Uncomfortable rash and recurrent pancreatitis in 40 yo man

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FINANCIAL DISCLOSURE:

Consultant
Akcea Therapeutics, Kaneka (apheresis), Novartis

Investigator
Amgen Inc, Akcea Therapeutics, Novartis, Regeneron, RegenXBio, Astra-Zeneca

UNLABELED/UNAPPROVED USES DISCLOSURE: none
Outline

• Brief case
  o Background: severe hypertriglyceridemia
  o Making the diagnosis
  o Treatment considerations
  o Future direction
Joe

- 37 yo obese (BMI 50) nonsmoker; referred bc of severe hyperTG.
- h/o pancreatitis x3 (1st at 35 yo)
- t2dm (A1C 8-10%)
- h/o gout, arthritis, OSA, fatty liver
  - Normal thyroid; no nephrotic syn
  - No EtOH
Joe

- Choline **fenofibrate** 135 mg daily
- **Niacin** ER 500 mg daily
- **Omega-3**-acid ethyl esters 1 gm twice daily
- **Rosuvastatin** calcium 20 mg daily

- Metformin 500 mg 2 times daily
- Saxagliptin hcl 5 mg daily
- Valsartan 160 mg daily

<table>
<thead>
<tr>
<th>Lipids (mg/dL)</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>592</td>
</tr>
<tr>
<td>TG</td>
<td>4565</td>
</tr>
<tr>
<td>HDL-C</td>
<td>34</td>
</tr>
</tbody>
</table>
Joe’s pedigree
Joe

→ Developed **painful xanthomas**

- 40 yo; conditions unchanged
- Deferring bariatric surgery (BMI 50)

<table>
<thead>
<tr>
<th>Lab Results</th>
<th>Units</th>
<th>12/2013</th>
<th>12/2013</th>
<th>1/2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOL</td>
<td>mg/dL</td>
<td>946</td>
<td>852</td>
<td>970</td>
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<tr>
<td>TRIG</td>
<td></td>
<td>6,922</td>
<td>6,100</td>
<td>8,860</td>
</tr>
<tr>
<td>CHOLHDL</td>
<td>mg/dL</td>
<td>13</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>CREATININE</td>
<td>mg/dL</td>
<td></td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>GLUCOSE</td>
<td></td>
<td></td>
<td></td>
<td>204</td>
</tr>
<tr>
<td>HEMOGLOBIN</td>
<td>%</td>
<td></td>
<td></td>
<td>10.0</td>
</tr>
<tr>
<td>A1C</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Images shared with permission from patient
<table>
<thead>
<tr>
<th>Lab Results</th>
<th>TRIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref Rng &amp; Units</td>
<td>mg/dL</td>
</tr>
<tr>
<td>7/15/2014</td>
<td>&gt;10,000 (H)</td>
</tr>
<tr>
<td>7/17/2014</td>
<td>7,719 (H)</td>
</tr>
<tr>
<td>7/21/2014</td>
<td>5,450 (H)</td>
</tr>
<tr>
<td>7/24/2014</td>
<td>5,758 (H)</td>
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<td>7/24/2014</td>
<td>2,861 (H)</td>
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<td>7/28/2014</td>
<td>6,016 (H)</td>
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<td>8/1/2014</td>
<td>4723</td>
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<td>8/4/2014</td>
<td>5,055 (H)</td>
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<td>8/7/2014</td>
<td>5,682 (H)</td>
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<td>8/11/2014</td>
<td>6,384 (H)</td>
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<td>8/14/2014</td>
<td>5226</td>
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<td>8/25/2014</td>
<td>5,729 (H)</td>
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<td>8/28/2014</td>
<td>3,375 (H)</td>
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<td>9/4/2014</td>
<td>1,863 (H)</td>
</tr>
<tr>
<td>9/8/2014</td>
<td>&gt;10,000 (H)</td>
</tr>
<tr>
<td>9/15/2014</td>
<td>2,909 (H)</td>
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<td>9/18/2014</td>
<td>2,909 (H)</td>
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<tr>
<td>9/19/2014</td>
<td>1,879 (H)</td>
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<td>9/25/2014</td>
<td>2,381 (H)</td>
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<td>10/2/2014</td>
<td>2,775 (H)</td>
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<tr>
<td>10/6/2014</td>
<td>1390</td>
</tr>
</tbody>
</table>

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### 2014 National Lipid Association (NLA) Classification of TG Levels

<table>
<thead>
<tr>
<th>Triglycerides (mg/dL)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>Normal</td>
</tr>
<tr>
<td>150–199</td>
<td>Borderline high</td>
</tr>
<tr>
<td>200–499</td>
<td>High</td>
</tr>
<tr>
<td>≥500</td>
<td>Very high</td>
</tr>
</tbody>
</table>

### Overall Prevalence of Hypertriglyceridemia by Age in NHANES (representative sample) 1999-2008

<table>
<thead>
<tr>
<th>Demographic</th>
<th>TG ≥150 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (age ≥20 y)</td>
<td>25.0%</td>
</tr>
<tr>
<td>Men</td>
<td>28.7%</td>
</tr>
<tr>
<td>Women</td>
<td>21.5%</td>
</tr>
</tbody>
</table>

U.S. Census Age 20 and above, July 1, 2010, was 226,113,653.


Plasma TG concentrations and expected genetic variants associated from ~70,000 adults (>20 years of age) from the Copenhagen General Population Study.

1 mmol/L = 88.57 mg/dL
2 mmol/L = 177.14

- Mild-to-moderate triglycerides increase
- Increased CVD risk

- Severe triglycerides increase
- Chylomicronaemia
- Pancreatitis risk
- Increased CVD risk likely

Very Severe Hypertriglyceridemia in a Large US County Health Care System (n ~70 000):
Associated Conditions and Management

103 of 71 495 → TG ≥ 2000 mg/dL (<0.1%)

Hypertriglyceridermia: etiology

Acquired/environmental (post-transcriptional)
• Diet, EtOH
• Meds
• Metabolic conditions
• Medical conditions

Inherited syndromes
• Monogenic (FCS, FDBL)
• Polygenic (MCS, FCH, FHTG)

“Most cases of HTG are felt to be polygenic, with strong influence by environmental factors.”

