GW is a 47 yo female who presents with a recent diagnosis of hyperlipidemia and chest pain. Both cholesterol and triglycerides are reported to be elevated.

PMH:
- possible hypertension
- gestational diabetes

Medications: none
What are Triglycerides?

Triglycerides in People

Internal

External
**Cholesterol in People**

**What Do Lipids Do?**

**Steroid Hormones:**
- Testosterone
- Estrogen
- Cortisol
- Aldosterone
- (Fat soluble vitamins)
Lipoprotein Pathophysiology

All lipoproteins carry:
- Cholesterol
- Triglycerides
- Phospholipids

Differ in relative concentrations of lipid

Differ in apolipoproteins

<table>
<thead>
<tr>
<th>Major Apolipoproteins</th>
<th>Lipoprotein association</th>
<th>Primary source</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoA-I</td>
<td>HDL</td>
<td>Intestine, liver</td>
<td>Structural protein for HDL; activator of LCAT; binds ABCA1, SR-B1</td>
</tr>
<tr>
<td>ApoA-II</td>
<td>HDL</td>
<td>Liver</td>
<td>Inhibits reverse chol transport</td>
</tr>
<tr>
<td>ApoA-IV</td>
<td>HDL, CM, VLDL</td>
<td>Intestine</td>
<td>Unknown (satiety?)</td>
</tr>
<tr>
<td>ApoB-48</td>
<td>CM</td>
<td>Intestine</td>
<td>Chylomicron synthesis and secretion</td>
</tr>
<tr>
<td>ApoB-100</td>
<td>VLDL, IDL, LDL Lp(a)</td>
<td>Liver</td>
<td>VLDL synthesis and secretion; ligand for binding to LDL-receptor</td>
</tr>
<tr>
<td>ApoC-I</td>
<td>CM, VLDL, HDL</td>
<td>Liver</td>
<td>Inhibit CETP &amp; particle removal</td>
</tr>
<tr>
<td>ApoC-II</td>
<td>CM, VLDL, HDL</td>
<td>Liver</td>
<td>Cofactor for LPL</td>
</tr>
<tr>
<td>ApoC-III</td>
<td>CM, VLDL, HDL</td>
<td>Liver</td>
<td>Inhibits LPL &amp; particle removal</td>
</tr>
<tr>
<td>ApoE</td>
<td>CM, IDL, HDL</td>
<td>Liver, Brain</td>
<td>Ligand for binding to LDL-receptor and LRP; chol efflux (macro)</td>
</tr>
<tr>
<td>Apo(a)</td>
<td>Lp(a)</td>
<td>Liver</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Lipoprotein Pathophysiology

- Where do triglyceride-rich lipoproteins come from? (CM & VLDL)
VLDL Composition:
Balance TG, PL, & Chol available from diff sources
One apoB per particle
Cholesterol is required
No TG → no particle
More TG → larger & more particles

Abetalipoproteinemia:
Homozyg defic of MTP

Lipoprotein Pathophysiology

- LPL removes TG from both CM & VLDL
• What are the possible genetic causes of Hypertriglyceridemia?
  – Total Lipoprotein Lipase Deficiency (Type I HLP)

**Lipoprotein Pathophysiology**

- Why is this not the likely diagnosis?

  This disease presents in **infancy** with severe lipemia, abdominal pain, and pancreatitis; later – eruptive xanthomas
GW is a 47 yo female who presents with a recent diagnosis of hyperlipidemia and chest pain. Both cholesterol and triglycerides are reported to be elevated.

PMH:
- possible hypertension
- gestational diabetes

Medications: none

Lipoprotein Pathophysiology

What are the possible genetic causes of Hypertriglyceridemia?
- Total Lipoprotein Lipase Deficiency (Type I HLP)
- Familial Combined Hyperlipidemia (Type IIb)

**Features:** (FCHL)
Over production of apoB

- Mixed lipid phenotypes in patient & family
- Increase in VLDL particles w/ normal composition
- Usually evident by age 30
- High risk of CVD (even in pre-meno women)
Endogenous Lipid Metabolism

IDL & LDL → LDL-R
(~90% in Liver)
IDL via apoE
LDL via apoB
~50% IDL → LDL
(requires apoE & HL)

