Update on Hypertriglyceridemia

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Program Outline

- Triglycerides basics
- Lipoproteins
  - structure, composition
- Hypertriglyceridemia
  - definition, incidence, ethnic and gender issues
- Pathologic consequences of high triglycerides
  - pancreatitis
  - atherosclerosis
Program Outline

• Secondary causes of high triglyceridemia
• Special genetic populations with high trigs
  – Familial Combined Hyperlipidemia (FCH)
  – Familial Hypertriglycerideridemia
  – Familial Hyperchylomicronemia (FC)
• Treatments for hypertriglycerideridemia
• Evolving treatment for hypertriglycerideridemia
  – MTP inhibition
  – genetic therapy
  – anti-sense oligonucleotides
Triglycerides
Triglycerides

• Formed via the esterification of glycerol with fatty acids
  – source of fatty acids in gut (i.e. exogenous pathway) from digestion of dietary fat
  – source of fatty acids in liver (i.e. endogenous pathway) is the circulating pool of non-esterified fatty acids [NEFA]

• Major energy source in mammals
Triglycerides

\[
\begin{align*}
&\text{CH}_3\text{(CH}_2\text{)}_7\text{CH}=\text{CH}\text{(CH}_2\text{)}_7\text{C(}\text{O}\text{)O-CH}_2 \\
&\text{CH}_3\text{(CH}_2\text{)}_7\text{CH}=\text{CH}\text{(CH}_2\text{)}_7\text{C(}\text{O}\text{)O-CH} \\
&\text{CH}_3\text{(CH}_2\text{)}_{14}\text{C(}\text{O}\text{)O-CH}_2
\end{align*}
\]
Triglycerides

• There are at least 14 naturally occurring fatty acids in humans

• There are 2,744 \( (14^3) \) distinct triglyceride molecules
Triglyceride Metabolism

• **Exogenous pathway**
  – delivery of cholesterol and triglycerides to the liver via the GI tract in the form of chylomicrons – energy source in the fed state

• **Endogenous pathway**
  – cholesterol and triglycerides leaving the liver and going to peripheral tissues in the form of VLDL – energy source in the fasting state
Lipoproteins
Lipoprotein Classes

Diameter (nm)
Density (g/ml)

Chylomicron
VLDL
IDL
LDL
HDL
Chylomicron Remnants
VLDL Remnants
HDL
HDL
HDL
HDL
## Lipoprotein Overview

<table>
<thead>
<tr>
<th>Particle</th>
<th>Diameter (Å)</th>
<th>Major Apo-Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>800 - 5,000</td>
<td>B48 (AI, CI, CII, E)</td>
</tr>
<tr>
<td>VLDL</td>
<td>300 - 450</td>
<td>B100, E, CI, CII, CIII</td>
</tr>
<tr>
<td>IDL</td>
<td>250 - 350</td>
<td>B100, E</td>
</tr>
<tr>
<td>LDL</td>
<td>180 - 280</td>
<td>B100</td>
</tr>
<tr>
<td>HDL</td>
<td>50 - 120</td>
<td>AI, AII, AIV (CI, CII, CIII, E)</td>
</tr>
</tbody>
</table>

*(apo-proteins in parenthesis are acquired after particle synthesis)*
Lipoprotein Overview

CHYLO

VLDL

LDL

HDL
Hypertriglyceridemia
Classification of Triglyceride Levels

- **Normal:** <150 mg/dL
- **Elevated:** >150 mg/dL and <500 mg/dL
- **High:** >500 mg/dL
  - at this level trigs become the primary target of lipid lowering therapy and pancreatitis is possible
- **Severe:** >2000 mg/dL
  - very high risk of pancreatitis
Prevalence of Hypertriglyceriderides

• Elevated triglycerides (150mg/dl or higher)
• Prevalence in US adults age 20 and higher
  Men – 35%
  Women 25%

• African American
  Men – 21%
  Women – 14%

• Mexican American
  Men – 40%
  Women – 35%

• Caucasian American
  Men – 37%
  Women – 25%
Epidemiology

- In the U.S. mean triglyceride (TG) levels have risen since 1976
- Correlates with growing epidemic of obesity, insulin resistance (IR), and type 2 diabetes mellitus (T2DM)
- Epidemiologic studies have failed to demonstrate a strong relationship between very high TG levels and CVD death
- Recent studies suggest that non-fasting TG levels (remnant lipoprotein particles) was a superior predictor of incident CVD compared with fasting levels
Prevalence of Abnormal Triglycerides Has Increased
Prevalence of Severe Hypertriglyceridemia