High TGs

Acute pancreatitis

ASCVD
TG risk >440 vs <88 mg/dL (women>men)

- MI (Myocardial infarction)
- IHD (Ischemic heart disease)
- Ischemic stroke
- All cause mortality

(MEN) Copenhagen Heart Study vs (WOMEN) from WHI

High TG/CM, genetic association \(\rightarrow\) Acute pancreatitis

High TRL/CM \(\rightarrow\) exposed to lipase in pancreatic capillaries

Inflammatory FFA \(\rightarrow\) trypsin activation/pancreatic necrosis

Lipase \(\rightarrow\) FFA release from TRL/CM; vicious cycle
TRL lifecycle: synthesis $\rightarrow$ clearance/atherosclerosis
ER  Endoplasmic reticulum
LMF1  Lipase maturation factor 1
SEL1L  Sel1-Suppressor of Lin-12-Like 1-HRD1 ER-associated degradation
HSPG  Heparan sulfate proteoglycan
GPIHBP1  glycosphatidyl-inositol HDL binding protein 1
Apos  Apolipoproteins
Schematic representation (Venn diagram) of associated conditions for serum triglyceride levels ≥2000 mg/dL ...

103 of 71,495 patients who had lipid testing in 2016, had TG > 2000 mg/dL (<0.1%)
Genetic testing in severe hypertriglyceridemia (SHTG) is generally **not indicated** because most SHTG is polygenic or multifactorial.

Genetic testing in severe hypertriglyceridemia **may be reasonable** if a monogenic disorder is suspected clinically such as familial chylomicronemia syndrome (eg, young age, failure to thrive, relapsing pancreatitis, and absence of secondary causes).

Is it FCS?

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Recruitment phase

Severe primary HTG (fasting TGs >10 mmol/L or 885 mg/dL)

Patient pre-selection in non-acute setting

1. Fasting TGs >10 mmol/L for 3 consecutive blood analyses (+5)\(^a\)
   • Fasting TGs >20 mmol/L at least once (+1)
2. Previous TGs <2 mmol/L (-5)
3. No secondary factor\(^b\) (except pregnancy\(^c\) and ethinylestradiol) (+2)
4. History of pancreatitis (+1)
5. Unexplained recurrent abdominal pain (+1)
6. No history of familial combined hyperlipidaemia (+1)
7. No response (TG decrease <20%) to hypolipidaemic treatment (+1)
8. Onset of symptoms at age:
   • <40 years (+1)
   • <20 years (+2)
   • <10 years (+3)

FCS score:
≥10: FCS very likely
≤9: FCS unlikely
≤8: FCS very unlikely
Joe

- Pathogenic mutations in $LPL$, $APOC2$, $APOA5$, $LMF1$, $GP1HBP1$, $GCKR$, $CREBH$; $APOE2/3$
- Polygenic TG risk score 21/28
## Should TGs be treated?

<table>
<thead>
<tr>
<th>Publication</th>
<th>Organization</th>
<th>Region</th>
<th>Mild-to-Moderately Elevated Triglycerides* (or Elevated Non-HDL Cholesterol)</th>
<th>Elevated LDL and Total Cholesterol</th>
<th>Reduced HDL Cholesterol</th>
<th>To Prevent Pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984, Grundy et al&lt;sup&gt;1&lt;/sup&gt;</td>
<td>AHA recommendation</td>
<td>US</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>1987, Lewis et al&lt;sup&gt;2&lt;/sup&gt;</td>
<td>EAS strategies</td>
<td>Europe</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>1988, Lewis et al&lt;sup&gt;3&lt;/sup&gt;</td>
<td>EAS policy statement</td>
<td>Europe</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>1998, Goodman et al&lt;sup&gt;8&lt;/sup&gt;</td>
<td>ATP-I-III-NCEP</td>
<td>US</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>1993, Grundy et al&lt;sup&gt;5&lt;/sup&gt;</td>
<td>ATP-II-III NCEP</td>
<td>US</td>
<td>(Yes)</td>
<td>Yes</td>
<td>(Yes)</td>
<td>Yes</td>
</tr>
<tr>
<td>1994, Pyörälä et al&lt;sup&gt;6&lt;/sup&gt;</td>
<td>ESC, EAS, and ESH recommendation</td>
<td>Europe</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>1997, Grundy et al&lt;sup&gt;7&lt;/sup&gt;</td>
<td>ESC, EAS, and ESH recommendation II</td>
<td>US</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2001, De Backer et al&lt;sup&gt;9&lt;/sup&gt;</td>
<td>ATP-III-NCEP</td>
<td>US</td>
<td>(Yes)</td>
<td>Yes</td>
<td>(Yes)</td>
<td>Yes</td>
</tr>
<tr>
<td>2003, De Backer et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>ESC, EAS, ESH, and others guidelines</td>
<td>Europe</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2007, Graham et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>ESC, EAS, ESH, and others guidelines</td>
<td>Europe</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2011, Chapman et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>EAS consensus</td>
<td>Europe</td>
<td>Yes</td>
<td>Yes</td>
<td>(Yes)</td>
<td>Yes</td>
</tr>
<tr>
<td>2011, Reiner et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>ESC/EAS guidelines</td>
<td>Europe</td>
<td>(Yes)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2011, Miller et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>AHA scientific statement</td>
<td>US</td>
<td>No</td>
<td>Yes</td>
<td>†</td>
<td>Yes</td>
</tr>
<tr>
<td>2012, Berglund et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Endocrine Society guidelines</td>
<td>US</td>
<td>Yes</td>
<td>†</td>
<td>†</td>
<td>Yes</td>
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<tr>
<td>2012, Perk et al&lt;sup&gt;16&lt;/sup&gt;</td>
<td>ESC, EAS, ESH, and others guidelines</td>
<td>Europe</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>†</td>
</tr>
<tr>
<td>2014, Stone et al&lt;sup&gt;17&lt;/sup&gt;</td>
<td>ACC/AHA guidelines</td>
<td>US</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>†</td>
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<tr>
<td>2014, Hegelie et al&lt;sup&gt;18&lt;/sup&gt;</td>
<td>EAS consensus</td>
<td>Europe</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Note: The table above summarizes the recommendations from various organizations and guidelines. The recommendations vary depending on the level of triglyceride elevation and other lipid parameters.

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### Severe Hypertriglyceridemia

**Recommendations for Hypertriglyceridemia**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>In adults 40 to 75 years of age with <strong>severe hypertriglyceridemia</strong> (fasting triglycerides $\geq 500$ mg/dL [$\geq 5.6$ mmol/L]) and <strong>ASCVD risk of 7.5%</strong> or higher, it is reasonable to address reversible causes of high triglyceride and to initiate <strong>statin therapy</strong>.</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>In adults with <strong>severe hypertriglyceridemia</strong> (fasting triglycerides $\geq 500$ mg/dL [$\geq 5.7$ mmol/L]), and especially fasting triglycerides $\geq 1000$ mg/dL (11.3 mmol/L), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a <strong>very low-fat diet</strong>, <strong>avoidance of refined carbohydrates and alcohol</strong>, <strong>consumption of omega-3 fatty acids</strong>, and, if necessary to prevent acute pancreatitis, <strong>fibrate</strong> therapy.</td>
</tr>
</tbody>
</table>

VERY LOW-FAT DIET

The main focus for CM clearing is very low-fat meal plan with no more than 20-30 g of fat per day.
Joe’s future

Complications from...

