHD.
  - A nonfasting remnant cholesterol increase of 1 mmol/L (39 mg/dL) is associated with a 2.8-fold causal risk for ischemic heart disease, independent of reduced HDL cholesterol.
- Elevated cholesterol content of triglyceride-rich lipoprotein particles causes ischemic heart disease.
Association of Nonfasting Remnant Cholesterol and LDL Cholesterol with C-reactive Protein (CRP)

- 48,250 participants from the Copenhagen general population study
- Elevated nonfasting remnant cholesterol is causally associated with low-grade inflammation and with ischemic heart disease, whereas elevated LDL cholesterol is associated causally with IHD without inflammation
- As LDL levels progressively there's a very nonsignificant relationship between LDL and CRP
  - Relationship between remnants and CRP: Significant 37% increase in CRP as remnant levels rise


Conclusions

- Elevated serum levels of remnant lipoproteins correlate highly with heightened levels of systemic inflammation and increased risk for acute cardiovascular events.
- Remnants represent a delivery vehicle for transferring cholesterol and triglycerides into the subendothelial space where both can potentiate atherogenesis.
- Clearly based on studies in Copenhagen, nonfasting triglyceride levels represent a very good surrogate for remnants in serum.
- A host of separation methods can be used to quantify remnants (analytical ultracentrifugation, ion mobility, electrophoresis, NMR). It will be of interest to establish how accurately these various technologies estimate and separate the distinct species of remnant lipoproteins in the serum and correlate each of these species with cardiovascular outcomes.
- In the meantime, until uniform and widely accepted quantitative approaches are adopted, the following has simple clinical utility and adds no cost:
  - For nonfasting specimens, consider the Copenhagen approach.
  - For fasting specimens, consider targeting non-HDL-C.

Secondary Hypertriglyceridemia—Medications, Dietary and Lifestyle Indiscretions, and Diseases

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Secondary Causes of HTG: Practical Hints

- Do not blame it on the genes too quickly.
- Consider every form of severe HTG as secondary and search for the cause.
- Think of alcohol as contributing cause if HDL is up with TG.
- Always get a direct LDL (low LDL is expected in exclusive HTG) non HDL cholesterol and/or apoB.
- If LDL is high, combined dyslipidemia is likely to be genetically determined.
- Do not be too stern on a fasting requirement.
- Consider a lipid panel 2 hours after a test meal (e.g., McDonald’s EVM1, QPC).
- Consider transient discontinuation of TG-lowering meds if you do not know the patient’s lipid baseline or if you are curious whether a panel adjustment is due to recent lifestyle adjustments.

Most Forms of HTG Are of Secondary Origin

<table>
<thead>
<tr>
<th>Cause</th>
<th>Additional details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess calories</td>
<td>Nutrients or alcohol</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>High-fructose foods, dietary fiber</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Chronic obesity, visceral adiposity, ethnicity</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Even if well controlled</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>If not adequately controlled with thyroid replacement therapy</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td>Antiretroviral regimens, some phenothiazines and atypical antipsychotics, nonselective beta blockers, thiazide diuretics, oral estrogen, tamoxifen, glucocorticoids, retinoids and rexinoids</td>
</tr>
<tr>
<td>Recreational drugs</td>
<td>Marijuana (ApoC-III)</td>
</tr>
</tbody>
</table>


-70 million persons (~1/3 of adult US population) have ↑TG (≥150 mg/dL)
Why is Hypertriglyceridemia Common?

Maintenance of normal TG levels is the exclusive responsibility of 1 extracellular enzyme – lipoprotein lipase (LpL) – whose function depends on:

- Genetic integrity
- Secretion from parenchymal cells
- Transfer from liver to capillary endothelium
- Anchoring to capillary endothelium
- Effectively interacting with lipoproteins

- Genetic integrity – subtle mutations are common (first hit)
- Secretion from parenchymal cells – sensitive to insulin action
- Transfer from parenchymal to capillary endothelium – subject to multiple modifiers
- Anchoring to capillary endothelium – subject to competition from other molecules
- Effectively interacting with lipoproteins – blocking auto-antibodies

Increasing TG Levels Increase Risk of Pancreatitis

Highlights from Lipid Forum 2015: Focus on Hypertriglyceridemia

**Meta-analysis of 29 Studies Shows TG Level Is a Significant CVD Risk Factor**

<table>
<thead>
<tr>
<th>Groups</th>
<th>CHD Cases</th>
<th>CHD Risk Ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 years</td>
<td>5902</td>
<td>2.25 (2.07-2.45)</td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>4556</td>
<td>1.92 (1.76-2.10)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7728</td>
<td>2.00 (1.82-2.19)</td>
</tr>
<tr>
<td>Female</td>
<td>1994</td>
<td>1.80 (1.63-1.99)</td>
</tr>
<tr>
<td>Fasting Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>7484</td>
<td>2.13 (1.96-2.33)</td>
</tr>
<tr>
<td>Nonfasting</td>
<td>2674</td>
<td>1.94 (1.77-2.12)</td>
</tr>
<tr>
<td>Adjusted for HDL-C</td>
<td>No</td>
<td>4469</td>
</tr>
<tr>
<td>Yes</td>
<td>5880</td>
<td>1.92 (1.75-2.10)</td>
</tr>
<tr>
<td>Overall CHD Risk Ratio*</td>
<td>Decreased</td>
<td>2</td>
</tr>
</tbody>
</table>

*Individuals in top vs bottom third of usual log-TG values, adjusted for at least age, sex, smoking status, lipid concentrations, and (in most studies) blood pressure.


**TG ≥150 mg/dL Predicts Higher CHD Risk in Statin Takers with LDL-C <70 mg/dL**

PROVE IT-TIMI 22 Trial

(N=1162)

<table>
<thead>
<tr>
<th>LDL-C &lt;70 mg/dL</th>
<th>TG &lt;150 mg/dL</th>
<th>CHD Event Rate After 30 Days (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C &lt;70 mg/dL</td>
<td>TG ≥150 mg/dL</td>
<td>11.7%</td>
</tr>
</tbody>
</table>

HR: 0.72
P=0.017

LDL-C ≥70 mg/dL

TG ≥150 mg/dL

Event Rate = 17.9%

**High TG and Low HDL-C Correlate with CVD Risk Even When LDL-C is Well Controlled**

TNT Study

Patients with LDL-C ≥70 mg/dL on statin

<table>
<thead>
<tr>
<th>HDL-C Quintile</th>
<th>Q1: &lt;37</th>
<th>Q2: 37 to &lt;42</th>
<th>Q3: 42 to &lt;47</th>
<th>Q4: 47 to &lt;55</th>
<th>Q5: ≥55</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG=147</td>
<td>0.86</td>
<td>0.75</td>
<td>0.65</td>
<td>0.60</td>
<td>0.51</td>
</tr>
<tr>
<td>TG=186</td>
<td>0.84</td>
<td>0.74</td>
<td>0.64</td>
<td>0.59</td>
<td>0.50</td>
</tr>
<tr>
<td>TG=166</td>
<td>0.82</td>
<td>0.72</td>
<td>0.63</td>
<td>0.58</td>
<td>0.49</td>
</tr>
<tr>
<td>TG=122</td>
<td>0.80</td>
<td>0.70</td>
<td>0.61</td>
<td>0.56</td>
<td>0.47</td>
</tr>
<tr>
<td>TG=139</td>
<td>0.78</td>
<td>0.68</td>
<td>0.59</td>
<td>0.54</td>
<td>0.45</td>
</tr>
</tbody>
</table>

39% Lower Risk

HDL-C and TG levels in mg/dL.