LDL left over → arteries
LDL-R saturated: [LDL] 25

Phenotype
is determined by
the effectiveness of
TG and apoB clearance

Lipoprotein Pathophysiology

- What are the possible genetic causes of Hypertriglyceridemia?
  - Total Lipoprotein Lipase Deficiency (Type I HLP)
  - Familial Combined Hyperlipidemia (Type IIb)

Hypobetalipoproteinemia:
Truncated apoB (89, 75, 55, 31)
Rapid clearance of VLDL & IDL
shorter → faster
T. Chol frequently < 120 mg/dl
Heterozyo: low CVD
Homozyo: vitamin defic (A, E, K)
acantho, retinitis pigmentosa,
neuromuscular degeneration
• What are the possible genetic causes of Hypertriglyceridemia?
  – Total Lipoprotein Lipase Deficiency (Type I HLP)
  – Familial Combined Hyperlipidemia (Type IIb)
  – Familial Hypertriglyceridemia (Type IV)

**Lipoprotein Pathophysiology**

**Features:** (FHT)
- Over production of TG
- Single phenotype
- Increase in size of VLDL particles with high TG/apoB
- Usually evident by age 30
- Some families at high risk of CVD
GW is a 47 yo female who presents with a recent diagnosis of hyperlipidemia and chest pain. Both cholesterol and triglycerides are reported to be elevated.

Family Hx:
- Critical

Suggestive of FCHL:
+ CVD
Multiple affected
High TG & Chol

What are the possible genetic causes of Hypertriglyceridemia?
- Total Lipoprotein Lipase Deficiency (Type I HLP)
- Familial Combined Hyperlipidemia (Type IIb)
- Familial Hypertriglyceridemia (Type IV)
- Another diagnosis?
Lipoprotein Pathophysiology

• **Dysbeta1ipoproteinemia (Type III)**
  • abnormal apoE (apoE-2)

---

**CM-R and IDL cannot be cleared by liver and IDL cannot be converted to LDL**
Lipoprotein Pathophysiology

- **Dysbetalipoproteinemia (Type III) Metabolism**

Transfer of chol-esters from HDL to IDL causes it to enlarge back to the size of VLDL.

**beta-VLDL**

particles the size of VLDL but w/ chol-rich core

Lipoprotein Pathophysiology

- **Dysbetalipoproteinemia (Type III) Isolation**

Transfer of chol-esters from HDL to IDL causes it to enlarge back to the size of VLDL.

**beta-VLDL**

particles the size of VLDL but w/ chol-rich core
Dysbetalipoproteinemia (Type III)

Because apoE isotypes have different charges, they can be identified by IEF gels.

Most apoE-2 homozygotes do not have Type III HLP.

Why?

Lipoprotein Pathophysiology

Because apoE isotypes have different charges, they can be identified by IEF gels.

Most apoE-2 homozygotes do not have Type III HLP.

Why?
Lipoprotein Pathophysiology

- **Dysbetalipoproteinemia (Type III) Diagnosis**
  - abnormal apoE (apoE-2)

GW is a 47 yo female

Lab reports:
- High VLDL, IDL, LDL
- Normal total HDL
- Low HDL-L
- Fasting glucose = 119 mg/dl
- ApoE-2/E-4 heterozyg
  - Probably not Type III
  - How would this impact LP metabolism?
Lipoprotein Metabolism

- What are the possible genetic causes of Hypertriglyceridemia?
  - Total Lipoprotein Lipase Deficiency (Type I HLP)
  - Familial Combined Hyperlipidemia (Type IIb)
  - Familial Hypertriglyceridemia (Type IV)
  - **Dysbetalipoproteinemia (Type III)**
    - abnormal apoE (apoE-2)
    - accumulation of remnants (CM-R and IDL)
    - cholesterol enrichment of these remnants
    - high incidence of CVD, esp PVD
    - exacerbated by environmental factors
      - obesity, diabetes, etc
    - specific laboratory diagnostic tests available
• GW is a 47 yo female who presents with a recent diagnosis of hyperlipidemia and chest pain. Both cholesterol and triglycerides are reported to be elevated.

• **Physical Exam:**
  - Weight: 186 pounds  Height: 65 inches
  - WHR: 0.91  BP: 135/92
  - Otherwise unremarkable except for skin exam
  - How do these finding contribute to her possible diagnosis?