- **HyperCM/TG**
  - Recurrent AP
  - Recurrent xanthomas
  - ASCVD risk

- obesity, diabetes and OSA
  - Arthritis
  - Neuropathy
  - CKD
  - Ophtho
  - ED
  - Cor pulmonale
  - Liver dz
  - Etc...

- Plasma exchange
- Bariatric surgery

- ASO-APOC3
- Anti-AngPTL3 (ASO, mAb)
Severe hypertriglyceridemia

• ...the consequence of combined impact from genes and environment
• ...associated with ASCVD and acute pancreatitis
• Tx
  o ASCVD risk: environment and lifestyle modification/statins
  o AP risk: environment and lifestyle modification/TG-lowering Rx
• Genetic testing may inform expectations and novel therapy
Uncomfortable rash and recurrent pancreatitis in 40 yo man

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UNLABELED/UNAPPROVED USES DISCLOSURE: none
Severe Hypertriglyceridemia – Pharmacotherapy

Allison Hester, PharmD, BCACP
Disclosures

Allison Hester, PharmD, BCACP has no financial relationships to disclose in relation to this presentation.
Outline

1. Medications that contribute to HTG
2. TG treatment goals
3. Current medications to treat HTG
4. Pipeline medications for HTG

HTG: hypertriglyceridemia; TG: triglyceride
Medications that can contribute to hypertriglyceridemia

<table>
<thead>
<tr>
<th>Beta-blockers (non-selective)</th>
<th>Thiazides</th>
<th>Corticosteroids</th>
<th>Tamoxifen, raloxifene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogens (oral, not topical)</td>
<td>Protease inhibitors</td>
<td>Retinoic acid, isotretinoin</td>
<td>Immunosuppressants (i.e., sirolimus)</td>
</tr>
<tr>
<td>L-Asparaginase</td>
<td>Bile acid resins</td>
<td>Phenothiazines</td>
<td>Antipsychotics (second generation)</td>
</tr>
</tbody>
</table>
### Two categories of HTG

<table>
<thead>
<tr>
<th>Moderate HTG</th>
<th>Severe HTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG 175-499 mg/dL</td>
<td>TG ≥500 mg/dL (fasting)</td>
</tr>
<tr>
<td>Excess TG are carried in VLDL</td>
<td>Most patients will carry TG in VLDL + chylomicrons</td>
</tr>
<tr>
<td>When TG &gt;200 mg/dL, reduce TG to reduce risk of ASCVD</td>
<td>When TG &gt;500 (especially &gt;1000), reduce TG to reduce risk of pancreatitis</td>
</tr>
<tr>
<td>Agents to reduce ASCVD risk: statins, omega-3 PUFA</td>
<td>Agents to reduce pancreatitis risk: fibrates</td>
</tr>
</tbody>
</table>

ASCVD: atherosclerotic cardiovascular disease; HTG: hypertriglyceridemia; PUFA: polyunsaturated fatty acid; TG: triglycerides; VLDL: very low density lipoprotein
Severe HTG Treatment

- **Fibrates**
  - ~30%-50% reduction in TG

- **Omega-3 PUFA**
  - ~20%-50% reduction in TG

- **Statins**
  - ~10%-30% reduction in TG

Approximate effectiveness when used as monotherapy to lower triglycerides

HTG: hypertriglyceridemia; PUFA: polyunsaturated fatty acid; TG: triglycerides


Severe HTG Treatment

**Lifestyle modifications**

**First-line therapy: statins**

**First-line therapy for moderate HTG**

- If TG 150-499 mg/dL while on statin: Icosapent ethyl 2g twice daily
  - Reduce CV risk
  - Reduce TG

**Recommended for severe HTG when 10-year CV risk >7.5%**

- If TG >500 mg/dL while on statin: Fenofibrate is recommended
  - Reduce TG
  - Prevent pancreatitis

*Omega-3 PUFA or fibrates may be a first-line option in severe HTG when preventing pancreatitis is the primary objective of lipid management (i.e., when ASCVD risk is otherwise very low)
Treating HTG with Statins - Considerations

- Inhibit rate-limiting step in hepatic biosynthesis of cholesterol (HMG-CoA reductase)
- Myalgias, myopathies
- ALT elevations
- Risk of DM
- Drug interactions and risk of rhabdomyolysis

Some common statin interactions:
- Ketoconazole, itraconazole, posaconazole
- Erythromycin, clarithromycin
- HIV protease inhibitors (i.e., ritonavir)
- Verapamil, diltiazem, amlodipine
- Amiodarone
- Gemfibrozil
- Ranolazine
- Grapefruit juice
Treating HTG with Omega-3 PUFA

- Multiple mechanisms:
  - Reduce hepatic secretion of TG-rich VLDL particles
  - Reduce the TG content of secreted VLDL particles
  - Lower concentration of Apo C-III in the blood to enable more lipoprotein lipase activity and thereby increase TG clearance from the blood

- Carboxylic acids vs ethyl esters
- EPA vs DHA
## Omega-3 PUFA Options to Treat Severe HTG

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
<th>EPA (g)</th>
<th>DHA (g)</th>
<th>Dosing</th>
<th>CV Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epanova®</td>
<td>Omega-3-carboxylic acids</td>
<td>0.55</td>
<td>0.2</td>
<td>2 g daily or 4 g daily</td>
<td>STRENGTH trial closed early due to low likelihood of showing CV benefit</td>
</tr>
<tr>
<td>Lovaza</td>
<td>Omega-3-acid ethyl esters</td>
<td>~0.465</td>
<td>~0.375</td>
<td>4 g daily or 2 g BID</td>
<td>No data to show CV benefit</td>
</tr>
<tr>
<td>Omtryg™</td>
<td>Omega-3-acid ethyl esters A</td>
<td>~0.465</td>
<td>~0.375</td>
<td>4 g daily or 2 g BID with food</td>
<td>No data to show CV benefit</td>
</tr>
<tr>
<td>Vascepa®</td>
<td>Icosapent ethyl</td>
<td>1</td>
<td>0</td>
<td>2 g BID with food</td>
<td>REDUCE-IT showed ~25% relative risk reduction in CV events</td>
</tr>
</tbody>
</table>