TNNT=Treating to New Targets

*P=0.03 for differences among quintiles of HDL-C

Meta-analysis with >1 Million Subjects
Reaffirms Link between Plasma TG and Death

<table>
<thead>
<tr>
<th>TG quartile (mg/dL)</th>
<th>CVD mortality RR</th>
<th>P</th>
<th>All-cause mortality RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. &lt; 90</td>
<td>0.83 .001</td>
<td>0.94 .15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II. 90 to &lt;150 (referent)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III. 150 to &lt;200</td>
<td>1.15 .015</td>
<td>1.09 .011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV. &gt;200</td>
<td>1.25 .013</td>
<td>1.20 .011</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median duration of study follow-up was 12.0 years. Studies in subjects with diabetes, CVD, dyslipidemia or cancer were excluded.

Genetic Causes of Hypertriglyceridemia (HTG)

**Common**
- Familial combined hyperlipidemia (FCHL)
  - Variable TG and cholesterol genetic defects in lipoprotein metabolism
- Familial hypertriglyceridemia (FHTG)
  - High TG levels only, related to hepatic VLDL production and/or polygenic vs environmental lipoprotein lipase (LPL) activity

**Rare**
- Familial dysbetalipoproteinemia (Fredrickson Type III)
- LPL deficiency
- ApoC-II deficiency
- GPIHBP1 deficiency
- ApoA-V mutations
- Lipase maturation factor 1 deficiency (LMF1)

Genetic testing for causes of HTG is not useful clinically and is not recommended as a routine practice.


Reduced ApoC-III Loss-of-function Mutations Show Reduced CHD Risk

Odds ratio of CHD of subjects with any of 4 APOC3 loss-of-function mutations among 110,970 participants (34,002 patients with CHD and 76,968 controls) in 14 studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ancestry</th>
<th>CHD Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHS</td>
<td>EA</td>
<td>0.39</td>
</tr>
<tr>
<td>MHS</td>
<td>AA</td>
<td>0.00</td>
</tr>
<tr>
<td>MDC</td>
<td>EA</td>
<td>1.70</td>
</tr>
<tr>
<td>MDC</td>
<td>AA</td>
<td>0.00</td>
</tr>
<tr>
<td>FHY</td>
<td>EA</td>
<td>0.59</td>
</tr>
<tr>
<td>FHY</td>
<td>AA</td>
<td>2.40</td>
</tr>
<tr>
<td>FHY1+2</td>
<td>EA</td>
<td>1.00</td>
</tr>
<tr>
<td>FHY1+2</td>
<td>AA</td>
<td>0.00</td>
</tr>
<tr>
<td>FHY1+2</td>
<td>MA</td>
<td>0.62</td>
</tr>
<tr>
<td>FHY1+2</td>
<td>EA+MA</td>
<td>0.43</td>
</tr>
<tr>
<td>EPIC</td>
<td>EA</td>
<td>0.35</td>
</tr>
<tr>
<td>EPIC</td>
<td>AA</td>
<td>0.56</td>
</tr>
<tr>
<td>IPM</td>
<td>EA</td>
<td>0.00</td>
</tr>
<tr>
<td>IPM</td>
<td>HA</td>
<td>0.51</td>
</tr>
<tr>
<td>IPM</td>
<td>AA</td>
<td>0.62</td>
</tr>
<tr>
<td>ARIC</td>
<td>EA</td>
<td>0.59</td>
</tr>
<tr>
<td>ARIC</td>
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<td>2.40</td>
</tr>
<tr>
<td>MDC</td>
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<td>1.70</td>
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<td>MDC</td>
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<td>RAFIC</td>
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<tr>
<td>RAFIC</td>
<td>AA</td>
<td>0.00</td>
</tr>
<tr>
<td>RAFIC</td>
<td>MA</td>
<td>0.62</td>
</tr>
<tr>
<td>RAFIC</td>
<td>EA+MA</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Loss-of-Function mutations reduced TG levels by 39%.
### Treating the Underlying Factors

- Dietary intervention (fats, sugars, alcohol, calories)
- Body weight management
- Physical activity to activate beta-oxidation
- Treat underlying co-morbidities
- Evaluate options for changing TG-raising medications

### Treating Hypertriglyceridemia

- Omega-3 fatty acids, prescription
- Fish oil, krill oil, flax seed supplementation
- Fibrates
- Niacins
- Statins
- Novel drugs and pathways

### Conclusions

- Consider every hypertriglyceridemia as secondary, even the most severe.
- Hypertriglyceridemia is common because LpL is an easy target of genetic and non-genetic modifiers.
- Investigate and go after the primary cause.
- Aggressive lifestyle intervention produces large benefits.
  1. TG can only go down if one does not eat.
  2. The body burns fat after 40 minutes of aerobic activity.
- Use appropriate therapy of prescription omega 3 at full dose as the first complement to diet and exercise. Use fibrates for more resistant forms, and statins as appropriate for CV risk management.
Highlights from Lipid Forum 2015: Focus on Hypertriglyceridemia

Pancreatitis

- Severe hypertriglyceridemia (HTG) is etiologic for approximately 10% of cases of acute pancreatitis and 56% of gestational pancreatitis.¹
- Hypertriglyceridemia correlates with both:
  - Increased availability of pro-inflammatory fatty acids produced by pancreatic lipase, and
  - Increased serum chylomicrons which can slow blood flow through intra-pancreatic capillaries.²
- Serum triglyceride threshold for precipitating pancreatitis is inadequately defined.
- The severity of pancreatitis induced by HTG is greater than with gallstone or alcoholic pancreatitis (higher mortality and long-term complications). There is no correlation between magnitude of HTG and severity of pancreatitis.³


Very High TGs Can Cause Acute Pancreatitis

- ~100,000 patients hospitalized for acute pancreatitis in the United States annually²
- ~2000 patient deaths per year from complications related to acute pancreatitis²
- Elevated TG or chylomicronemia is the underlying cause in up to 7% of all acute pancreatitis cases²
- Critical to recognize and appropriately manage these patients at risk, as most can be effectively treated with lifestyle modification and drug therapy²

### Chylomicrons Suspected of Causing Acute Pancreatitis

**Mechanisms Through Which Hypertriglyceridemia Causes Pancreatitis Are Not Fully Elucidated**

#### Chylomicrons Are a Prime Suspect
- Large TG-rich chylomicrons (CMs) are present in the circulation when serum TG levels exceed 885 mg/dL.
- Size of particles can impair circulatory flow in capillary beds.
- TGs, but not cholesterol or glucose, associated with pancreatitis.
- CMs and remnants can impair pancreatic capillary blood flow.
- Can lead to ischemia, disrupting the similar structure and exposing CMs to pancreatic lipase.
- Produce pro-inflammatory, non-esterified free fatty acids, damaging the acinar cells and microvasculature.
- Resulting inflammatory cascade of cytokines & free radicals may lead to necrosis, edema, and inflammation of the pancreas.