• Defined as triglycerides greater than 2000 mg/dl
  – 1.8 cases per 10,000 white adults
  – higher prevalence in patients with diabetes and alcoholism.
  – LPL deficiency (most severe form) occurs in approximately 1 case per 1 million.
  – apo C-II deficiency is even lower.
Causes of Hypertriglycerideridemia
Potential Causes of Elevated Triglycerides

- Obesity and overweight
- Physical inactivity
- Excess alcohol intake – genetic predisposition
- High-carbohydrate diets (>60% of energy intake)
- Comorbidities (hypothyroidism, type 2 diabetes, chronic renal failure, nephrotic syndrome)
- Medications (β-blockers, protease inhibitors, corticosteroids, oral estrogens, retinoids, etc)
- Genetic dyslipidemias
Pathologic Effects of High Triglycerides
Hypertriglyceridemia and Pancreatitis

• After gallstones and excessive alcohol consumption, significantly elevated serum triglycerides are the 3rd most common cause of acute pancreatitis.
• TG are typically > 500 mg/dl, often times much higher.
• Characterized by recurrent abdominal pain, nausea, vomiting.
Indirect Effects of Hypertriglyceridemia on Atherosclerosis

- Shifts LDL particle density and particle number
- Decreases HDL, especially HDL2
- Induces vasospasm
- Up-regulates coagulation cascade mediators – factors VIII and X, fibrinogen
- Causes inflammation
  - increased hs-CRP, Lp-PLA2
Direct Effects of Hypertriglycerideridemia on Atherosclerosis

• Small, dense triglyceride-rich lipoproteins can be recognized by scavenger receptors on foam cells
  – apoB48: chylomicron remnants
  – apoB100: small dense VLDL (i.e. VLDL3)
Triglycerides Are Independently Associated With Premature CHD

CHD odds ratio

Serum triglycerides (mg/dL)

- <100: 1.0
- 100-149: 1.2
- 150-199: 1.1
- 200-299: 1.7
- 300-499: 2.8
- 500-799: 11.4
Triglycerides Are an Independent Risk Factor for CHD, Irrespective of LDL-C

Incidence of CHD Events According to Serum LDL-C and TG Concentration

<table>
<thead>
<tr>
<th>LDL-C Concentration (mg/dL)</th>
<th>Baseline TG &lt;200 mg/dL</th>
<th>Baseline TG ≥200 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;130</td>
<td>18</td>
<td>43</td>
</tr>
<tr>
<td>130-159</td>
<td>38</td>
<td>47</td>
</tr>
<tr>
<td>160-189</td>
<td>56</td>
<td>112</td>
</tr>
<tr>
<td>≥190</td>
<td>107</td>
<td>255</td>
</tr>
</tbody>
</table>

CHD cases/1000 in 8 years
Relationship Between Triglycerides and Events: PROVE IT-TIMI 22* Subanalysis

- TG ≥150
- TG <150

27% risk reduction

HR=0.73
(0.62-0.87)
P<0.001
For every increase in serum TG level of 89 mg/dL, the risk of CHD increases 32% in men and 76% in women.
Genetic Causes of Hypertriglyceridemia
Genetic Causes of Severe Hypertriglyceridemia

- Familial Combined Hyperlipidemia (FCH)
- Familial Hypertriglyceridemia
- Familial Hyperchylomicronemia (FC)
- Familial Beta-Dyslipoproteinemia
Familial Combined Hyperlipidemia (FCH)

- Most common genetic dyslipidemia
  - first described in 1973 by Goldstein
- Incidence: ~2% of the American population
- Includes IIa, IIb and / or IV
- Autosomal dominant
  - expression usually delayed to adulthood (25-30 yo)
  - 10% FCH patients present in childhood
    - usually with elevated triglycerides
FCH: Pathophysiology

- Basic abnormality is over-production of apo-B leading to secretion of increased # of VLDL
- Phenotype then dependent upon activity of lipoprotein lipase and hepatic lipase
- Tendency for phenotype to change over time and/or with Rx
- Most commonly seen in the setting of obesity, hypertension and insulin resistance
  - 65% FCH patients meet the criteria for the metabolic syndrome
FCH: Lipid Abnormalities

- TC average 250-350 mg% and/or trigs average 300 – 600 mg%
  - LDL is small, dense Pattern B
  - VLDL is normal/smaller (very high “particle number”)
  - HDL reciprocally depressed
- Apo-B greatly increased
FCH: Physical Findings