BID: twice daily; CV: cardiovascular; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; HTG: hypertriglyceridemia; PUFA: polyunsaturated fatty acid; REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial; STRENGTH: Statin Residual Risk Reduction With EpaNova in HiGh Cardiovascular Risk PatienTs With Hypertriglyceridemia

Treating HTG with Fibrates - Considerations

- Agonists of PPARα, which regulates gene expression
- Increased expression of LPL → increased catabolism of TG-rich lipoproteins
- Reduced expression of Apo C-III → increased LPL activity
- Increased expression of genes for fatty acid oxidation in the liver → reduced secretion of TG-rich VLDL

- No established CV benefit
- No data proving prevention of pancreatitis
- Gemfibrozil contraindicated for use with some statins (increased risk of myopathy and rhabdomyolysis)
- Adverse effects: increased serum creatinine and aminotransferases
When might we use niacin for severe HTG?

• Niacin at doses up to 3 g/d can lower plasma TG levels by 30% to 50%
• Multiple mechanisms:
  • Inhibition of TG synthesis via diacylglycerol acyltransferase-2
  • Accelerated ApoB degradation in liver cells
  • Decreased secretion of VLDL and LDL particles
• Limited by adverse events
  • Common: cutaneous flushing, pruritis
  • Less common, but serious: elevated liver enzymes, gastrointestinal distress and worsened glucose tolerance.
Niacin for HTG?

**AIM-HIGH**
- Extended release niacin vs placebo as add-on to statin therapy
- 3414 patients with CVD, low HDL-C, and TG between 125-400 mg/dL
- Patients had relatively low LDL-C at baseline
- Planned 5 year follow up but stopped at 3 years
- Interim analysis: lack of efficacy, slightly higher rate of ischemic stroke
- No significant difference in primary composite CV endpoint

**HPS2-THIRVE**
- Niacin-laropiprant vs placebo
- 25,673 patients with CVD
- Niacin-laropiprant was associated with 33 mg/dL reduction in TG, but no reduction in rate of CV events
- Increased adverse events:
  - Serious disturbances in glucose control
  - New diagnoses of diabetes
  - Serious GI events
  - Infection
  - Bleeding

CV: cardiovascular; CVD: cardiovascular disease; GI: gastrointestinal; HDL-C: high density lipoprotein cholesterol; HTG: hypertriglyceridemia; TG: triglycerides; VLDL: very low density lipoprotein
Other meds that contribute to lower TG

- **Ezetimibe** (~8% reduction)
- **PCSK9i** (~26% reduction)
- (indirectly) levothyroxine
- (indirectly) anti-diabetic meds

PCS9i: Proprotein convertase subtilisin/kexin type 9 inhibitor; TG: triglycerides
Possible Future Mechanisms to Lower TG

Selective modulators of PPARα

Blockade of ANGPTL3 and ANGPTL4

Blockade of Apo C-III

Antisense oligonucleotides

Monoclonal antibodies

Silencing RNA

ANGPTL3: angiopoietin-like protein 3; ANGPTL4: angiopoietin-like protein 4; PPAR: Peroxisome proliferator-activated receptor; RNA: ribonucleic acid; TG: triglycerides
SPPARMα – Pemafibrate

• Current fibrates are limited by low potency and low selectivity for PPARα, which result in hepatic and renal side effects as well as drug interactions.

• Pemafibrate is a more selective modulator of PPARα (SPPARMα) with increased potency and decreased off-target adverse effects.

• No interaction with statins (unlike gemfibrozil).

• Predominantly metabolized by liver, rather than kidney.

• Pemafibrate 0.4 mg/day had similar reduction in triglycerides compared to fenofibrate 200 mg/day, but without the elevations in liver enzymes and serum creatinine.

• Phase 3 study called PROMINENT is ongoing; estimated completion date on clinicaltrials.gov is May 2022.


PPAR: Peroxisome proliferator-activated receptor; SPPARMα: selective PPARα modulator; TG: triglycerides.
Pemafibrate vs Fenofibrate
Blocking ANGPTL3 and ANGPTL4

• ANGPTL3 is a protein inhibitor of TG hydrolysis, mostly expressed in the liver
• ANGPTL3 blockade lowers lipids through mechanisms independent of LDL receptors and work mostly by reducing hepatic VLDL secretion
• Genetic studies show ANGPTL3 deficiency is associated with lower TG (and lower HDL-C and LDL-C), as well as reduced CV risk
• ANGPTL4 inactivates LPL, favoring dissociation of active LPL dimers into inactive monomers
• Both ANGPTL3 and ANGPTL4 are amenable to inhibition by antisense oligonucleotides or antibodies
Blocking ANGPTL3 and ANGPTL4

• Evinacumab: monoclonal antibody given subcutaneously or intravenously at intervals of 1 to 4 weeks
• Vupanorsen: antisense oligonucleotide targeting ANGPTL3 given as subcutaneous injection every 1 to 4 weeks
• ARO-ANG3: silencing RNA currently in phase 1
• REGN1001: human monoclonal antibody that was tested mice and non-human primates in the 2010s
Antibody to ANGPTL3 – evinacumab

• Evinacumab is a monoclonal antibody targeting ANGPTL3 that can be given subcutaneously or intravenously at intervals of 1 to 4 weeks

• Early phase 2 data:
  • Nine homozygous FH patients who were already being treated with varying combinations of statins, ezetimibe, PCSK9 inhibitors, etc., were given four weeks of therapy with evinacumab
  • LDL-C (−44%) and TG (−47%) were reduced in all patients
  • In Europe, evinacumab is now designated as breakthrough therapy for homozygous FH

• Currently a clinical trial is investigating evinacumab in the setting of pediatric homozygous FH patients

ANGPTL3: angiopoietin-like protein 3; ANGPTL43: angiopoietin-like protein 4; FH: familial hypercholesterolemia; HDL-C: high density lipoprotein cholesterol; LPL: lipoprotein lipase; LDL-C: low density lipoprotein cholesterol; TG: triglycerides; VLDL: very low density lipoprotein
Antisense oligonucleotide to ANGPTL3 – vupanorsen

- Vupanorsen is an antisense oligonucleotide targeting ANGPTL3 given as subcutaneous injection every 1 to 4 weeks
- Early phase 2 data:
  - Dose-ranging safety and efficacy study in 105 patients with HTG (fasting TG levels >150 mg/dL), type 2 diabetes and NAFLD
  - Patients received six months of subcutaneous treatment, randomized to placebo or one of 3 treatment groups of vupanorsen: 40 mg every 4 weeks, 80 mg every 4 weeks, or 20 mg every week
  - Dose-dependent reductions in fasting TGs at all dose levels; highest reduction of 53% from 80 mg every four weeks (44% mean reduction compared to placebo, P<0.0001)
  - A favorable tolerability and safety profile. The most common treatment-emergent adverse events were injection site reactions, which were mostly mild.
- TRANSLATE-TIMI-70 is a phase 2b safety and efficacy study that is currently recruiting; estimated completion date is January 2022.
Silencing RNA to ANGPTL3 – ARO-ANG3

• Currently a phase 1 trial is investigating safety and tolerability of subcutaneous injections of ARO-ANG3 given to healthy volunteers and dyslipidemic patients.

