Role of Lipids (Lipoproteins) in Metabolism

<table>
<thead>
<tr>
<th>Triglycerides</th>
<th>Major energy source for cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>Cell growth, cell division, membrane repair, steroid hormone production</td>
</tr>
<tr>
<td>Lipids</td>
<td>Transport of fat soluble vitamins</td>
</tr>
</tbody>
</table>

Normal Plasma Lipid Levels (mg/dl)

<table>
<thead>
<tr>
<th></th>
<th>Triglyceride</th>
<th>Total Chol.</th>
<th>HDL-Chol</th>
<th>TC/HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult female</td>
<td>80</td>
<td>190</td>
<td>55</td>
<td>3.5</td>
</tr>
<tr>
<td>Adult male</td>
<td>120</td>
<td>200</td>
<td>43</td>
<td>4.7</td>
</tr>
<tr>
<td>Neonate</td>
<td>35</td>
<td>70</td>
<td>35</td>
<td>2.0</td>
</tr>
</tbody>
</table>

OUTLINE

- Metabolism of Lipoprotein
- Dyslipidemia of the Metabolic Syndrome
- Management of Combined Hyperlipidemia in children
- Case Presentations
Lipoprotein Nomenclature and Composition

- **CM**: chylomicron
- **VLDL**: very low density lipoprotein
- **IDL**: intermediate density lipoprotein
- **LDL**: low density lipoprotein
- **HDL**: high density lipoprotein
- **apoB**: apolipoprotein B
- **apoA-I**: apolipoprotein A-I

### Major Apolipoproteins and Their Function

<table>
<thead>
<tr>
<th>Apo</th>
<th>Lipoprotein</th>
<th>Origin</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoA-I</td>
<td>HDL</td>
<td>Liver, intestine</td>
<td>Activate LCAT, Cholesterol efflux via ABCA1 transporter</td>
</tr>
<tr>
<td>ApoB-100</td>
<td>VLDL, LDL</td>
<td>Liver</td>
<td>Ligand LDL receptor, TG transport from cells</td>
</tr>
<tr>
<td>Apo(a)</td>
<td>Lp(a)</td>
<td>Liver</td>
<td>Inhibits fibrinolysis</td>
</tr>
<tr>
<td>ApoCII</td>
<td>HDL, VLDL</td>
<td>Liver</td>
<td>Activates lipoprotein lipase</td>
</tr>
<tr>
<td>ApoE</td>
<td>VLDL, IDL</td>
<td>Liver, intestine</td>
<td>Ligand, LDL receptor, LRP receptor</td>
</tr>
</tbody>
</table>

**LCAT**: lecithin:cholesterol acyltransferase
**ABCA1**: ATP binding cassette protein A1
**LRP**: LDL receptor related protein

Table 2-3. Composition and Properties of the Major Lipoproteins

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Origin</th>
<th>Core Lipids</th>
<th>Primary Apolipoproteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>Gut</td>
<td>TG</td>
<td>C, E, B-48</td>
</tr>
<tr>
<td>VLDL</td>
<td>Liver</td>
<td>TG</td>
<td>C, E, B-100</td>
</tr>
<tr>
<td>IDL</td>
<td>VLDL</td>
<td>CE</td>
<td>E, B-100</td>
</tr>
<tr>
<td>LDL</td>
<td>VLDL, IDL</td>
<td>CE</td>
<td>B-100</td>
</tr>
<tr>
<td>HDL</td>
<td>Liver, gut, intravascular metabolic reactions</td>
<td>CE</td>
<td>A, A II, C, E</td>
</tr>
</tbody>
</table>

Table 4-1. Classification of Hyperlipoproteinemias by Phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Lipoprotein Elevated</th>
<th>Lipid Elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chylomicrons</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>II A</td>
<td>LDL</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>II B</td>
<td>VLDL, LDL</td>
<td>Cholesterol, triglycerides</td>
</tr>
<tr>
<td>III</td>
<td>IDL</td>
<td>Cholesterol, triglycerides</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>V</td>
<td>Chylomicrons, VLDL</td>
<td>Triglycerides, cholesterol</td>
</tr>
</tbody>
</table>

Role of Genes
DOES ATHEROSCLEROSIS BEGIN IN CHILDHOOD? IS IT RELATED TO DYSLIPIDEMIA?

PREVALENCE OF FIBROUS PLAQUE LESIONS IN CHILDREN

Berenson G et al, NEJM 1998

Relations between Carotid IMT and quartiles of LDL-C measured in Childhood and Adulthood.

Shengstu L et al JAMA, 2003

Is Total Cholesterol a Useful Measure?

• LDL-C, not TC, is the primary target of cholesterol lowering therapy
• Serum LDL-C <130 mg/dL is the goal
• Total Cholesterol is useful for initial detection, with LDL-C used for risk assessment and therapy selection
• If used alone, TC may underestimate CAD risk
**CAD Risk Intervention Goals in Childhood**

- LDL-C < 130 mg/dl ( < 100 mg/dl in children with diabetes)
- Fasting TG < 150 mg/dl
- HDL-C > 35 mg/dl
- Blood Pressure < 95th percentile for age, sex, and height
- Body weight < 95th for gender and age
- Smoking: complete cessation

**Major modifiable Risk Factors for CAD**

- Elevated LDL-Chol
- Hypertension
- Smoking
- Obesity
- DM
- Physical Inactivity

**THE DYSLIPIDEMIA OF THE METABOLIC SYNDROME:**

- High TGs and Low HDL

How do we get there?

