Inherited Triglyceride Disorders

Anne Carol Goldberg, MD, FNLA
Professor of Medicine
Washington University School of Medicine
May 20, 2016
Disclosures

- Board and committee membership—National Lipid Association, Foundation of National Lipid Association
- Research contracts— Merck, Genzyme/ISIS, Genzyme/Sanofi-Aventis, Glaxo-Smith-Kline, Regeneron/Sanofi-Aventis, Amarin, Amgen, Pfizer, Genentech/Roche, Regeneron, IONIS (all grants to medical school)
- Consulting/Advisory Board—Sanofi-Aventis, OptumRx, uniQure
- Editorial—Merck
Outline

• Case
• General approach to hypertriglyceridemia
• Inheritance patterns
• Specific disorders
• Secondary causes and contributors to hypertriglyceridemia
• Some practical aspects to treatment
Case

- 27 year old man with severe hyperlipidemia
- Presents with rash, triglycerides 8910 mg/dL
- Drinks ½ gallon of Gatorade daily and soda and juices
- Father-hyperlipidemia; mother-high cholesterol
- Power plant worker, no tobacco, rare alcohol
- Exam: BMI 30.6, central obesity
- Diffuse eruptive xanthomas in clusters and singly over back, upper arms, legs, feet
- Referring labs: triglycerides 8910, cholesterol 1156
- Repeat labs: triglycerides 6540 cholesterol 1150 glucose 426 mg/dL, hemoglobin A1c 14.4%
Approach to evaluation of lipid disorders

- What lipoproteins are elevated?
- Likely genetic disorder?
  - Age, symptoms, physical exam, lipids
  - Family history
  - Dominant or recessive pattern
- Contributing conditions?
  - Factors affecting production and clearance
Lipoprotein Subclasses

Uncentrifugation Density gradient

Density (g/mL)

Diameter (nm)

ApoAl

Lp(a)

IDL

LDL

Chylomicron Remnants

Triglycerides (mainly)

PP TG

HDL2

HDL3

HDL Cholesterol

LDL Cholesterol

Apo B

VLDL

Chylomicrons

Uncentrifugation Density gradient

5 10 20 40 60 80 1000

0.95 - 1.006 - 1.02 - 1.06 - 1.10 - 1.12
Composition of Plasma Lipoproteins

<table>
<thead>
<tr>
<th>Chylomicrons</th>
<th>VLDL</th>
<th>IDL</th>
<th>LDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density (g/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.95</td>
<td>0.95-1.006</td>
<td>1.006-1.109</td>
<td>1.019-1.063</td>
<td>1.063-1.21</td>
</tr>
<tr>
<td>Apo B48, CII, CIII, E</td>
<td>Apo B100, CII, CIII, E</td>
<td>Apo B100, CIII, E</td>
<td>Apo B100</td>
<td>Apo Al, All, CII, III, E</td>
</tr>
</tbody>
</table>
LIPOPROTEIN PATHWAYS
Exogenous

Chylomicron remnant uptake

LIVER

GUT

Chylomicron

Chylomicron remnant

CAPILLARIES

Lipoprotein lipase

Fatty acid delivery
### Classification of Lipoprotein Disorders

(Frederickson / Levy / Lees)

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicron</td>
<td>LDL</td>
<td>LDL+ VLDL</td>
<td>Remnants</td>
<td>VLDL</td>
<td>CM+ VLDL</td>
<td></td>
</tr>
</tbody>
</table>

| TG                | N         |           |          |            |             |            |
| Xanthomas         | eruptive  | tendon    | none     | palmar tubero-eruptive | none | eruptive |

| Clinical          | pancreatitis | CHD       | CHD      | CHD        | CHD        | pancreatitis |
| Etiology          | Def. LPL apoC-II | Def LDLR+ | unknown  | apoE2+     | unknown    | unknown     |

| Name              | Familial Chylo Synd | Familial Hyperchol | Mixed Dyslip | Familial Dyslip | Fam Endog HTG |
# Classification of Serum TG Levels