• A Phase 1 Single and Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamic Effects of ARO-ANG3 in Adult Healthy Volunteers and in Dyslipidemic Patients

• Projected completion date for the study (clinicaltrials.gov) is May 2021
Antibody to ANGPTL4 – REGN1001

• REGN1001 is a human monoclonal antibody targeting ANGPTL4

• Animal data:
  • Tested in mice and non-human primates in 2016
  • Significant TG reductions were observed
  • Accumulation of lipid-filled Touton cells in mesenteric lymph nodes
Blocking ApoC-III

- The rapid development of gene-silencing technology has allowed the targeting of proteins such as Apo C-III that are
- Apo C-III
  - Inhibitor of LPL, regulates clearance of TG-rich lipoproteins
  - Circulates on chylomicrons and VLDL particles
  - Independent of LPL, also reduces uptake of TG-rich lipoproteins by LDL receptors in liver
- APOC3 gene
  - Encodes for apo C-III
  - Carriers of one APOC3 LOF allele have a 50% reduction of plasma apo C-III
  - Associated with lower TG levels and LDL-C levels, higher HDL-C levels
Antisense oligonucleotide to Apo C-III – volanesorsen

• Volanesorsen is a subcutaneous antisense oligonucleotide targeting ApoC-III mRNA given every 1 to 2 weeks
• Binds to APOC3 mRNA and induces its degradation, resulting in reduced Apo C-III protein synthesis.
• Phase 3 COMPASS trial:
  • Weekly injections in patients with severe HTG of various causes.
  • Monotherapy or combination therapy with fibrate
  • Decreases in Apo C-III and in TG from 30 to 71%
• Phase 3 APPROACH trial
  • Thirteen weeks of volanesorsen in patients with FCS
  • Plasma APOC3 levels were reduced by 71 to 90%; TG levels reduced by 56 to 86%
  • During the study, all patients achieved at least one TG level of less than 500 mg /dL.
• Approved in Europe for genetically confirmed FCS patients at high-risk for pancreatitis
• Rejected by FDA in 2018, likely due to thrombocytopenia, increased risk of bleeding, need for platelet count monitoring
Orphan drug for hoFH: Lomitapide

- Inhibitor of microsomal transfer protein (MTP), a protein for lipid transfer on Apo B particles
- Initially developed to lower LDL-C levels, then abandoned due to concerns about hepatic steatosis, then revived and approved by FDA as orphan drug for hoFH.
- Never approved or tested for HTG management, but does result in reduction of plasma TG through reduced Apo B particles secretion
- Clinically significant effects on TG levels were observed in two studies with higher dose
- Reports of success treating intractable, severe HTG and recurrent pancreatitis due to LOF mutation in LPL. Lomitapide 40 mg daily brought TG levels from average 3900 mg/dL to average 564 mg/dL, which prevented pancreatitis and eliminated chronic abdominal pain. However, due to blockade of lipid secretion as VLDL, lipid buildup in the liver occurred and the pre-drug hepatic steatosis developed into steatohepatitis and fibrosis after 12 years.
- Lomitapide has risks to therapy, but can be used for severe forms of intractable HTG when the aiming is to increase LPL activity.
Several medications can contribute to elevated triglycerides, so a full medication reconciliation is warranted for any patient presenting with elevated TG.

For moderate hypertriglyceridemia, the main goal of therapy is to reduce TG to reduce ASCVD risk. For severe hypertriglyceridemia, the main goal of therapy is to reduce TG to reduce risk of pancreatitis.

The choice of an agent to treat hypertriglyceridemia should be based on whether the primary goal of therapy is to reduce ASCVD risk or to prevent pancreatitis.

There are several new medications on the horizon that demonstrate novel approaches to target hypertriglyceridemia.
Take Home Points

Some of the common medications that can contribute to elevated triglycerides are non-selective beta-blockers, thiazides, second-generation antipsychotics, immunosuppressants, bile acid resins, and corticosteroids.

Severe HTG is classified as TG >500 mg/dL, at which point excess TG are likely being carried via both VLDL particles (which increase ASCVD risk) and chylomicrons (which increase pancreatitis risk).

The main medication classes to treat severe hypertriglyceridemia are statins, omega-3 PUFA, and fibrates. Fibrates are the most effective monotherapy at lowering TG, but they do not have conclusive evidence demonstrating cardiovascular benefit.
SEVERE HYPERTTRIGLYCERIDEMIA: DIET MANAGEMENT

Lauren Williams, MCN, RDN, LD
Division of Endocrinology – Pediatric Lipid Clinic
Cook Children’s Medical Center – Fort Worth, TX
FINANCIAL DISCLOSURES

- No disclosures
Review chylomicron clearing diet recommended for severe hypertriglyceridemia
- Very low-fat, no concentrated sweets

Discuss nutrition supplements
- Medium Chain Triglyceride (MCT) oil
- Omega-3 fatty acids

Review additional considerations such as associated conditions and weight management

Discuss the use of alternative diets for triglyceride (TG) lowering

Address ways to make a very low-fat diet more approachable
MEDICAL NUTRITION THERAPY FOR SEVERE HYPERTRIGLYCERIDEMIA

- Very low-fat diet
  - Meet needs for calories, essential fatty acids (EFA), protein, fluid, and micronutrients
- Choose lean protein options
- Limit total carbohydrates
  - Choose complex carbohydrates
  - Avoid alcohol
- Supplement with MCT oil
- Meet needs for additional condition, such as type 2 diabetes
- Weight management, if needed, and physical activity
MACRONUTRIENT BALANCE