![Image of mechanisms](image_url)


### Severe Acute Pancreatitis Caused by Very High TGs May Result in Increased Morbidity and Mortality

**Causes of HTG Associated with Pancreatitis**
- Genetic Factors:
  - Familial combined hyperlipidemia
  - Familial hypertriglyceridemia
  - Familial dysbetalipoproteinemia
  - Familial chylomicronemia
- Secondary Factors:
  - Untreated and/or poorly controlled diabetes
  - Alcohol abuse
  - Pregnancy
  - Medications

**Clinical Presentation**
- APK have abdominal pain, nausea & vomiting in 85%.
- Sharp pain in left upper quadrant radiating to back, hips, lower abdomen & chest.
- Mild cases: Restlessness, fever, epigastric tenderness.
- Severe cases: Guarding, reduced bowel sounds, signs of HTN, possible shock, etc.
- Diagnosis: Supported by elevation of serum amylase & lipase levels (>3x normal).

**Mortality Among Adults with Severe Acute Pancreatitis**

![Mortality graph](image_url)


### Incidence of Pancreatitis by TG Level

**Effect of TG Level on Acute Pancreatitis Risk**
- Significant dose response relationship between TG level and incident AP (adjusted HR, 1.04 [95% CI, 1.02-1.06]).
- Risk of incident acute pancreatitis increased by 4% for every 100 mg/dL increase in TG level.*

![Incidence graph](image_url)

*Mortality according for covariates and removal of patients hospitalized for gallstones, chronic pancreatitis, alcohol-related morbidities, renal failure, and other biliary disease.

Pancreatitis

- Acute pancreatitis develops when intracellular mechanisms to inhibit trypsin activation are overbalanced by biochemical/structural injury.\(^1\)

Pancreatitis induction depends on a cascade of events\(^2,3\):

1. NF-κB activation
2. Increase production of Acute pancreatitis
3. TNF-α
4. Interleukins
5. MCP-1
6. Adhesion molecules
7. Selectins
8. Drive and sustain the inflammatory mediator "storm"

Mechanistic Basis for Pancreatitis

VESSEL

1. Rolling
2. Adhesion
3. Migration
4. Infiltration and enzyme release

Acute phase response

Pancreatitis

Demographic Features of Pancreatitis

1. Among patients with fasting triglycerides >1500 mg/dL who develop acute pancreatitis (AP), mean age was 46.4 years, and patients were predominantly male.

2. Patients with AP likelier to have diabetes (52.7% vs 36.3%) and hypertension (61.1% vs 47.2%) relative to patients without the condition, and to have liver disease (16% vs 3.3%), alcohol abuse (21.4% vs 7.5%) and acute and chronic pancreatitis (29.8% vs 2.3%) at baseline (all \(P<.001\)). Patients with acute pancreatitis were found to have higher mean TG (3622 vs 2402 mg/dL) and total cholesterol (492 vs 383 mg/dL) levels.

3. In a multivariable logistic regression model among patients with TG levels >1500 mg/dL, a 100 mg/dL increase in TG level was associated with a significant 4% increase in the risk of an acute pancreatitis event over the follow-up period (OR 1.04; 95% CI 1.03-1.05; \(P<.0001\)).

4. Higher TG ranges were typically associated with a higher risk of acute pancreatitis, with a pronounced risk increase for TG levels >2000 mg/dL (OR 12.8; 95% CI 8.8-18.6; \(P<.0001\)).

Serum Triglyceride Levels and Risk of Acute Pancreatitis

- As serum triglycerides rise there is a progressive gradient rise in risk for acute pancreatitis

Conclusions

1. Hypertriglyceridemia is an important risk factor for acute pancreatitis.
2. Risk for pancreatitis becomes significant when serum triglyceride levels exceed 1000 mg/dL. Above this value, there is a rising gradient of risk for AP.
3. Triglyceride-bearing lipoproteins can induce alterations in intra-pancreatic blood flow and trigger a massive inflammatory response leading to the destruction of acinar and beta-islet cell mass.
4. Complications of AP include diabetes mellitus, pseudocyst, hemorrhage, chronic pain, chronic pancreatitis, and death.

Pharmacologic Treatment of Severe Hypertriglyceridemia

Peter P. Toth, MD, PhD, FAAFP, FICA, FNLA, FCCP, FAHA, FACC
Director of Preventive Cardiology
CGH Medical Center, Sterling, Illinois
Professor of Clinical Family and Community Medicine
University of Illinois School of Medicine, Peoria, Illinois
Professor of Clinical Medicine
Michigan State University College of Osteopathic Medicine
East Lansing, Michigan
Adjunct Associate Professor
Johns Hopkins University School of Medicine, Baltimore, Maryland
Overview of Triglyceride Metabolism

**Overview of Triglyceride Metabolism**

- **Biliary Fat**
- **Adipose Tissue and Muscle**
- **Vascular Wall Microvasculature**

- Apo A-V: apolipoprotein A-V
- CMR: chylomicron remnant
- FFA: free fatty acid
- HTGL: hepatic triglyceride lipase
- IDL: intermediate-density lipoprotein
- LDL-R: LDL receptor
- LPL: lipoprotein lipase
- LRP: LDL receptor–related protein
- VLDL: very low-density lipoprotein
- VLDL-R: VLDL receptor


Metabolic Consequences of Elevated Triglycerides

**Metabolic Consequences of Elevated Triglycerides**

- Insulin Resistance
- CETP: cholesteryl ester transfer protein


Effect of Lipid-lowering Therapies on TG Reduction

- **Fibrates**: 30%-50%
- **Niacin**: 20%-50%
- **Omega-3**: 10%-40%
- **Statins**: 10%-30%
- **Ezetimibe**: 5%-10%


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Treating Hypertriglyceridemia: Niacin Therapy

Nicotinic Acid ER: A Broad Spectrum Lipid-modulating Agent

- Dose-dependent effects on HDL-C, LDL-C, Lp(a), and TG

AIM HIGH: Baseline Lipids

<table>
<thead>
<tr>
<th></th>
<th>On Statin, mg/dL (n = 3,196)</th>
<th>Off Statin, mg/dL (n = 218)</th>
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<tbody>
<tr>
<td>LDL-C (mean)</td>
<td>71</td>
<td>119</td>
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<tr>
<td>HDL-C (mean)</td>
<td>35</td>
<td>33</td>
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<tr>
<td>Triglycerides (median)</td>
<td>161</td>
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<tr>
<td>Non-HDL (mean)</td>
<td>107</td>
<td>165</td>
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<tr>
<td>ApoB</td>
<td>81</td>
<td>111</td>
</tr>
</tbody>
</table>

AIM HIGH: Primary Outcome

Effect of High-risk Groups on Primary Outcome

Treating Hypertriglyceridemia: Fibrate Therapy
SAFARI: Combination Therapy in Patients With Combined Hyperlipidemia

Reduction in CV Events*: Fibrate Studies

<table>
<thead>
<tr>
<th>Study (Fibrate)</th>
<th>Primary Endpoint (All Patients)</th>
<th>Lipid Criteria, mmol/L</th>
<th>Primary Endpoint (Lipid Subgroup)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD (fenofibrate/simvastatin)</td>
<td>−8% (P&lt;.32)</td>
<td>TG ≥ 2.3 + HDL-C ≤ 0.88</td>
<td>−31%</td>
</tr>
<tr>
<td>FIELD (fenofibrate)</td>
<td>−11% (P=.16)</td>
<td>TG ≥ 2.3 + low HDL-C</td>
<td>−27% (P=.005)</td>
</tr>
<tr>
<td>BIP (bezafibrate)</td>
<td>−7.3% (P=.24)</td>
<td>TG ≥ 2.3 + HDL-C ≤ 0.9</td>
<td>−39.5% (P=.02)</td>
</tr>
<tr>
<td>HHS (gemfibrozil)</td>
<td>−34% (P&lt;.02)</td>
<td>TG &gt; 2.3 + LDL/HDL &gt; 5.0</td>
<td>−71% (P&lt;.005)</td>
</tr>
</tbody>
</table>

*: Comparator treatments: simvastatin in ACCORD Lipid and placebo in other studies.
< 1.03 in men and < 1.29 in women.