<table>
<thead>
<tr>
<th>2011 AHA Scientific Statement</th>
<th>2012 Endocrine Society</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglyceride Designation</td>
<td>Triglyceride Designation</td>
</tr>
<tr>
<td>mg/dL</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>Borderline-high</td>
<td>150 – 199</td>
</tr>
<tr>
<td>High</td>
<td>200 – 499</td>
</tr>
<tr>
<td>Very high</td>
<td>≥ 500</td>
</tr>
<tr>
<td>Very severe HTG</td>
<td>≥ 2000</td>
</tr>
</tbody>
</table>

Miller, M et al. Circulation. 2011;123:2292-33,
Very-High and Severe HTG are Usually Genetic

- 150 to 500 mg/dL—mild to moderate triglyceride elevations associated with increased cardiovascular risk—possibly polygenic
- Over 500 mg/dL—possibly polygenic
- Over 885 mg/dL (10 mmol/L)—more likely monogenic, associated with risk of pancreatitis

Causes of severe hypertriglyceridemia

- Gene mutations of lipoprotein lipase, apoC2, apoA5, apoE and others—homozygous and heterozygous
- Polygenic less severe mutations
- Combination of genetic and secondary factors
- Congenital and acquired lipoatrophic disorders

Hereditary Dyslipidemias

• Monogenic
  – Less common or rare
  – Large effect mutations

• Polygenic
  – Common small effect mutations
  – Combination of mutations and secondary factors
  – Combination of multiple variants (SNPs)
Hereditary Hypertriglycerideridemia

• Monogenic Hyperchylomicronemia
  • Lipoprotein lipase deficiency
  • ApoCII deficiency
  • Also mutations in apo A5, GPIHBP1 (glycosylphosphatidylinositol-anchored HDL-binding protein 1), LMF1 (lipase maturation factor 1 and others)

• Dysbetalipoproteinemia
  • ApoE mutations

• Polygenic hypertriglycerideridemia
  • Familial hypertriglycerideridemia
  • Familial combined hyperlipidemia: overproduction of apoB

Berglund L et al, J Clin Endocrinol Metab 97: 2969–2989, 2012
Hyperchylomicronemia—monogenic or polygenic/secondary

• Monogenic
  – Very high chylomicrons (absent or very decreased lipoprotein lipase function →delayed chylo clearance)
  – Acute/recurrent pancreatitis
  – Eruptive xanthomas/lipemia retinalis
  – Neuropathy, memory loss
  – Fatty liver
• Polygenic
  – Increased VLDL (hepatic overproduction + delayed VLDL clearance)
  – Adult onset
  – Obesity-related
  – Diabetes-related
  – Multifactorial and variable LPL and other mutations

Secondary hypertriglycerideridemia

- Dietary: high calorie, fat, sugar
- Alcohol
- Obesity
- Metabolic syndrome
- Drugs including: thiazides, beta-blockers, oral estrogens, isotretinoin, corticosteroids, bile acid-binding resins, protease inhibitors, cyclophosphamide, asparaginase, antipsychotics
- Untreated diabetes mellitus
- Endocrine diseases: hypothyroidism
- Renal disease (nephrotic syndrome, uremia)
- Pregnancy (especially third trimester)
- Autoimmune disorders—SLE
- Paraproteinemia

Berglund L et al, J Clin Endocrinol Metab 97: 2969–2989, 2012
Familial hyperchylomicronemia

• Mutations of lipoprotein lipase or apo CII (and other rare gene mutations)
• Autosomal recessive inheritance
• Frequency 1:1,000,000 or higher with founder effect, heterozygotes 0.04-22%
• Impaired intravascular lipolysis
• Severely elevated triglycerides and chylomicrons, LDL-C low, HDL-C low, severe post-prandial lipemia
• Abdominal pain, eruptive xanthomas, hepatosplenomegaly, lipemia retinalis, acute pancreatitis, neuropathy, onset in childhood
• Treat with very low fat diet

Berglund L et al, J Clin Endocrinol Metab 97: 2969–2989, 2012
Hyperchylomicronemic Disorders

- Lipemia retinalis
- Eruptive xanthoma
- Hepatosplenomegaly
Eruptive xanthomas
Familial dysbetalipoproteinemia

- Autosomal recessive, mutations of ApoE (rare mutation causes autosomal dominant form)
- Impaired hepatic uptake of VLDL and chylomicron remnants
- E2/E2 genotype plus a second genetic or acquired defect
- High cholesterol and triglyceride levels-300 to 1000 mg/dL and roughly equal
- Increased vascular disease
- Palmar and tuberoeruptive xanthomas
- May be very sensitive to lifestyle change