---

**Lipoprotein Pathophysiology**

• What are the possible environmental causes of Hypertriglyceridemia?
  - Obesity, especially visceral obesity

**Connection between WHR and HTG is insulin resistance**

Visceral obesity determined by waist to hip ratio

Connection between WHR and HTG is insulin resistance
## Relation Between Insulin Resistance and Hypertriglyceridemia

![Graph showing the relation between plasma triglycerides and insulin response to oral glucose.](image)

- **Insulin Response to Oral Glucose**: Total area under 3-hour response curve (mean of 2 tests).
- **Plasma TG (mg/dL)**
  - r = 0.73
  - \( P < 0.0001 \)

### Key Points
- **Lipoprotein Pathophysiology**
  - What are the possible environmental causes of Hypertriglyceridemia?
    - Obesity, especially visceral obesity

### Fat Cell Size
- Determined by balance of incoming TG and outgoing FFA

### Footnotes
What are the possible environmental causes of Hypertriglyceridemia?
- Obesity, especially visceral obesity, free fatty acids

Visceral fat cells are always releasing FFAs which go directly to the liver.

Visceral Obesity: Etiology

Pituitary-Adrenal Arousal Hypothesis

Stress

Defeat

FFA ➔ ACTH ➔ Cortisol, Androgens, Aldosterone

FSH, LH ➔ Testosterone, Estradiol (ovarian androgens)

“Hypercortisolism + Transitional Androgenic State”
• What are the possible environmental causes of Hypertriglyceridemia?
  – Obesity, especially Visceral Obesity
  – Type 2 Diabetes or Hyperglycemia

Typically, fructose is the major dietary sugar that contributes to HTG

DM: plasma glucose is high enough to be shunted into TG synthesis

• GW is a 47 yo female who presents with a recent diagnosis of hyperlipidemia and chest pain. Both cholesterol and triglycerides are reported to be elevated.
• PMH: Gestational Diabetes
• Diet: High starch, sugar, and fat (pastries)
• Physical Exam:
  – Weight: 186 pounds  Height: 65 inches
  – WHR: 0.91  BP: 135/92
  – Otherwise unremarkable except for skin exam
Lipoprotein Pathophysiology

- GW is a 47 yo female
- Physical Exam: What do these lesions mean?

Would you expect these skin findings?
Lipoprotein Pathophysiology

- GW is a 47 yo female
- Physical Exam:

Would you expect these skin findings?

Lipoprotein Pathophysiology

- GW is a 47 yo female
- Physical Exam:

Would you expect these skin findings?
Lipoprotein Pathophysiology

- GW is a 47 yo female
- Physical Exam:

What are these and what do they mean?

Lipoprotein Pathophysiology

- What are the possible genetic causes of Hypercholesterolemia?
  - Familial Combined Hyperlipidemia (apoB - Type IIb)
  - Dysbetalipoproteinemia (apoE2 - Type III)
  - Familial Hypercholesterolemia (LDL-R - Type IIa)
Lipoprotein Pathophysiology

• What are the possible genetic causes of Hypercholesterolemia?
  – Familial Combined Hyperlipidemia (Type IIb)
  – Dysbetalipoproteinemia (Type III)
  – Familial Hypercholesterolemia (Type IIa)
Lipoprotein Pathophysiology

• Could this patient have FH?

Lipoprotein Pathophysiology

• What are the possible genetic causes of Hypercholesterolemia?
  – Familial Combined Hyperlipidemia (Type IIb)
  – Dysbetalipoproteinemia (Type III)
  – Familial Hypercholesterolemia (Type IIa)
  – Polygenic Hypercholesterolemia

Multiple minor genetic abnormalities that together increase cholesterol
• What is an important non-genetic cause of Hypercholesterolemia?
  – Hypothyroidism

Lipoprotein Pathophysiology

GW is a 47 yo female who presents with a recent diagnosis of hyperlipidemia and chest pain. Both cholesterol and triglycerides are reported to be elevated.

• PMH: Gestational Diabetes
• Diet: High starch, sugar, and fat (pastries)

• Physical Exam:
  – Weight: 186 pounds  Height: 65 inches
  – WHR: 0.91  BP: 135/92
  – Otherwise unremarkable except for skin exam
Lipoprotein Pathophysiology

### HDL:
- What is the importance of her HDL composition?
  - Low HDL-L but normal total HDL
- Where does HDL come from and what does it do?