Meta-regression for TG Lowering with Fibrates and Reduction in Risk of a Major CV Event

Consistent with results from genetic studies; each 1 mmol/L (88.5 mg/dL) reduction in TG is equivalent to −17.7 mg/dL reduction in TRL-C

Treating Hypertriglyceridemia: Omega-3 Fatty Acid Therapy

Relative Risk of Sudden Cardiac Death and Blood Omega-3 Levels: Physicians’ Health Study

- 90% reduction in risk
- P for trend = .001

GISSI-Prevenzione: Time Course of Clinical Events

- >11,300 post-MI patients were given usual care with or without 850 mg EPA+DHA for 3.5 years
- Total mortality reduced by 28% (P=.027)
- Sudden death reduced by 47% (P=.0136)
Structure of Omega-3 and Omega-6 Fatty Acids

Omega-6 fatty acids
- C18:2n-6: Linoleic acid
- C20:4n-3: Arachidonic acid
- C22:5n-6: Docosapentaenoic acid

Omega-3 fatty acids
- Plant derived
  - C18:3n-3: α-Linolenic acid
- Marine derived
  - C20:5n-3: Eicosapentaenoic acid
  - C22:6n-3: Docosahexaenoic acid


AHA Recommendations for Omega-3 Fatty Acid Intake

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without documented CHD</td>
<td>Eat a variety of (preferably oily) fish at least twice a week; include oils and foods rich in alpha-linolenic acid (flaxseed, canola, and soybean oils; flaxseeds; and walnuts)</td>
</tr>
<tr>
<td>Patients with documented CHD</td>
<td>Consume ~1 g of EPA+DHA per day, preferably from oily fish; EPA+DHA supplements could be considered in consultation with the physician</td>
</tr>
<tr>
<td>Patients needing triglyceride lowering</td>
<td>2-4 g of EPA+DHA per day provided as capsules under a physician’s care</td>
</tr>
</tbody>
</table>


GISSI-Prevenzione: Effects of 850 mg/day of EPA+DHA on Serum Lipids

- Compared with baseline values, total and LDL-C levels increased slightly at 6 months and then declined, reaching approximately the same levels as measured at baseline.
- HDL-C levels were increased in a similar way in active and control groups.
- Mean triglyceride values during follow-up were 155.1 mg/dL and 162.6 mg/dL for the n-3 PUFA and control groups, respectively.

But ... minimal (5%) net triglyceride-lowering effect

**JELIS Study: Ethyl-EPA Reduced CV Events**


**Addition of EPA to Statin Therapy in Japanese Patients**


**Patient Subgroup: TG > 150 mg/dL and HDL < 40 mg/dL (JELIS)**

Conclusions

1. The specific etiology for hypertriglyceridemia is variable, and includes genetic, metabolic, and iatrogenic causes.
2. Statins reduce triglycerides in a dose-dependent manner, largely by decreasing VLDL production and secretion.
3. The fibrates and omega-3 fish oils reduce VLDL production and secretion and activate lipoprotein lipase.
4. Clinical trial experience with the fibrates is decidedly mixed, likely due to shortcomings in design. In subgroup analyses, fibrate therapy reduces risk for CVD in patients with the high triglyceride/low HDL-C phenotype.
5. The omega-3 fish oils reduced CV endpoints in GISSI-3 and JELIS. It remains to be determined if triglyceride reduction with omega-3 agents in patients with hypertriglyceridemia reduces risk for CVD events. STRENGTH and REDUCE-IT trials are currently underway to evaluate this issue.

The Role of Diet and Exercise in Managing Hypertriglyceridemia

R. Scott Wright, MD
Professor of Medicine
Mayo Clinic College of Medicine
Rochester, MN

Objectives

- Discuss evidence-based dietary and exercise recommendations for patients with hypertriglyceridemia
- Understand differences in recommendations for patients with mild, moderate, or severe hypertriglyceridemia or chylomicronemia
Dietary Management of Hypertriglyceridemia

- Nutrition measurements that affect triglyceride levels include:
  - Body weight status
  - Body fat distribution
  - Weight loss
  - Macronutrient profile of the diet
    - Type and amount of dietary carbohydrate and fat
  - Alcohol consumption

Weight Loss

- Weight loss of 5% to 10% results in:
  - 20% decrease in TG
  - Approximate 15% reduction in LDL-C
  - 8% to 10% increase in HDL-C

- Magnitude of decrease in TGs is directly related to the amount of weight loss

- Meta-analyses: For every 1 kg of weight loss, TG decrease 1.9%, or 1.5 mg/dL

Macronutrient Composition in Hypertriglyceridemia

- Dietary management of HTG goes beyond total fat intake
  - Dietary fat
    - Trans fat
    - Saturated fat
    - Monounsaturated fat
    - Omega-3 FA
  - Carbohydrates

Reduction of macronutrient intake = replacement with alternative macronutrient
Carbohydrates and Lipogenesis

- Important interrelationships among CHO, fats, and proteins.
- Carbohydrates - Generally go through glycolysis to produce ATP.
  - This can be accomplished in the absence of oxygen but with a relatively low yield in energy or ATP. Pyruvate is also produced and, in the absence of deficiency of oxygen, is converted to lactic acid (lactate).
- Proteins - Deaminated in the liver and they can then enter the Krebs cycle at a couple of different spots and result in energy in this method:
  - Because it must be deaminated (remove an ammonia group on a chemistry level) before this can occur, it takes more energy to break it down. ATP is produced as well as some intermediate products (NADH, FADH) that ultimately result in ATP after going through the Electron Transport System (ETS).
- Fats - Stored, and often consumed, in the form of triglycerides.
  - Fatty acids are removed and enter the mitochondria where they go through a process called 'Beta-Oxidation' where 2 carbon molecules are removed at a time. Fats can store a tremendous amount of energy within them. However, protein & fat catabolism requires oxygen in order to yield the energy needed.

Sugars and Triglycerides

- Sucrose is a disaccharide consisting of 1 molecule of glucose and 1 molecule of fructose.

Carbohydrates and Hypertriglyceridemia: Fructose

- Fructose is considered the most hypertriglyceridemic sugar.
  - Enhance lipogenesis and triglyceride synthesis.

Because fructose bypasses a rate-limiting step in glycolysis, high fructose influx promotes TG synthesis and VLDL production.

Fasting Plasma TG Concentrations and Fructose Intake

An increase in fructose intake is associated with an increase in TGs in multiple health states.