Tuberous Xanthomas
Tuberous Xanthoma
Familial combined hyperlipidemia

- Common; 1 to 2% of population
- Classically, autosomal dominant
- “Familial” implies genetic cause but actual molecular basis is unclear
- Likely a number of genetic causes
  Multiple genes, heterozygosity for defects in lipoprotein lipase
- Variable phenotype—high cholesterol or high triglycerides or both
- Overproduction of apoB, increased VLDL particles, small dense LDL
- Increased risk of CHD

Familial hypertriglyceridermia

- Common (1% of population), possibly autosomal dominant
- Increased triglyceride synthesis, large VLDL particles
- Triglycerides 250 to 1000 mg/dL
- No clear risk of CHD but risk of chylomicronemia with obesity, high carbohydrate diet, estrogen, alcohol, diabetes
- Likely polygenic
- No typical physical findings: but findings of chylomicronemia syndrome if triglycerides are higher enough

Endocrine Society Clinical Practice Guidelines on the Evaluation of Hypertriglyceridemia

• Recommend screening adults for hypertriglyceridemia as part of a lipid panel at least every 5 years

• The diagnosis should be based on fasting triglyceride levels

• Individuals found to have any elevation of fasting triglycerides should be evaluated for secondary causes of hyperlipidemia

• Patients with primary hypertriglyceridemia should be assessed for other CV risk factors and for a family history of dyslipidemia and CV disease to assess genetic causes and future CV risk

From Berglund et al. J Clin Endocrinol Metab 2012; 97: 2969
Causes of hypertriglyceridemia—
dietary factors

Increased chylomicrons
  Fat

Increased VLDL production
  • Excess calories
  • Alcohol
  • Obesity
  • Sugar, simple carbohydrates
  • Fats
  • Weight gain

Berglund L et al, J Clin Endocrinol Metab 97: 2969–2989, 2012
Causes of hypertriglyceridemia—disorders and conditions

- Metabolic syndrome
- Untreated diabetes mellitus
- Insulin resistance
- Endocrine diseases: hypothyroidism
- Renal disease (nephrotic syndrome, chronic kidney disease)
- HIV infection
- Pregnancy (especially third trimester)
- Polycystic ovary syndrome
- Autoimmune disorders—SLE
- Paraproteinemia

Berglund L et al, J Clin Endocrinol Metab 97: 2969–2989, 2012
Drugs that raise triglycerides

- Oral estrogens, tamoxifen, raloxifene
- Retinoids
- Immunosuppressive drugs (cyclosporine, sirolimus)
- Interferon
- Beta-blockers (especially non-beta 1-selective)
- Atypical antipsychotic drugs (clozapine, olanzapine)
- Protease inhibitors
- Thiazide diuretics
- Glucocorticoids
- Bile acid sequestrants
- L-asparaginase
- Cyclophosphamide

Berglund L et al, J Clin Endocrinol Metab 97: 2969–2989, 2012
Treatment of hypertriglyceridemia

• Moderately high (150 to 880 mg/dL—1.7 to 10 mmol/L)
  – Prevent cardiovascular disease
  – Treat secondary factors (i.e. diabetes)
  – Reduce body weight, reduce alcohol, reduce simple sugars and total carbohydrate, increase dietary omega-3 fatty acids
  – Statins if high risk or high LDL-C
  – Fibrates, omega-3, niacin for triglycerides that remain above 500 mg/dL
Treatment of hypertriglyceridemia

• High (500 mg/dL and above, especially >880 mg/dL--10 mmol/L)
  – Prevent pancreatitis
  – Treat secondary factors (i.e. diabetes)
  – No oral intake if having pancreatitis
  – Post pancreatitis fat intake <20% of calories
  – Reduce body weight, reduce alcohol, reduce simple sugars and total carbohydrate, increase dietary omega-3 fatty acids; increased physical activity
  – Fibrates, omega-3, niacin for triglycerides that remain above 500 mg/dL
  – Statins once triglycerides are down
### Dietary Measures to Lower TG Levels