Average American Diet

- Carbohydrates: 48%
- Fat: 36%
- Protein: 16%

Chylomicron Clearing Diet

- Carbohydrates: 60%
- Fat: 15%
- Protein: 25%

What We Eat in America, NHANES 2017-2018
- <20g fat daily (<10-15% daily caloric intake from fat)
- Meet EFA needs
  - 2-4% daily caloric intake from linoleic acid (LA) and alpha-linolenic acid (ALA)
  - Monitor for EFA deficiency
    - Phenotypic signs: hair loss, hair depigmentation, dry/scaly skin, poor wound healing
    - Laboratory test: triene:tetraene ratio
Fat-free or low-fat protein with each meal and snack

<table>
<thead>
<tr>
<th>Food Item</th>
<th>Total Fat (g)</th>
<th>Protein (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat free ground turkey, 3oz</td>
<td>2.3</td>
<td>27</td>
</tr>
<tr>
<td>Roasted chicken breast, skin removed before cooking, 3oz</td>
<td>3.8</td>
<td>26.4</td>
</tr>
<tr>
<td>Cooked large shrimp, 6 pieces</td>
<td>0.6</td>
<td>7.5</td>
</tr>
<tr>
<td>Fat-free cheddar cheese, 1oz</td>
<td>0</td>
<td>9.1</td>
</tr>
<tr>
<td>Cooked dark meat chicken, skin removed before cooking, 3oz</td>
<td>8.9</td>
<td>23</td>
</tr>
<tr>
<td>Ground beef, 93% lean, 3oz</td>
<td>7.6</td>
<td>22.3</td>
</tr>
<tr>
<td>Cooked Atlantic salmon, 3oz</td>
<td>6.9</td>
<td>22</td>
</tr>
<tr>
<td>Raw almonds, 1 oz</td>
<td>14</td>
<td>6</td>
</tr>
</tbody>
</table>

CARBOHYDRATES

- <60% total daily caloric intake
- Choose complex carbohydrates
  - Look for added sugar on the food label
  - Limit fruit (high in natural sugar) to 1-4 servings per day
- Avoid alcohol

<table>
<thead>
<tr>
<th>Complex</th>
<th>Simple</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oats</td>
<td>Sugary cereal</td>
</tr>
<tr>
<td>Brown rice</td>
<td>White rice</td>
</tr>
<tr>
<td>Legumes</td>
<td>White bread or sweet breads</td>
</tr>
<tr>
<td>Whole wheat pasta</td>
<td>White pasta</td>
</tr>
<tr>
<td>Lentils</td>
<td>Desserts such as cookies or cakes</td>
</tr>
<tr>
<td>Quinoa</td>
<td>Sugary beverages – including 100% fruit juice</td>
</tr>
</tbody>
</table>

PLANNING MEALS

- Use plate method with ½ plate vegetables
- Prepare foods without added fats or oils
  - MCT oil may be used for low-temperature cooking or salad dressings
- Consider the fat content of ALL foods

USDA MyPlate, www.myplate.gov
SUPPLEMENTS – MCT OIL

- Source of additional fat and calories
  - Helps to improve satiety and balance percentage of caloric intake from fat/carbs/protein
- Ensure only caprylic acid (C8) and capric acid (C10)
  - Medical, prescription-grade MCT available
  - Coconut oil ≠ MCT oil
- Barriers to use: cost, shelf-life, tolerability

SUPPLEMENTS – OMEGA-3 FATTY ACIDS

- Over-the-counter omega-3 or fish oil not recommended
- Dietary sources must be limited due to fat restricted diet
- Studies have demonstrated ≥30% reduction in TG levels with 4g/day prescription omega-3
  - After underlying causes addressed and lifestyle strategies are implemented
  - Variability is study results regarding reduction in cardiovascular events

ADDITIONAL RISK FACTORS AND WEIGHT REDUCTION

- Lifestyle and pharmacological intervention to address associated conditions, such as hypertension and type 2 diabetes
- Overweight/Obesity: BMI >25 kg/m²
  - 5-10% weight reduction
  - Reduced-calorie meal plan and increased physical activity for goal of 1-2 lbs weight loss per week
- Type 2 diabetes mellitus
  - Weight loss, as needed
  - Limit carbohydrates to 60% daily caloric intake and choose complex carbohydrates
  - Increase physical activity to 150 minutes moderate-intensity physical activity or 75 min vigorous physical activity per week

ALTERNATIVE DIET RECOMMENDATIONS

- Chylomicron clearing diet indicated for TG > 1000mg/dL
- Other diets contraindicated when TG > 1000mg/dL
  - Mediterranean, DASH, and vegetarian/vegan diets can help achieve weight loss and glycemic control in type 2 diabetes, but only after TG < 500mg/dL
  - Very-low-carb, high-fat diet and ketogenic diet can exacerbate chylomicronemia and precipitate pancreatitis

FOLLOWING THE DIET: MAKING IT APPROACHABLE

- Multi-disciplinary team approach to care, including nutrition counseling and plan with a registered dietitian nutritionist (RDN)
- Base recommendations on the individual’s usual/cultural foods
- Break it down - discuss recommendations per meal rather than per day
- Teach label reading

FOLLOWING THE DIET: MAKING IT APPROACHABLE

- Make a plan for special occasions and eating out
- Discuss fat-free cooking techniques and gadgets
- Identify barriers to change
SUMMARY/TAKE HOME MESSAGES

- Recommended diet for severe hypertriglyceridemia
  - Very low-fat diet (<20g fat daily or <10-15% daily caloric intake from fat); meet EFA needs
  - Controlled carbohydrate intake with no concentrated sweets
  - Avoidance of alcohol

- MCT oil and omega-3 supplementation, as needed
  - MCT oil is a prescription-grade oil and is not equivalent to coconut oil

- If BMI >25 kg/m2, weight loss can assist with TG lowering

- Associated conditions, such as type 2 diabetes, should be addressed when formulating plan for lifestyle modification

- Individualized counseling can make the diet more approachable and improve overall adherence
THANK YOU!
Severe Multifactorial Hypertriglyceridemia: Management in Patients Without Pancreatitis

P. Barton Duell, M.D.
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Director, LDL Apheresis Unit
Knight Cardiovascular Institute and
Division of Endocrinology, Diabetes, & Clinical Nutrition
Oregon Health & Science University
Portland, OR 97239
Disclosure

Institutional Grants and/or Consultant: Akcea, Amryt, Esperion, Regeneron, RegenxBio, Retrophin
Objectives

I. Present Clinical Case

II. Review risk factors for hypertriglyceridemia

III. Discuss goals of treatment

IV. Review treatment options
Clinical Case

40 yo man with
  Combined hyperlipidemia (h/o TG > 500 mg/dl)
  Impaired Glucose Tolerance (IGT)
  Hypertension (HTN)
  Metabolic Syndrome
  Hypercoagulable state
  Prior Vitamin D deficiency