Dietary Carbohydrate Intake and TGs: Fiber

- Increases in TG and reduced HDL-C may occur when carbohydrate is consumed with viscous (soluble) fiber.
- It has not been demonstrated definitively that viscous fiber can fully negate the TG-raising or HDL-lowering actions of very high intakes of CHOs.


Dietary Carbohydrate and TGs: Fiber

- Meta-analysis of 7 studies compared moderate CHO and high fiber vs moderate CHO and low fiber in T2DM
  - TG decreased by 8% in the high-fiber groups
- Meta-analysis of 9 studies (n=119) compared high CHO and high fiber vs moderate CHO and low fiber in T2DM
  - TG decreased 13% in the high-fiber group
- Data support TG-lowering effect for dietary fiber (T2DM)

Dietary Management of Hypertriglyceridemia

- 1) Implement a Mediterranean style diet
   - Mean reduction in triglycerides 10%-15%

- 2) Add long chain omega-3 polyunsaturated fatty acids
   - Mean reduction: 5%-10% per gram

- 3) Decrease carbohydrate intake (1% energy replacement with monounsaturated or polyunsaturated fatty acids)
   - Mean TG reduction: 1%-2%

- 4) Eliminate trans fats (1% replacement with monounsaturated fatty acids or polyunsaturated fatty acids)
   - Mean reduction: 1%-2%

HYPERTRIGLYCERIDEMIA: Diet Recommendations

<table>
<thead>
<tr>
<th>Carbohydrates</th>
<th>High Triglycerides</th>
<th>Very High Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50%-55%</td>
<td>45%-50%</td>
</tr>
<tr>
<td>Added Sugars</td>
<td>5%-10%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Fructose</td>
<td>50 g - 100 g</td>
<td>&lt;50 g</td>
</tr>
<tr>
<td>Protein</td>
<td>15%-20%</td>
<td>15%-20%</td>
</tr>
<tr>
<td>Fat</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Saturated fat</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Trans fatty acids</td>
<td>AVOID</td>
<td>AVOID</td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td>10%-20%</td>
<td>10%-20%</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>10%-20%</td>
<td>10%-20%</td>
</tr>
<tr>
<td>EPA/DHA</td>
<td>1-2 g</td>
<td>&gt;2 g</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Decrease consumption</td>
<td></td>
</tr>
</tbody>
</table>

Total Fat and HTG

- Meta-analysis of 19 studies published by IOM
  - Relationship between % total fat intake and change in TG and HDL-C concentrations
  - Compared low-fat, high-CHO diets vs higher-fat diets
  - For every 5% decrease in total fat, TG level was increased by 6% and HDL-C to decrease by 2.2%
Total Fat and HTG

- Meta-analysis of 30 controlled feeding studies in patients with or without T2DM (n=1213)

- Moderate-fat diet (32.5% to 50% of calories from fat) vs lower-fat diet (18% to 30% of calories from fat) resulted in a decrease in TG level of 9.4 mg/dL (range 6.1 to 12.2 mg/dL, P<0.0001) without T2DM

- In T2DM, moderate-fat diet resulted in greater TG reduction (24.8 mg/dL, P<.05) than seen with the low-fat diet


HYPERTRIGLYCERIDEMIA: Diet Recommendations

<table>
<thead>
<tr>
<th>Carbohydrates</th>
<th>High Triglycerides 50%-55%</th>
<th>Very High Triglycerides 45%-50%</th>
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<tbody>
<tr>
<td>Added Sugars</td>
<td>2%-10%</td>
<td>2%-10%</td>
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<tr>
<td>Fructose</td>
<td>10 g - 50 g</td>
<td>10 g - 50 g</td>
</tr>
<tr>
<td>Protein</td>
<td>20%-30%</td>
<td>20%-30%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fat</th>
<th>30%-35%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans</td>
<td>Avoid</td>
</tr>
<tr>
<td>Saturated</td>
<td>10%</td>
</tr>
<tr>
<td>Polyunsaturated</td>
<td>10%-20%</td>
</tr>
<tr>
<td>Monounsaturated</td>
<td>10%-20%</td>
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<tr>
<td>EPA/DHA</td>
<td>1-2 g</td>
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<td>Alcohol</td>
<td>Decrease consumption</td>
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Dietary Management of Hypertriglyceridemia

- Moderate intake of predominantly unsaturated fat (≥30% to 35% of) and plant-based proteins (17% to 25% of energy) may produce a TG-lowering effect.

Types of Dietary Fat and HTG

- Meta-analysis of 60 controlled feeding studies
  - Replacement of any fatty acid class with CHOs increased fasting TG levels
  - Each 1% isoenergetic replacement of CHOs, decreases in TG resulted with
    - Saturated fat (SFA; 1.9 mg/dL)
    - MUFA (1.7 mg/dL)
    - PUFA (2.3 mg/dL)
    - All P = .001
  - Approximate 1% to 2% decrease in TG levels


Trans Fats

- Eliminate dietary trans fatty acids
  - TFA increase TGs and atherogenic lipoproteins (Lp[a], LDL-C)
- Small proportion of total caloric intake
  - Bakery shortening and stick margarine contain high trans fatty acid concentrations (30% to 50%)
- Each 1% replacement of trans fatty acids for monounsaturated fat (MUFA) or polyunsaturated fat (PUFA) lowers TGs by 1%


HYPERTRIGLYCERIDEMIA: Diet Recommendations

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<th>Very High Triglycerides</th>
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<tbody>
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<tr>
<td>Alcohol</td>
<td>Decrease consumption</td>
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</tr>
<tr>
<td>Fat</td>
<td>30%-35%</td>
<td>&gt;2 g</td>
</tr>
<tr>
<td>trans fat</td>
<td>AVOID</td>
<td></td>
</tr>
<tr>
<td>saturated fat</td>
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</tr>
<tr>
<td>monounsaturated fat</td>
<td>10%-20%</td>
<td></td>
</tr>
<tr>
<td>polyunsaturated fat</td>
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</tr>
<tr>
<td>EPA/DHA</td>
<td>1.2 g</td>
<td>&gt;2 g</td>
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</tbody>
</table>

Mediterranean Dietary Pattern and TGs

- Several RCTs have reported beneficial effects of Mediterranean-style diet on TGs compared with low-fat diet.
- Mediterranean-style diet = more foods rich in MUFA, PUFA, and dietary fiber.
- Total fruit, vegetables, nuts, whole grains, and olive oil were higher in the intervention group.