• Arcus
• Xanthalsma
• NEVER tendon xanthomas
FCH: Clinical Consequences

- Associated with increased CHD risk
- 20% FCH patients have their first MI before age 55 yo
  - males present with Sx’s before females

- Treatment considerations:
  - TLC and lipid guidelines (i.e. NLA guidelines)
Familial Hypertriglycerideridemia

• Genetically heterogeneous
  – usually autosomal dominant but recessive cases have been described

• Prevalence of ~ 1:500

• Lipid levels:
  – trigs (VLDL) 200 – 1000 mg%
  – moderately increased TC

• Drawn plasma looks cloudy-pink
Familial Hypertriglycerideridemia

• Physical signs:
  – eruptive xanthomas
  – hepatosplenomegaly
  – lipemia retinalis

• Pathophysiology:
  – secretion of enlarged VLDL rather than increased numbers of VLDL particles, therefore Apo-B levels normal

• Clinical significance
  – slight increased risk CHD
  – dramatic increased risk of acute pancreatitis
Familial Hyperchylomicronemia

• Also referred to as “Fredrickson Type I Dylipidemia”
• Caused by: homozygous lipoprotein lipase deficiency and/or apoprotein CII deficiency
• Incidence of about one in a million
  – LPL def more common than apoCII def
• Trig levels typically in the 2,000 to 10,000 mg/dL range
Familial Hyperchylomicronemia

• Patients typically get recurrent pancreatitis in childhood (but it can be delayed until early adulthood)
• Patients have eruptive xanthomas
• Serum looks like it has a layer of cream on the top
Familial Dysbetalipoproteinemia

• aka Genetic Type III aka “Broad β Disease”
• Autosomal recessive (with respect to apo ε genotype)
  – genotype ε₂:ε₂ incidence ~1-2% US population
  – actual disease incidence 1 : 10,000 (1/50 of ε₂:ε₂)
  – expresses in ♂ in early adulthood and in ♀ after menopause
• Clinical syndrome requires ε₂:ε₂ genotype plus a metabolic trigger
  – obesity, insulin resistance, diabetes, hypothyroidism, EtOH, menopause
Familial Dysbetalipoproteinemia

- $\varepsilon_2:\varepsilon_2$ doesn’t bind normally to the LDL apo B/E receptor
- Get TC ~300-600 with trigs ~400-800
  - get accumulation of chylomicron remnants, IDL and VLDL$_3$
  - typically low levels of directly measured LDL
- Physical findings:
  - tendon and tuberous xanthomas
  - orange palmar xanthomas (pathognemonic)
  - xanthalsmas
  - arcus
Familial Dysbetaalipoproteinemia

• Treatment considerations
  – EXTREMELY sensitive to diet and lifestyle
    • decrease in sat’d fat and weight loss can restore lipid levels to normal
  – also responds very well to low dose combination therapy of niacin and statins
Treatments for Hypertriglyceridemia
Treatment Options

- Diet and lifestyle
- Fibrates
- Fish oil
- Niacin
- Statins
- Plasmaphoresis
Dietary Approaches

- The patient must work closely with a dietician
  - focus on low fat diet to cut off the production of chylomicrons
  - usually < 20 g/d and sometimes as low as 10g/d
  - medium-chain TG-rich foods, such as coconut oil, can be used for cooking, as they are absorbed directly into the portal vein without becoming incorporated chylomicron TG
Physical Activity and Hypertriglyceridemia

• Aerobic activity enhances lipid oxidation, thereby facilitating the hydrolysis and utilization of TG in skeletal muscle.

• Overall, exercise is most effective in lowering TG (eg, 20% to 30%) when baseline levels are elevated (ie, >150 mg/dL), activity is moderate to intensive, and total caloric intake is reduced.
# Effects of Nutrition Practices on TG-Lowering

<table>
<thead>
<tr>
<th>Nutritional Practice</th>
<th>TG-Lowering Response, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (5% to 10% of body weight)</td>
<td>20%</td>
</tr>
<tr>
<td>Implement a Mediterranean-style diet vs. low-fat diet</td>
<td>10-15%</td>
</tr>
<tr>
<td>Add marine-derived PUFA (EPA/DHA) (per gram)</td>
<td>5-10%</td>
</tr>
<tr>
<td>Decrease carbohydrates 1% Energy replacement with MUFA/PUFA</td>
<td>1-2%</td>
</tr>
<tr>
<td>Eliminate trans fat 1% Energy replacement with MUFA/PUFA</td>
<td>1%</td>
</tr>
</tbody>
</table>
Fibrates