Weight 90.2 kg, Height 1.702 m
BMI 31.1 kg/m$^2$
BP 129/84
Clinical Case

Exercise: Runs and walks 3 hours weekly

No alcohol intake

Heart healthy dietary habits (after consultation with our dietitian)

Never smoker
Medications

Atorvastatin 10 mg/d
Omega-3 fatty acid ethyl esters 2 grams BID
Niacin ER 1000 mg q hs
Quinapril 40 mg/d
Atenolol 50 mg/d
Apixaban 5 mg BID
Vitamin D3 5000 units/d

Intolerant of fenofibrate due to transaminase elevation
<table>
<thead>
<tr>
<th>Component</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUCOSE, PLASMA</td>
<td>70 - 99 mg/dL</td>
</tr>
<tr>
<td>BUN, PLASMA</td>
<td>6 - 20 mg/dL</td>
</tr>
<tr>
<td>CREATININE PLASMA</td>
<td>0.70 - 1.30 mg/dL</td>
</tr>
<tr>
<td>EGFR</td>
<td>&gt;60 mL/min</td>
</tr>
<tr>
<td>SODIUM, PLASMA</td>
<td>136 - 145 mmol/L</td>
</tr>
<tr>
<td>POTASSIUM, PLASMA</td>
<td>3.4 - 5.0 mmol/L</td>
</tr>
<tr>
<td>CHLORIDE, PLASMA</td>
<td>97 - 108 mmol/L</td>
</tr>
<tr>
<td>TOTAL CO2, PLASMA</td>
<td>21 - 32 mmol/L</td>
</tr>
<tr>
<td>CALCIUM, PLASMA</td>
<td>8.6 - 10.2 mg/dL</td>
</tr>
<tr>
<td>BILIRUBIN TOTAL</td>
<td>0.3 - 1.2 mg/dL</td>
</tr>
<tr>
<td>TOTAL PROTEIN, PL</td>
<td>6.4 - 8.2 g/dL</td>
</tr>
<tr>
<td>ALBUMIN, PLASMA</td>
<td>3.5 - 4.7 g/dL</td>
</tr>
<tr>
<td>ALK PHOS</td>
<td>53 - 128 U/L</td>
</tr>
<tr>
<td>AST(SGOT)</td>
<td>&lt;=41 U/L</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>&lt;=60 U/L</td>
</tr>
<tr>
<td>ANION GAP</td>
<td>4 - 11 mmol/L</td>
</tr>
<tr>
<td>BUN/CREATININE RATIO</td>
<td>8 - 25</td>
</tr>
<tr>
<td>GLOBULIN LVL</td>
<td>2.3 - 3.5 g/dL</td>
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<tr>
<td>ALBUMIN/GLOBULIN RATIO</td>
<td>0.9 - 2.0</td>
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<tr>
<td>CHOLESTEROL</td>
<td>&lt;200 mg/dl</td>
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<tr>
<td>VLDL CHOLESTEROL</td>
<td>&lt;=31 mg/dl</td>
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<tr>
<td>LDL CHOLESTEROL</td>
<td>&lt;100 mg/dl</td>
</tr>
<tr>
<td>HDL CHOLESTEROL</td>
<td>&gt;45 mg/dl</td>
</tr>
<tr>
<td>TOTAL TRIGLYCERIDE</td>
<td>&lt;150 mg/dl</td>
</tr>
<tr>
<td>NON-HDL CHOLESTEROL</td>
<td>&lt;=130 mg/dL</td>
</tr>
<tr>
<td>HEMOGLOBIN A1C</td>
<td>&lt;5.7 %</td>
</tr>
<tr>
<td>ESTIMATED AVERAGE GLUCOSE</td>
<td>mg/dL</td>
</tr>
<tr>
<td>hsCRP</td>
<td>&lt;=2.00 mg/L</td>
</tr>
<tr>
<td>VITAMIN D 25 HYDROXY</td>
<td>30 - 80 ng/mL</td>
</tr>
</tbody>
</table>
HgbA1c 2016-2020
Plasma Non-HDL-C 2016-2020
CT Coronary Artery Calcium Score Imaging Feb 2020

CAC Score 29 (89th percentile)
Plan: February 2020

Add ezetimibe 10 mg/d (LDL-C 131 mg/dl)
Further dietary modification
Increase physical activity
Weight loss
Monitor BP
RTC 3 months
COVID-19 Pandemic

Oregon’s Epi Curve: COVID-19 cases
This chart shows the number of Oregonians who have been identified as COVID-19 cases and whether they were ever hospitalized for their illness.

March 1, 2020

https://govstatus.egov.com/OR-OHA-COVID-19
https://www.ohsu.edu/health/coronavirus-resources#section-1117926
Next Follow-Up January 30, 2021

No follow-up visits for 11 months due to the COVID-19 pandemic
Sedentary
Dietary habits are suboptimal (> 80 g fat intake daily)
Next Follow-Up January 30, 2021

No follow-up visits for 11 months due to the COVID-19 pandemic
Sedentary
Dietary habits are suboptimal (> 80 g fat intake)
Involuntary 20 lb weight loss over a few months
Polyuria and polydipsia
Otherwise feels well
What is his diagnosis?
Lab Results

Glucose 315 mg/dl
AST 47 U/L
ALT 71 U/L
Cholesterol 558 mg/dl
Direct LDL-C 81 mg/dl
HDL-C 28 mg/dl
Triglycerides 3010 mg/dl
HgbA1c 10.1%
Next?
Overt diabetes mellitus (LADA?)