Mediterranean Dietary Pattern and TGs

- Intervention diet
  - 28% of calories from total fat, with 8%, 12%, and 8% of calories from SFA, MUFA, and PUFA, respectively (reduced total fat, reduced SFA, increased MUFA and PUFA vs control)
- Control diet
  - 30% of calories from total fat, with 14%, 10%, and 7% of calories from SFA, MUFA, and PUFA, respectively
- After 2 years, TGs decreased 19% in intervention group (P=0.001 vs control diet)
- In addition, subjects on the intervention diet decreased body weight by 6.2 lb or 2.8 kg (P=0.001) and waist circumference by 0.8 inches or 2 cm (P=0.01) compared with the control group


Mediterranean Dietary Pattern and TGs

With few exceptions, implementation of a Mediterranean-style diet vs low-fat diet is more commonly associated with an approximately 10% to 15% lowering of TG levels.
Highlights from Lipid Forum 2015: Focus on Hypertriglyceridemia

**Omega-3 Fatty Acids and HTG**

- AHA recommends 2 to 4 g EPA and DHA provided as capsules to lower TGs
- Large body of evidence showing TG-lowering effects of marine-derived omega-3 PUFA
- Dose-response relationship between omega-3 PUFA and TG lowering
  - Approximate 5% to 10% reduction in TGs for every 1 g of EPA/DHA consumed
- Efficacy is greater in individuals with higher TG levels before treatment

**HYPERTRIGLYCERIDEMIA: Diet Recommendations**

<table>
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<th>Carbohydrates</th>
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<th>Very High Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of intake</td>
<td>50%-55%</td>
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<td>Fructose</td>
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</tbody>
</table>

**Alcohol and Hypertriglyceridemia**

- Moderate alcohol intake has limited association with TG levels
- At higher intake, TGs increase:
  - 1 ounce per day = 5%-10% higher TG than in non-drinkers
- Nearly 1 in 5 hospitalized alcoholic have TG ≥ 250 mg/dL
- Exaggerated increase in TG with high SFA diet
- May be due to inhibition of LPL-mediated hydrolysis of chylomicrons
HYPERTRIGLYCERIDEMIA: Diet Recommendations

<table>
<thead>
<tr>
<th>Carbohydrates</th>
<th>High Triglycerides</th>
<th>Very High Triglycerides</th>
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<td>Fat</td>
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<tr>
<td>Trans Fat</td>
<td>≤1%</td>
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<tr>
<td>Saturated Fat</td>
<td>≤10%</td>
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Dietary Management of Hypertriglyceridemia

1) Implement a Mediterranean style diet
   - Mean reduction in triglycerides: 10%-15%

2) Add long chain omega-3 polyunsaturated fatty acids
   - Mean reduction: 5%-10% per gram

3) Decrease carbohydrate intake (1% energy replacement with monounsaturated or polyunsaturated fatty acids)
   - Mean reduction: 1%-2%

4) Eliminate trans fats (1% replacement with monounsaturated fatty acids or polyunsaturated fatty acids)
   - Mean reduction: 1%-2%


Practical Algorithm for Screening and Management of Elevated Triglycerides

  http://circ.ahajournals.org/content/123/20/2292/F5.expansion.html
**Physical Activity and HTG**

- Sedentary lifestyle, visceral obesity, insulin resistance, high SFA intake
  - Increased content of intramyocellular TG
  - Ineffective utilization of fat/reduced muscle fatty acid oxidation
- Aerobic activity enhances lipid oxidation
  - Facilitates hydrolysis and utilization of TG in skeletal muscle


**Physical Activity (PA) and HTG**

- PA effect in lowering TG depends on:
  - Baseline TG
  - Caloric expenditure
  - Duration of exercise
- PA most effective in lowering TG when baseline levels >150 mg/dL. Activity is moderate to intensive, and total caloric intake is reduced
  - Approximately 20%-30% decrease


**Dietary Management of Acute Pancreatitis (AP) and Severe HTG/Chylomicronemia**

- Early aggressive IV hydration
  - ≥250-500 mg/hr isotonic crystalloid solution
    (Lactated Ringer’s preferred)
- Mild AP: oral feedings may be started immediately
  - Low-residue, low-fat soft/solid diet as safe as clear liquid diet
  - Bowel rest associated with intestinal mucosal atrophy and infectious complications due to bacterial translocation from the gut
- Severe AP: enteral nutrition recommended
  - Avoid parenteral nutrition
  - Associated with infectious complications and line-related complications

Highlights from Lipid Forum 2015: Focus on Hypertriglyceridemia

**Summary: Diet and HTG**

- Weight loss and implementation of Mediterranean dietary pattern result in greatest reduction in TG
- Increase intake of marine-derived PUFA (EPA/DHA)
- Elimination trans fat and reduction of refined carbohydrates result in more modest reductions in TGs
- Eliminate or limit alcohol intake


**Are All Omega-3 Fish Oils the Same?**

*Examining the Evidence: EPA, DHA, or Both?*

R. Scott Wright, MD
Professor of Medicine
Mayo Clinic College of Medicine
Rochester, MN

**Overview of ω-3 Fatty Acids and ω-3 Products**

- Objectives
  - Discuss differences in forms of EPA and DHA present in available fish oil preparations.
  - Understand differences in the amounts of ω-3 fatty acids in currently available prescription fish oil products and in OTC dietary supplements.
  - Review differences in the effects of EPA and DHA formulations on lipid, lipoprotein levels, and apoC-III.
Overview of ω-3 Fatty Acids and ω-3 Products

- Formulations
- Metabolism
- Bioavailability: Short-term, long-term
- Dosing: With or without high-fat meal
- EPA vs DHA
- Lipid / lipoprotein effects

Overview of ω-3 Fatty Acids

- Long-chain omega-3 fatty acids are primarily found in cold-water organisms.
- The High number of double bonds lowers the melting point.
- At low temperatures, biological structures retain the fluidity necessary for life processes.
- Coldwater fish, microalgae, and Antarctic krill are the greatest sources.

Different Forms of EPA and DHA

- Triglyceride (triacylglycerol)
- Ethyl Ester
- Free Fatty Acid (carboxylic acid)
- Phospholipid
Different Forms of EPA and DHA

- **Triglyceride (triacylglycerol)**
  - EPA or DHA, along with 2 other fatty acids, connected to all 3 carbons of glycerol (3-carbon) backbone
  - Predominant omega-3 form in food supply, including in fish and seafood, fish oils, and re-esterified triglyceride

- **Ethyl Ester**
  - EPA/DHA chemically connected to ethanol, allows the ethyl ester forms of EPA/DHA to be concentrated via molecular distillation to produce omega-3 “concentrates.”
  - Used directly as sources of EPA/DHA in dietary supplements, or can be converted back to the triglyceride form for supplements (“re-esterified” triglycerides).

- **Free Fatty Acids (carboxylic acids)**
  - EPA/DHA fatty acids that are not connected to a glycerol backbone, as they are in the triglyceride and phospholipid forms, nor chemically linked to ethanol as in the ethyl ester form
Different Forms of EPA and DHA

- **Phospholipid**
  - EPA, DHA, and other fatty acids connected to a glycerol (3-carbon) backbone so that 2 fatty acids are present on 2 of the carbons, and 1 carbon is associated with the "head group" of the phospholipid
  - Minor components of most marine oils (krill oil)


Different Forms of EPA and DHA

- Metabolism
- Bioavailability
- Dosing
- Lipid/lipoprotein effects


Omega-3 Fatty Acids: Ingestion to Tissue

- After emulsification of fats in the stomach, they enter small intestine where the n-3 FA are cleaved off from their various types of bonds to form free fatty acids and 2-monooacylglyceride (2-MAG). Free n-3 FA and 2-MAG are taken up as mixed micelles. Bile salts must also be present in small intestine to allow for incorporation of fatty acids and other fat digestion products into mixed micelles. Fat absorption from mixed micelles occurs throughout the small intestine and is 85%-95% efficient under normal conditions.