<table>
<thead>
<tr>
<th>Change</th>
<th>TG Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>10% – 20%</td>
</tr>
<tr>
<td>(5-10% ↓ body weight : 1 kg ↓ → 2% TG ↓)</td>
<td></td>
</tr>
<tr>
<td>“Mediterranean” diet (fiber, fish, fruits/veg) (vs. high-carb/low-fiber diet)</td>
<td>10% – 15%</td>
</tr>
<tr>
<td>Marine-derived omega-3 (EPA/DHA)/gram (herring ≈ salmon &gt; trout &gt; tuna)</td>
<td>5% – 10%</td>
</tr>
<tr>
<td>↓ Carbohydrates by 5-10% of energy (1-2% ↓ per 1% energy replacement w/MUFA or PUFA)</td>
<td>5% – 20%</td>
</tr>
<tr>
<td>Eliminate <em>trans</em> fats (1% ↓ per 1% energy replacement with MUFA/PUFA)</td>
<td>1% – 3%</td>
</tr>
</tbody>
</table>

MUFA = monounsaturated FA; PUFA = polyunsaturated FA.
Physical Exercise Lowers TG

• ↓TG is usually the first/strongest lipid effect of ↑physical activity
• % ↓TG is directly proportional to:
  – Baseline TG
  – Amount of exercise (no minimum threshold)
• Aerobic activity better
• Frequency and intensity important
• Exercise can block CHO-induced ↑TG
• ↓VLDL production and ↑VLDL clearance

Jensen MD et al. *J Am Coll Cardiol*. 2013;Nov 7 [Epub ahead of print]
Case

• 27 year old man with severe hyperlipidemia
• Presents with rash, triglycerides 8910 mg/dL
• Drinks ½ gallon of Gatorade daily and soda and juices
• Father-hyperlipidemia; mother-high cholesterol
• Power plant worker, no tobacco, rare alcohol
• Exam: BMI 30.6, central obesity
• Diffuse eruptive xanthomas in clusters and singly over back, upper arms, legs, feet
• Referring labs: triglycerides 8910, cholesterol 1156
• Repeat labs: triglycerides 6540 cholesterol 1150 glucose 426 mg/dL, hemoglobin A1c 14.4%
Initial approach to the patient with triglycerides over 2000

• History
  – Past history of lipid disorders, pancreatitis, rash
  – Medications
  – Detailed family history

• Assess diet
  – Food records or recall
  – Ask about beverages: alcohol, soda, juice, sweetened drinks
Initial approach to the patient with triglycerides over 2000

• Physical exam
  – Fundoscopic: lipemia retinalis (trig >4000)
  – Skin--eruptive xanthomas, palmar xanthomas, tuberous xanthomas

• Laboratory
  – Measure blood glucose, TSH, creatinine
  – Urine dipstick for protein
  – Fasting lipid profile
  – CBC, ANA
Diabetes and lipids

- Increased triglycerides, low HDL-C, small dense LDL
- Increased free fatty acids to the liver increase VLDL production
- Decreased insulin affects lipoprotein lipase function
- Saturation of lipoprotein lipase at trig > 400
- Triglycerides can spiral up quickly, especially with underlying lipid disorder
Lowering triglycerides

- Glycemic control & lifestyle modification including diet and exercise
- Statins provide some lowering
- Fibrates, omega 3 fatty acids and niacin better triglyceride lowering medications
- Niacin second line therapy
- Fish oil with statin or added to combination drug therapy
- Fenofibrate preferred in combination with statins
Hypertriglyceridemia: diet and diabetes

- Diet can be critical—calories, fat, sugar, alcohol
- Have the patient bring in food records and blood sugar logs
- Assess beverage intake
- Give specific diet recommendations and refer to dietitian and diabetes educator
- Diabetes and pre-diabetes: metformin helps lower triglycerides
Hypertriglyceridemia practical issues

• Bedtime insulin can be very useful
• LDL cholesterol will often increase when you lower triglycerides
• Always check the medication list
• Acute illness can raise triglycerides
• Assess cardiovascular risk and use statins when applicable
Take home points

• Hereditary triglyceride disorders may be monogenic or polygenic
• Diet, other conditions and medications can contribute to high triglyceride levels.
• Treatment needs to address secondary issues as well as the hereditary