Chylomicronemia

No history of pancreatitis
Chylomicronemia (triglycerides >1000 mg/dl)

Risk factor for pancreatitis

Infrequently caused by mutations in LPL or LPL-related genes (familial chylomicronemia syndrome [FCS])

More commonly related to polygenic defects in triglyceride metabolism and acquired metabolic disorders

Aggravated by insulin resistance/hyperglycemia/relative insulin deficiency, alcohol intake, high fat diet, medications (oral estrogen, prednisone, beta-blockers, thiazides, retinoic acid, etc)

Key interventions:
- Very low fat diet
- Control secondary hypertriglyceridemia
- TG-lowering drugs - often have limited efficacy
Causes of Chylomicronemia

Monogenic chylomicronemia is rare $\sim 1:10^6$
LPL, APOC2, LMF1, APOA5, GPIHBP1

Polygenic chylomicronemia is about 100 times more common
1:10,000-20,000

Lipodystrophy

Multifactorial chylomicronemia (including polygenic + secondary hypertriglyceridemia) occurs in about 1:600
Chylomicronemia-Induced Pancreatitis

Third most common cause of pancreatitis

Gallstones and alcohol are #1 and #2

Triglyceride threshold for pancreatitis is about 2500-3000 mg/dl, but the triglyceride level drops after being NPO prior to ED visit

Some patients never experience pancreatitis and others have > 30 episodes despite intensive preventive efforts
Genetic Risk Factors for Pancreatitis

Genes associated with risk of pancreatitis in patients without hypertriglyceridemia:

Gain-of-function polymorphisms in the cationic trypsinogen gene (PRSS1)

Loss-of-function polymorphisms in the genes that increase trypsin activity:
  Protective anionic trypsinogen (PRSS2)
  Cystic fibrosis transmembrane regulator (CFTR)
  Serine protease inhibitor kazal type 1 (SPINK1)
    [encoding pancreatic secretory trypsin inhibitor (PST1)]

CTFR, SPINK1 (Miniature Schnauzer dogs) and TNF associate with triglyceride-induced pancreatitis
Treatment of Chylomicronemia
Rapid Resolution of Hypertriglyceridemia in Response to Zero Fat Intake and Insulin Administration in a Patient with Pancreatitis and Type 2 Diabetes
Goals of Treatment of Severe Hypertriglyceridemia

Prevention of pancreatitis

Prevention/treatment of hepatic steatosis

Prevention of ASCVD events

Efforts to lower triglycerides are secondary to LDL-C lowering with statins, ezetimibe, +/- bempedoic acid, +/- PCSK9i
Treat Causes of Secondary Hyperlipidemia First

High dietary fat intake

Obesity/Overweight

Hypothyroidism - cholesterol 200 → 350 mg/dl (3-5% of hyperlipidemic patients)

Diabetes Mellitus - ↑ triglycerides, ↓ HDL-C

Drugs (oral estrogen, prednisone, beta-blockers, thiazides, retinoic acid, etc)

Alcohol - ↑ triglycerides, (↑ HDL-C)

Renal Disease - ↑ LDL-C, triglycerides, Lp(a), ↓ HDL-C

Rare (Cushing’s, acromegaly)
Strategies For Dietary and Lifestyle Treatment of Severe Hypertriglyceridemia

Consultation with a dietitian is often invaluable

May allow up to 6 months for dietary implementation (triglycerides can decrease dramatically within the first week after severe reduction in fat intake)

Goals: Decreased caloric intake (sustainable weight loss)

- Limit alcohol intake
- Increased dietary fiber (whole grains)
- Very low dietary fat intake for chylomicronemia (initially < 10-15% of energy intake)
- Increased physical activity
- Avoid fad “diets”
Exogenous and Endogenous Sources of Plasma Lipids

**Exogenous Pathway**

- Dietary Fat (TG)
- INTESTINE
- Apo B-48
- TG
- Chylomicrons

**Endogenous Pathway**

- Fatty Acids
- Glucose
- LIVER
- Apo B-100
- TG
- VLDL

Adapted from Duell & Steiner: Inborn errors of metabolism: Disorders of plasma lipids, lipoproteins and bile acids.
In: Forfar and Amelis Textbook of Pediatrics 2008
**Triglyceride-Lowering Drugs**

**Fibrates:** gemfibrozil 600 mg BID, fenofibrate (120, 130, 145, 160, 200 mg/d [& 1/3 doses]), fenofibric acid (35, 45, 105 and 135 mg/d) - 20-50% TG ↓

**Niacin** 500-4500 mg/d, **Niacin ER** ≤ 2 g/d

**Fish Oil Products:** usually requires 2-4 g EPA + DHA daily regular fish oil (30% EPA/DHA), distilled EPA/DHA ethyl esters, icosapent ethyl (EPA) - 20-50% TG ↓

(Treat diabetes, avoid EtOH, low fat diet)
(Statins are not first line agents; modestly effective for TG lowering: 20-35%)

In Development: volanesorsen (ASO for apo C3), evinacumab (anti-ANGPTL3 mAb), others
Management of Our Patient

Overt diabetes mellitus (LADA?)

Chylomicronemia

No history of pancreatitis

CAD (CAC Score 89th percentile)
Management of Our Patient

Overt diabetes mellitus (LADA?)

PCP prescribed metformin: CBGs 315 --> 170 mg/dl
Refused insulin. Wants to increase exercise, improve diet

Chylomicronemia

No history of pancreatitis

CAD (CAC Score 89th percentile)
Management of Our Patient

Overt diabetes mellitus (LADA?)
  PCP prescribed metformin: CBGs 315 --> 170 mg/dl
  Refused insulin. Wants to increase exercise, improve diet

Chylomicronemia
  Very low dietary fat intake
  Increased exercise

No history of pancreatitis

CAD (CAC Score 89th percentile)
Management of Our Patient

Overt diabetes mellitus (LADA?)
   PCP prescribed metformin: CBGs 315 --> 170 mg/dl
   Refused insulin. Wants to increase exercise, improve diet

Chylomicronemia
   Very low dietary fat intake
   Increased exercise

No history of pancreatitis (so far)
   Advised to go to ED prn symptoms/signs of pancreatitis

CAD (CAC Score 89th percentile)
Management of Our Patient

Overt diabetes mellitus (LADA?)

PCP prescribed metformin: CBGs 315 --> 170 mg/dl

Refused insulin. Wants to increase exercise, improve diet

Chylomicronemia

Very low dietary fat intake

Increased exercise

No history of pancreatitis (so far)

Advised to go to ED prn symptoms/signs of pancreatitis

CAD (CAC Score 89th percentile): LDL-C goal at least < 70 mg/dl
Summary/Take Home Messages

Hypertriglyceridemia is a risk factor for ASCVD, even when LDL-C is well controlled.

Severe hypertriglyceridemia is a risk factor for pancreatitis, but some patients never have pancreatitis.

Rare recessive defects in genes related to LPL cause severe hypertriglyceridemia, often with pancreatitis, but polygenic and multifactorial hypertriglyceridemia is more than 100-fold more common.

Key therapeutic interventions are:

1. Lifestyle modification (eat less, reduce fat intake, lose weight, exercise more, reduce alcohol)
2. Control of secondary hypertriglyceridemia

Drug therapy can be helpful, but will have limited efficacy without the above.

Promising new therapies are under development (apo CIII ASO, ANGPTL3 mAb and ASO, others)

(Volanesorsen is available in the EU)