- In enterocytes, n-3 FA are re-esterified to triacylglycerides, which are then incorporated into chylomicrons and transferred via the basolateral membrane to the lymph and thus to systemic circulation. Blood then transports n-3 FA to the target tissues, where they are primarily incorporated in membranes.


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Omega-3 Fatty Acids: Bioavailability

- Proposed differences in "bioavailability" based on formulation:
  - Short-term availability based on levels in serum and plasma
    - Omega-3 fatty acids not physiologically active in bloodstream
  - Long-term availability in erythrocyte membranes
    - Omega-3 index
    - Sum of EPA and DHA as percentage of total FA in erythrocyte membranes
    - Measure of long-term incorporation of FA in tissue
- Most studies of bioavailability evaluate only short-term availability


ECLIPSE Study: Short-term Bioavailability of FFA vs EE

- Randomized, open-label, single dose, 4-way crossover, bioavailability study of Omega-3 (OM-3) FFA and OM-3 EE administered during periods of low-fat and high-fat consumption to 54 overweight adults
- Baseline-adjusted AUC for total EPA + DHA during the low-fat period was 4.0-fold greater with OM-3 FFA compared with OM-3 EE
- During the high-fat period, AUC(0-t) for OM-3 FFA was approximately 1.3-fold greater than OM-3 EE
- Although a trend for greater bioavailability of total plasma EPA + DHA from krill oil was noted, likely attributable to the FFA content, plasma phospholipid AUC0-72 of EPA + DHA among all 3 treatments were not significantly different


Omega-3 Fatty Acids: Ingestion to Tissue

- Short-term availability based on levels in serum and plasma
  - Omega-3 fatty acids in TG and FFA forms appear to have better short-term availability compared to those in EE form
  - EE form is more available when consumed with high-fat meal
  - Limited information on bioavailability of omega-3 PL from krill oil compared to TG from fish oils, primarily animal studies
- Clinical or therapeutic implications of these differences are unknown
- Not valid to interpret differing absorption characteristics of a single dose as relevant to the efficacy of chronic therapy.

Overview of ω-3 Fatty Acids and ω-3 Products

- Currently 6 FDA-approved prescription fish oil formulations are available for management of patients with severe HTG (TG ≥ 500 mg/dL)
  - 4 contain ω-3-acid ethyl esters (EPA and DHA)
    - 2 branded, 2 generic
  - 1 contains ω-3-carboxylic acids or free fatty acids (EPA and DHA)
    - Branded
  - 1 contains icosapent ethyl (EPA only)
    - Branded


ω-3 FA Content of Available Fish Oil Preparations

<table>
<thead>
<tr>
<th>Product</th>
<th>Active ingredient(s)</th>
<th>EPA/DHA Content</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>ω-3-acid ethyl esters (Rx)</td>
<td>Ethyl esters of EPA/DHA</td>
<td>Each 1 gram capsule contains EPA ethyl ester ~465 mg and DHA ethyl ester ~375 mg</td>
<td>2 grams twice daily or 4 grams once daily</td>
</tr>
<tr>
<td>Icosapent ethyl ester (Rx)</td>
<td>Ethyl ester of EPA only</td>
<td>Each capsule contains 1 gram of icosapent ethyl ester</td>
<td>2 grams twice daily</td>
</tr>
<tr>
<td>Free fatty acids (carboxylic acids) (Rx)</td>
<td>Free fatty acid forms of EPA/DHA</td>
<td>Each 1 gram capsule contains 75% EPA and DHA in free fatty acid form</td>
<td>2 or 4 grams daily</td>
</tr>
<tr>
<td>OTC fish oil supplements</td>
<td>EPA, DHA, primarily in triglyceride form, other components</td>
<td>Purity and amount of EPA (median 202 mg; range 160-386 mg) and DHA (median 206 mg; range 120-240 mg) per capsule</td>
<td>NR</td>
</tr>
<tr>
<td>OTC Krill oil supplements</td>
<td>EPA and DHA as phospholipids, other components</td>
<td>Each 1 gram capsule contains 30% EPA and DHA, 40% phospholipids, vitamin A, vitamin E, other fatty acids, astaxanthin</td>
<td>NR</td>
</tr>
</tbody>
</table>


ω-3 FA: Ethyl Ester Preparations

- First ω-3 FA product approved in 2004 for treatment of severe HTG (TG ≥ 500 mg/dL)
- Reduced baseline TG levels by up to 45% in small, prospective, double-blind, RCTs
- LDL-C increased 17%-31%, likely associated with the DHA and not the EPA component, although both elicit TG-lowering effects

ω-3 FA: Icosapent Ethyl (EPA only)

- Icosapent ethyl approved for severe HTG (≥500 mg/dL) in 2012
- ω-3 formulation without DHA
- Does not cause an increase in LDL-C
  - 4-g daily dose reduced total LDL-C by 16.3%
  - 2-g daily dose led to non-significant increase in LDL-C
- TG reduced 25%-45% with 4-g daily dose in multicenter, placebo-controlled, randomized, double-blind, 12-week study


ω-3 FA: Carboxylic Acid Form

- Approved for severe HTG in May 2014
- EPA and DHA in FFA form
  - 50%-60% EPA and 15-25% DHA
- 12-week RCT (151 pts with severe HTG between 500 and 2000 mg/dL)
  - TG reduced 33% compared to placebo
  - No significant change in LDL-C or HDL-C
- Not yet commercially available


ω-3 FA: Dietary Supplement Fish Oils

- Numerous preparations—not subject to same regulatory and manufacturing oversight by the FDA
- EPA and DHA content per recommended serving can vary
- Accuracy of the stated amount of EPA and DHA can vary
- Concentrations of EPA and DHA range from 20%-80% and may require ≥11 servings for TG-lowering efficacy

**ω-3 FA: Phospholipid Form**

- Krill oil
  - Processed from crustacean: Antarctic krill (*Euphausia superba*)
  - Major part of EPA/DHA occurs naturally in phospholipid form
  - Lower concentrations compared to OTC fish oils
    - EPA ~14% and DHA ~6.5%
  - Different ratio of EPA:DHA compared to OTC fish oils
    - Krill oil: EPA:DHA ratio, ~2:1
    - OTC Fish oils: EPA:DHA ratio, ~1.12:1
  - Marketing claims more effective than fish oil, but this is based on flawed interpretation of evidence

**Lipid and Lipoprotein Effects of ω-3 FA Preparations**

- No direct comparisons of prescription preparations
  - 4-g dose of each prescription ω-3 FA product (± statins) has been evaluated in randomized, placebo-controlled, double-blind, parallel-group trials including patients with very high TG

**Lipid Effects of Prescription Omega-3 in TG >500 mg/dL**

<table>
<thead>
<tr>
<th>EVOLVE (EPA+DHA FFA)</th>
<th>MARINE (EPA EE)</th>
<th>EPA+DHA EE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>Median Change from Baseline (%)</td>
<td>Median Change from Baseline (%)</td>
</tr>
<tr>
<td>Icosapent ethyl 4g</td>
<td>-3%</td>
<td>-4.5%</td>
</tr>
<tr>
<td>Placebo Corrected</td>
<td>-4.8%</td>
<td>-4.2%</td>
</tr>
<tr>
<td>OMG3EE 4g</td>
<td>+45%*</td>
<td>+39.2%</td>
</tr>
<tr>
<td>EVOLVE (EPA+DHA FFA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMG3CA 2g</td>
<td>+17.2%*</td>
<td>+16%</td>
</tr>
<tr>
<td>OMG3CA 4g</td>
<td>+19.4%*</td>
<td>+19.2%</td>
</tr>
<tr>
<td>EVOLVE (EPA+DHA FFA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMG3EE 4g</td>
<td>+12%</td>
<td>+11%</td>
</tr>
<tr>
<td>EVOLVE (EPA+DHA FFA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMG3EE 4g</td>
<td>+11%</td>
<td>+10%</td>
</tr>
</tbody>
</table>