• Agents
  – clofibrate (1962)
    • no longer available in the US
  – gemfibrozil (1982)
    • available as a generic
    • available since 1975 in Europe
    • in US available as generic, Tricor (nanocrystal) and Lofibra, Triglide, Antara, Fenoglide (micronised) and Lipofen (hard gelatin capsule)
  – fenofibric acid (2009)
    • TriLipix
    • Fibricor
  – bezofibrate / ciprofibrate (Europe only)
Fibrates - Mechanism of Action

- Decreased hepatic secretion of VLDL
- Decreased release of ffa from adipose tissue
- PPAR-\(\alpha\) activation
  - nuclear hormone receptor gene superfamily
  - function as a transcription activator / suppressor for genes involved in lipoprotein metabolism
    - decreased apo C-III
    - increased LPL
    - increased apo AII
    - decreased HMG-Co-A reductase activity
Fibrates - Effects on Lipid

- increase / decrease LDL
- decrease triglycerides
- increase HDL
- lower Lp(a)
<table>
<thead>
<tr>
<th></th>
<th>Trigs</th>
<th>TC</th>
<th>LDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>gemfibrozil</td>
<td>-(31-35%)</td>
<td>-10%</td>
<td>-14%</td>
<td>+(6-10%)</td>
</tr>
<tr>
<td>600 mg bid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fenofibrate</td>
<td>-(32-53%)</td>
<td>-(17-27%)</td>
<td>-(17-35%)</td>
<td>+(2-26%)</td>
</tr>
<tr>
<td>160 mg qD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Usual dose of gemfibrozil is 600 mg bid before meals. Usual dose of fenofibrate is 145 / 160 / 200 mg qD with food. Fenofibric acid has the same lipid effects as fenofibrate.
Omega - 3 - Fatty Acids

• Long chain n-3 polyunsaturated fatty acids found in cold water fish (a.k.a. “fish oils”)
  – eicosapentaenoic acid (EPA)
  – docosahexaenoic acid (DHA)
• Mechanism of action is unknown
• FDA indicated to lower triglycerides if >500 mg%
# Omega - 3 -Fatty Acids: OTC Agents

<table>
<thead>
<tr>
<th>CAPSULE</th>
<th>EPA</th>
<th>DHA</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marine 500</td>
<td>90</td>
<td>60</td>
<td>150</td>
</tr>
<tr>
<td>MaxEpa 1000</td>
<td>180</td>
<td>120</td>
<td>300</td>
</tr>
<tr>
<td>ProtoChol 1000</td>
<td>180</td>
<td>120</td>
<td>400</td>
</tr>
<tr>
<td>SeaOmega 1000</td>
<td>300</td>
<td>200</td>
<td>500</td>
</tr>
<tr>
<td>Super EPA 1200</td>
<td>360</td>
<td>240</td>
<td>600</td>
</tr>
</tbody>
</table>

NOTE: potential for confusion regarding dosages: 1 gm / day may contain 300, 400, or 500 mg of actual omega-3 fatty acids; also be alert for “serving size” information.
Omega - 3 - Fatty Acids: Prescription Agents

- Lovaza and generic EPA / DHA mix
  - lowers triglycerides about 45%
  - raises LDL-C up to 35%

- Vascepa: pure EPA
  - lowers triglycerides about 45%
  - has no effect on LDL-C levels
Niacin

• Agents
  – crystalline
    • nicotinic acid NOT nicotinamide
  – sustained release
    • Slo-Niacin, Niacor, Nicolar, Nicobid…
  – “programmed release”
    • Niaspan, generic niacin-ER
    • combination products: Advacor and Simcor
      – Niaspan plus lovastatin or simvastatin

• Vitamin B3
  – RDA: 13 mg ♀ / 18 mg ♂
  – dose to effect lipids: 1000 - 6000 mg/ day

• First used in 1955 to lower lipids
Niacin - Differences Among Agents

• Sustained release
  – less flushing & itching
  – more (serious) liver toxicity
  – less effect on triglycerides & HDL

• Programmed release (Niaspan)
  – same lipid effects as crystalline
  – less liver toxicity than SR
  – less effect on uric acid than SR or crystalline
  – less flushing & itching than crystalline
Niacin - Mechanism of Action

- Poorly understood
- Decreased VLDL production
- New evidence suggests a direct effect on SREBP activity
Niacin - Lipid Effects

- Decreases LDL (10 – 25%)
  - shifts LDL density gradient to larger, buoyant
- Increases HDL (25 – 35%)
  - HDL2 >> HDL3
- Decreases VLDL (20 – 50%)
  - shifts VLDL to larger, more buoyant
- Decreases Lp(a) (25 – 35%)
- Increases homocysteine
Niacin - Efficacy