Reverse Cholesterol Transport

Movement of cholesterol from peripheral tissues to the liver
Fam ApoA-I Deficiency:
HDL-C < 5 (absent synth) nl TG
CVD, Planar Xanth, Cataracts

Fam ApoA-I mutants
HDL 15-30 (rapid clearance) HTG
Cataracts, CVD? (A-I Milano)

LCAT Deficiency:
HDL-C < 10, HTG
Complete – Fam LCAT Def
Anemia, Renal D (prot),
Cataracts
Partial – Fish Eye D
VLDL, LDL Activity OK

ABC-A1 Deficiency:
HDL-C < 5, HTG
Tangiers Disease
CVD, Orange tonsils,
Cataracts, Neuropathy,
Hepatosplenomegaly

Figure 28-2. HDL metabolism.
Reverse Cholesterol Transport

CETP Deficiency:
- Very high HDL-C, low LDL
- Some Families: low CVD
- Others: High CVD

An increase in LPL activity (exercise) increases HDL-C (HDL-2)
Reverse Cholesterol Transport

An increase in HL activity decreases HDL (HDL-2 & 3) (Liver, adrenal, gonads)

Removes PL and TG
Removes entire particle
Prefers smaller particles

Stimulate († HDL):
T₃, Insulin, Testosterone

Inhibit (↓ HDL):
Estrogens, Adiponectin

Fam HL Defic: Severe HTG, Chol ~600

Atherosclerosis: Effects of Hypertriglyceridemia

Excess VLDL, IDL, and CM’s:

Exchange TG and CE: "Chol. Ester Transfer Protein" (CETP)

LDL and HDL --> TG-enriched

Hepatic Lipase (HL) removes TG and PL († insulin and androgens)

HDL and LDL become small and more dense
ApoA-I is shed from smaller HDL particles → ↑ catabolism
**Atherosclerosis: Small, Dense LDL**

**Atherogenicity of Small, Dense LDL:**

- Reduced binding to LDL receptor ---> prolonged plasma circulation
- More easily glycated and oxidized ---> removed by scav. receptor
- LDL catabolism diverted from Liver ---> Arterial Plaques
- Better substrate for Hepatic Lipase ---> further size reduction
- Easier transit through endothelial layer
- Increased binding to collagen in subendothelial space

---

**Cumulative Distribution of Adjusted Plasma TG Levels: LDL Phenotypes A and B**

Cumulative Distribution of Adjusted HDL-C: LDL Phenotypes A and B

HDL Recept in Liver

Particle vs Chol Ester Uptake

Re-cycle


HDL-C (mg/dL)

% Cumulative frequency

20 25 30 35 40 45 50 55 60 65 70 75 80

Phenotype A
Phenotype B

Small, Dense LDL

HDL Recept in Liver

Hepatic Lipase

Cholesterol

CE Lipase

Amino Acids Deplete apoA-I

SR-B1

Re-cycle
Reverse Cholesterol Transport

Multiple potential pathways for cholesterol transport

Reverse Cholesterol Transport

Multiple potential pathways for cholesterol transport
Reverse Cholesterol Transport

Increase in Cellular Cholesterol $\rightarrow$ Increase HDL-C, LDL-C

Control of Cholesterol Transport

Tissue concentration of cholesterol critical to plasma [HDL]
Modulators of Cholesterol Transport

Multiple potential pathways for cholesterol transport

Atherosclerosis

Plasma total HDL cholesterol concentration does not necessarily reflect reverse cholesterol transport

Clinical Question:
How does a therapy affect reverse cholesterol transport?
**HDL Subfractions**

- "A-I + A-II" HDL (HDL-M)
- (HDL-D)
- HDL (HDL-D)

**Reverse Cholesterol Transport**

Separation of (A-I + A-II) particles from (A-I alone) HDL particles by affinity chrom

Cheung et al., J Lipid Res 28:913-929, 1987
Reverse Cholesterol Transport

Separation of (A-I + A-II) particles from (A-I alone) HDL particles by affinity chrom

Cheung et al., J Lipid Res 28:913-929, 1987

Niacin & Gemfibrozil --> LpA-I
Sakai et al, Arterioscler 21:1783-1789, 2001

LpAl delivered more Cholesterol to HepG2 cells than LpAI:AII (SR-B1)