**Metabolic Syndrome: A Constellation of Cardiometabolic Risk factors**

- Abdominal Obesity
- Dyslipidemia
- Elevated BP
- Fasting Hyperglycemia < 100mg/dl

**Effects of Adiposity on Metabolism of Plasma Very-Low-Density Lipoprotein**

**Model for Origins of Atherogenic Dyslipidemia of Obesity and MetS**

- Pattern A: < 90
- Pattern B: > 175

- Adiposity
- High carbohydrate diet
- Insulin resistance
- Genetic predisposition

- CETP, cholesteryl ester transfer protein
- Chol, cholesterol
- HDL, high-density lipoprotein
- HL, hepatic lipase
- IDL, intermediate-density lipoprotein
- LDL, low-density lipoprotein
- LPL, lipoprotein lipase
- MetS, metabolic syndrome
- TG, triglycerides
- VLDL, very-low-density lipoprotein


Low-Density Lipoprotein (LDL) Consists of Multiple Distinct Subclasses Differing in Size and Lipid Content*

Association with Cardiovascular Disease Risk

- Large
  - 1
  - 2
  - Weak

- Small
  - 3
  - 4
  - Strong

* Distribution of subclasses is independent of LDL-cholesterol.


Association with Cardiovascular Disease Risk

- Weaker
- Stronger

- Reduced clearance
- Greater entry into artery
- Greater retention
- Faster oxidation

LDL-Cholesterol Underestimates the Number of LDL Particles in Subjects with Small LDL

Pattern A
- Larger LDL
- More cholesterol/particle

Pattern B
- Smaller LDL
- Less cholesterol/particle

Apo B, apolipoprotein B; LDL, low-density lipoprotein.


Relationship of Plasma Triglyceride to Peak Diameter of Low-Density Lipoprotein (LDL)

- A: Large LDL
- B: Small LDL

Krauss RM, in press.

 DOES THE TYPE OF FAT IN THE DIET AFFECT THE LIPOPROTEIN PROFILE?

Current Guidelines for Management of Atherogenic Dyslipidemia of Obesity and Metabolic Syndrome (MetS)

- MetS is an indication for more aggressive lipid lowering
  - Target LDL-cholesterol < 100 mg/dL or total cholesterol minus HDL-cholesterol < 130 mg/dL
  - With cardiovascular disease, target LDL-cholesterol < 70 mg/dL; usually requires statin therapy (Grundy et al., 2004)

- Important roles for:
  - Weight loss, exercise
  - Drugs that lower triglycerides and raise HDL (fibrates or nicotinic acid)


Table 2: Effects of Dietary Lipids on Plasma Lipoprotein Cholesterol

<table>
<thead>
<tr>
<th>Saturated fatty acids</th>
<th>Trans-mono-unsaturated fatty acids</th>
<th>C16 mono-unsaturated fatty acids</th>
<th>ω-6 poly-unsaturated fatty acids</th>
<th>ω-3 poly-unsaturated fatty acids</th>
<th>Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Lipid lowering therapy in children

- Bile Acid Sequestrants
- Nicotinic Acid
- Reductase Inhibitors
- Fibric Acid Derivatives

Efficacy and Safety of Statins in children and adolescents with Hyperlipidemia

1- RCT with Artovastatin (10-20 mg) on 140 boys/girls, mean age 14 yrs (11-21 yrs) for 26 weeks (McCrindle B et al J Pediatr 2003)

2- RCT with Pravastatin (20-40mg) 106 boys/girls, mean age 13 yrs, for 2 years (Wiegman A. et al. JAMA 2004)

REDUCTASE INHIBITORS

Advantages:
Most effective reduction of LDL cholesterol.
Well tolerated.
Effective for atherosclerosis regression when used in combination with bile acid binding resins.
Results from the Statins trials in children and adolescents

1- Two years of Pravastatin therapy induced a significant regression of carotid atherosclerosis in children with familial hypercholesterolemia.

2- No adverse effects on growth, sexual maturation, hormone levels or liver or muscle tissue.

Homozygous Familial Hypercholesterolemia

Name: AB
DOB: 4-19-2001
Pakistan
FH: Parents First Cousins. Both Father and Mother have elevated Cho (>350mg/dl)
Labs on 6/4/03
Chol: 1080 mg/dl
Hdl: 25 mg/dl
Tg: 189
LDL: 1010 mg/dl
Cardiac Echo: normal
Diagnosis: FH
Therapy: Crestor 2.5 mg

Follow-up
6/9/03 Chol 984 (9%) LDL 897 (12%)
Increased Crestor 5mg
12/5/03 Chol 915 (16%) LDL 829 (18%)
Increased Crestor 7.5mg
Zetia 10mg
4/7/04 Chol 791 (27%) LDL 714 (30%)

Heterozygous Hypercholesterolemia

Name: JW
DOB: 7/23/92
Family History: Father died at the age of 55 of MI
Lipid profile at the age of 8 yrs
Chol 284 mg/dl
Hdl 59 mg/dl
LDL 201 mg/dl
Tg 119 mg/dl
Therapy: Lipitor 5 mg
The patient has been Lipitor 10mg for 7 yrs
he is now 15 yrs and his last lipid profile:
Chol 197mg/dl, LDL: 131 mg/dl

Follow-up
6/9/03 Chol 984 (9%) LDL 897 (12%)
Increased Crestor 5mg
12/5/03 Chol 915 (16%) LDL 829 (18%)
Increased Crestor 7.5mg
Zetia 10mg
4/7/04 Chol 791 (27%) LDL 714 (30%)

The Pediatric Obesity and Lipid Disorder Clinic

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Amy Syme, EP
Thank you!