- Effect on LDL and triglycerides seen in 3 to 6 weeks
  - effect on HDL seen over several months
- Effect on HDL effected by baseline HDL and triglycerides
  - get +44% increase in HDL with 3 gm/s crystalline niacin if baseline [HDL]<28 mg%
- Effect on HDL classic dose response
  - Niaspan 1.0 gm - +15% increase in HDL
  - Niaspan 1.5 gms - +22% increase in HDL
  - Niaspan 2.0 gms - +26% increase in HDL
Statins

- lovastatin / Mevacor (1987): Merck
  - (Altocor) / Altoprev (2002): Andrx
- pravastatin / Pravachol (1991): BMS
- fluvastatin / Lescol (1993): Novartis
  - Lochola (2004): Novartis
- atorvastatin / Lipitor (1997): Pfizer / (Parke-Davis)
- pitavastatin / Livalo (2010): Kowa
Statins - Efficacy
Other Lipid Parameters

- **Triglycerides**
  - **ALL** statins lower triglycerides **IF** triglycerides are elevated
    - little / no effect if [trigs] at baseline < 200 mg%

- **HDL**
  - rosuva raises HDL 8-14% across its dosing range
  - at higher doses, simva does better at raising HDL than atorva
    - simva 40: +6.7%  /  atorva 20: +4.0%
    - simva 80: +6.7%  /  atorva 40: +3.0%
  - effect of statins dependent on baseline HDL
    - if [HDL]<35 mg%: simva 40 causes +17%

- **Lp(a)**
  - no statin lowers [Lp(a)] / some (L,A) raise it
    - S, R, P, Pi are Lp(a) neutral
Plasmaphoresis

- Used for treatment of acute, severe hypertriglyceridemia associated with:
  - acute pancreatitis
  - gestational hypertriglyceridemia
  - iatrogenic hypertriglyceridemia
    - corticosteroids, HAART, Accutane
Evolving Treatment for Hypertriglyceridemia
MTP Inhibition

- Microsomal Triglyceride Transfer Protein is required to attach apoB100 and apoB48 to nascent lipoproteins.
- MTP activity in the proximal jejunal enterocytes is required for the formation of chylomicrons.
- MTP activity in the hepatocyte is required for the formation of VLDL.
VLDL and Chylomicron Synthesis

Liver Cell

Intestinal Epithelial Cell

Blood Vessel

VLDL

Chylomicron

Apo B100
MTP

Apo B48
MTP

Nascent VLDL

Nascent Chylomicron

TG

LDL

VLDL

Chylomicron Remnant

Chylomicron

Cytoplasm
ER
Lumen
Predicted Effects of MTP Inhibition

Liver Cell

Intestinal Epithelial Cell

Blood Vessel

Apo B100 Degraded

Apo B48 Degraded

Lower VLDL, LDL, chylomicrons, and chylomicron remnants

MTP Inhibited

TG

ER

Lumen

Cytoplasm
Lomitapide

- FDA approved oral MTP inhibitor indicated for the treatment of HoFH
- Currently being looked at as a treatment for severe hypertriglyceridemia in patients with a history of recurrent pancreatitis
- At the dose used to treat HoFH (10 to 40 mg qD) trigs are lowered 45%
Genetic Therapy of Severe Hypertriglyceridemia

- The main cause of Familial Hyperchylomicronemia is an absence or dysfunction mutation of lipoprotein lipase

- A functional lipoprotein lipase gene has been successfully cloned and implanted into a viral vector
Genetic Therapy of FC

• Currently in Phase II clinical trials:
  – patients with FC are put under general anesthesia
  – a large volume of the viral vector (actual dose not yet determined) is injected into all the patient’s large muscle groups
  – after a few days the LPL gene is incorporated into the patients genome and triglyceride levels are near normal
Apo CIII

- 79 amino acid glycoprotein
  - present on chylomicrons, VLDL and HDL
- The most abundant of the circulating apoC’s
- apoC-III covers the apoE on the chylomicron (and VLDL) until a certain size is reached, delaying uptake by the remnant receptors
Non-Sense Oligonucleotides

• ISIS-304801 is a nonsense oligonucleotide that competes with real apoCIII mRNA for translation but does not produce functional apoCIII

• In phase II clinical trials it lowered apoCIII levels 80% and triglyceride levels by 71% in patients whose baseline trigs were between 300 and 2000 mg%
Questions?