Neither drug altered this delivery

<table>
<thead>
<tr>
<th>TABLE 3. Effect of Niacin and Gemfibrozil on the Uptake of [3H]CE-Labeled Lp-AI and Lp-AI+AII Particles by Hep G2 Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Niacin, mg/mL</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>Gemfibrozil, µg/mL</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>200</td>
</tr>
<tr>
<td>400</td>
</tr>
</tbody>
</table>

Values are mean±SD.
*P<0.05 for Lp-AI vs Lp-AI+AII.
Niacin & Gemfibrozil --> LpA-I
Sakai et al, Arterioscler 21:1783-1789, 2001

Niacin inhibited the uptake of LpA-I particles
Neither drug affected the uptake of LpA-I:AII

Both increase HDL-C and apoA-I and decrease apoB
Gemfib increases LDL-C
Niacin & Gemfibrozil --> LpA-I
Sakai et al, Arterioscler 21:1783-1789, 2001

Both increase LpAI:AII
Only niacin increases LpA-I
(Gem may reduce LpA-I)

HDL “apoA-I alone” Particles

- ApoAI (HDL) particles initiate cholesterol efflux
- “ApoA-I alone” HDL particles:
  - More potent in effluxing cholesterol (ABC A1)
  - More efficient donors of CE (SR-B1)
  - Bind LCAT and CETP more efficiently
  - More closely associated with prevention
  - Higher in women
  - Synthesis stimulated by estrogen
  - Levels increased by niacin
**Niacin & Gemfibrozil --> LpAI**
Sakai et al, Arterioscler 21:1783-1789, 2001

- Conclusions:
  - Niacin increases LpAI but gemfib does not
  - Niacin blocks LpAI particle uptake by HepG2
  - CE uptake by HepG2 cells is 75% greater from LpAI than LpAI:AII
  - Neither drug affects selective CE uptake

- Niacin appears to increase LpAI by blocking particle removal by Hep Lipase

---

**Lipoprotein Composition Analysis**

Hughes et al, J Lipid Res 29:363-376, 1988
Lipoprotein Composition Analysis

Hughes et al, J Lipid Res 29:363-376, 1988

"Light" LpAI Deficiency

Four sisters with clinical CVD before menopause
never smoked
no DM (<130% IBW)
3 mild HBP, well controlled

TC = 236*  
TG = 248*  
apoB = 84  
HDL-C = 57  
apoA-I = 164  
apoA-II = 67*

Hughes et al, J Lab Clin Med 119:57-68, 1992
### Lipoprotein Compositional Analysis

#### Patient 1

<table>
<thead>
<tr>
<th>Lipoprotein Fraction</th>
<th>T. Chol (mg/dl)</th>
<th>Triglycerides (mg/dl)</th>
<th>HDL (mg/dl)</th>
<th>LDL (mg/dl)</th>
<th>LDL-C (mg/dl)</th>
<th>Lp(a) (mg/dl)</th>
<th>Total LDL-C to HDL-C Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL</td>
<td>119</td>
<td>31</td>
<td>28</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDL</td>
<td>254</td>
<td>63</td>
<td>19</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>154</td>
<td>47</td>
<td>111</td>
<td>29</td>
<td>9</td>
<td>13</td>
<td>2.62</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>0.06</td>
<td>0.07</td>
<td>0.74</td>
<td>0.70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-L</td>
<td>0.14</td>
<td>0.10</td>
<td>0.74</td>
<td>0.70</td>
<td>0.14</td>
<td>0.10</td>
<td>1.08</td>
</tr>
<tr>
<td>HDL-M</td>
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<td>0.74</td>
<td>0.70</td>
<td>0.14</td>
<td>0.10</td>
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<tr>
<td>HDL-D</td>
<td>0.14</td>
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<td>0.74</td>
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</table>

#### Patient 2

<table>
<thead>
<tr>
<th>Lipoprotein Fraction</th>
<th>T. Chol (mg/dl)</th>
<th>Triglycerides (mg/dl)</th>
<th>HDL (mg/dl)</th>
<th>LDL (mg/dl)</th>
<th>LDL-C (mg/dl)</th>
<th>Lp(a) (mg/dl)</th>
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Reverse Cholesterol Transport

Movement of cholesterol from peripheral tissues to the liver

HDL Recycles
Others do not
Atherosclerosis is an Occult Disease

This disease progresses for years before becoming symptomatic

Understand the disease and treat early