**Lipid and Lipoprotein Effects of α-3 FA Preparations: 4 g/day**

(TG 500-1500/200 mg/dL)

<table>
<thead>
<tr>
<th>Measure</th>
<th>α-3 FA EE</th>
<th>α-3 FA EE</th>
<th>α-3 FA EE</th>
<th>α-3 FFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>84</td>
<td>254</td>
<td>229</td>
<td>399</td>
</tr>
<tr>
<td>TG (%)</td>
<td>(P&lt;NR)</td>
<td>(P&lt;0.05)</td>
<td>(P&lt;0.001)</td>
<td>(P&lt;0.001)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>(P&lt;NR)</td>
<td>(P&lt;0.01)</td>
<td>(P=NR)</td>
<td>(P=NR)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>(P&lt;NR)</td>
<td>(P&lt;0.05)</td>
<td>(P=NR)</td>
<td>(P=NR)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>(P&lt;NR)</td>
<td>(P&lt;NR)</td>
<td>(P=NR)</td>
<td>(P=NR)</td>
</tr>
<tr>
<td>Apo B</td>
<td>NR</td>
<td>NR</td>
<td>(P&lt;0.05)</td>
<td>(P=NR)</td>
</tr>
</tbody>
</table>

**Statin + EPA/DHA EE (TG 200-500): COMBOS Lipid Endpoints**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Median Change from Baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>-14 (P&lt;0.05)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>+19 (P&lt;0.01)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>+19 (P&lt;0.001)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-9 (P=NR)</td>
</tr>
<tr>
<td>Apo B</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Statin + EPA EE (TG 200-500): ANCHOR Lipid Endpoints**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Median Placebo-adjusted Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>-21.5 (****)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-20.5 (****)</td>
</tr>
<tr>
<td>Apo B</td>
<td>-9 (NS)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>+2 (NS)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>+2 (NS)</td>
</tr>
</tbody>
</table>

- **P**, prescription
- **EPA**, eicosapentaenoic acid
- **DHA**, docosahexaenoic acid


<table>
<thead>
<tr>
<th>N</th>
<th>254</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>212</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>215</td>
</tr>
<tr>
<td>Apo B</td>
<td>82</td>
</tr>
<tr>
<td>LDL-C</td>
<td>82</td>
</tr>
<tr>
<td>HDL-C</td>
<td>37</td>
</tr>
</tbody>
</table>

**Statin + EPA Ethyl (4 g/day)**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Median Placebo-adjusted Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>-21.5 (****)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-20.5 (****)</td>
</tr>
<tr>
<td>Apo B</td>
<td>-9 (NS)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>+2 (NS)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>+2 (NS)</td>
</tr>
</tbody>
</table>

- **P**, prescription
- **EPA**, eicosapentaenoic acid
- **DHA**, docosahexaenoic acid

12-week trial in high-risk coronary patients (n = 702), with TG 200-500 and LDL-C 40-100.


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Lipid and Lipoprotein Effects of ω-3 FA Preparations: 4 g/day (TG ≥200 to <500 mg/dL)

<table>
<thead>
<tr>
<th>% vs placebo</th>
<th>ω-3 FA EE EPA + DHA + statin</th>
<th>ω-3 FA EE EPA + statin</th>
<th>ω-3 FFA EPA + DHA + statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>254</td>
<td>453</td>
<td>418</td>
</tr>
<tr>
<td>TG</td>
<td>-23 (P&lt;0.0001)</td>
<td>-22 (P&lt;0.0001)</td>
<td>-21 vs -6 (P&lt;0.001)</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo B</td>
<td>-2 (P&lt;0.05)</td>
<td>-9 (P&lt;0.0001)</td>
<td>-2 vs +0.3 (P&lt;0.05)</td>
</tr>
</tbody>
</table>


Lipid and Lipoprotein Effects of ω-3 FA Preparations: 4 g/day (TG ≥200 to <500 mg/dL)

• Bottom line:
  - EPA+DHA better for ↓TG & ↑HDL-C
  - EPA better for ↓LDL-C, ↓Non-HDL-C, ↓Apo B


EPA, DHA, or Both?

• Both EPA and DHA lower triglycerides
  - DHA only and EPA/DHA > EPA only
• EPA has negligible effect on LDL-C
• DHA may raise LDL-C, likely due to reduction in apoC-III production
  - Enhanced lipolysis and conversion of VLDL to LDL
  - May explain greater TG-lowering effect of DHA
  - Larger LDL particle size, increase in HDL-C

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EPA, DHA, or Both?

- EPA and DHA modify the composition of VLDL particles differently in patients with severe hypertriglyceridemia.
- Both EPA and DHA decrease the triglyceride composition of VLDL, but DHA also enhances the lipolysis of VLDL, resulting in greater conversion to LDL that is larger in size, as well as increases in HDL-C.

ApoC-III Promotes Dyslipidemia and Atherosclerosis

- Liver-derived apolipoprotein is present on TG-rich lipoproteins and HDL
- Promotes HTG by inhibiting LPL and inhibition of apo E binding to hepatic receptors
  - Thus reducing lipolysis and clearance of TG-rich lipoproteins
- ApoC-III–containing LDL is more strongly associated with CV risk than LDL without apoC-III

Apolipoprotein C-III has Significant Consequences for Lipoprotein Metabolism

ApoC-III Effects
- ApoC-III modifies particle composition
  - Inhibits the conversion of VLDL to LDL
  - Causes an increase in small, dense LDL and a decrease in HDL-C
- Glucose increases apoC-III gene expression and may link diabetes and TGs
- ApoC-III–enriched LDL can increase monocyte binding to endothelial cells
- ApoC-III in HDL+LDL is a marker of increased risk of recurrent coronary events
CARE Trial

- ApoC-III in VLDL + LDL was a marker of increased risk of recurrent coronary events

Omega-3 Fatty Acids Containing EPA + DHA Have Been Shown to Lower ApoC-III

Reductions in ApoC-III Are Associated with Omega-3 Products
Summary: ω-3 FA

- Insufficient evidence regarding clinical implications of short- and long-term bioavailability of different formulations of ω-3 FA
  - TG vs EE vs FFA vs PL?
- EPA and DHA both have TG-lowering effects
- DHA may raise LDL-C due to enhanced lipolysis
  - Increase in LDL particle size, increase in HDL-C
- EPA and omega-3 fatty acid products that contain DHA lower apoC-III

Summary: ω-3 FAs

- OTC fish oil preparations are not regulated by the FDA and may vary in consistency of concentrations of EPA and DHA
- Krill oil preparations have lower concentrations of ω-3 FAs and may require greater number of capsules to achieve maximum/adequate TG-lowering benefits