Lipoprotein Formation, Structure and Metabolism:

Cholesterol Balance and the Regulation of Plasma Lipid Levels

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Multiple Studies Showed a Relationship Between LDL-C Reduction and CHD Relative Risk

![Graph showing the relationship between LDL-C reduction and nonfatal MI and CHD death relative risk reduction. The graph includes data from various studies such as CARDS, POSCH, ASCOT-LLA, and others.](image-url)
### ATP 2004 Update: LDL-C Therapy by Risk Categories Based on Recent Clinical Trial Evidence

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Initiate Therapeutic Lifestyle Changes (TLC)</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk: CHD or CHD risk equivalents (10-year risk &gt;20%)</td>
<td>≥190 mg/dL (consider drug options if LDL-C 160–189 mg/dL)</td>
<td>≥160 mg/dL</td>
<td>≥100 mg/dL</td>
</tr>
<tr>
<td>Very high risk</td>
<td>≥160 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately high risk: ≥2 risk factors (10-year risk 10%–20%)</td>
<td>≥130 mg/dL (optional goal &lt;100 mg/dL)</td>
<td>≥130 mg/dL</td>
<td>≥130 mg/dL (consider drug options if LDL-C 100–129 mg/dL)</td>
</tr>
<tr>
<td>Moderate risk: ≥2 risk factors (10-year risk &lt;10%)</td>
<td>≥130 mg/dL</td>
<td></td>
<td>≥130 mg/dL</td>
</tr>
<tr>
<td>Low risk: ≤1 risk factor</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL (consider drug options if LDL-C 160–189 mg/dL)</td>
</tr>
</tbody>
</table>

Overview

- Digestive lipid metabolism
- Cholesterol balance
- Inhibitors of cholesterol synthesis and absorption
- Dual inhibition
Overview

- Digestive lipid metabolism
- Cholesterol balance
- Inhibitors of cholesterol synthesis and absorption
- Dual inhibition
Cholesterol

- Critical for membrane function
- Substrate for steroid hormone synthesis
- Synthesized by all cells in the body
- Toxic to cells when present in excess
- Broken down and eliminated by the liver only
Cholesterol

Cholesterol - *membranes*

Cholesteryl ester - *transport/storage*
Reverse Cholesterol Transport

Excess Cholesterol

PERIPHERAL TISSUES → BLOOD → LIVER → BILE
Cholesterol Catabolism Into Bile Salts

Liver Cell ONLY
Cholesterol Catabolism into Bile Salts

Cholesterol

7α-hydroxylase

Cholate
Bile Salts

- Breakdown products of cholesterol
- Amphipathic molecules
- Function to transport cholesterol in the digestive system
Structure of Biliary and Intestinal Micelles

- Bile Salt
- Cholesterol
- Phospholipid
Functions of Micelles

- Transport cholesterol from the liver into the intestine via the biliary tree
- Participate in fat digestion and absorption
Biliary Lipid Secretion

**BLOOD**

**HEPATOCYTE**

**BILE**

- **Sinusoidal Membrane**
- **ABCG5/G8**
- **Cholesterol**
- **ABCB4**
- **Phospholipid**
- **ABCB11**

- **Canalicular Membrane**
- **Bile Salt**
# Biliary Lipids

<table>
<thead>
<tr>
<th>Lipid Class</th>
<th>Daily secretion (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile salts</td>
<td>24</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>11</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>2</td>
</tr>
</tbody>
</table>
Biliary Lipid Transport

Liver → Duodenum → Jejunum → Ileum → Colon
Fat Digestion

Liver

Duodenum

Jejunum

Ileum

Colon

Biliary Transport and Storage
Fat Digestion

Dietary Cholesterol
Fat Digestion

Dietary Cholesterol
Fat Digestion

**Lipase**

- **Triglycerides**
- **Fatty Acids + Monoglycerides**
Fat Digestion

Lipase

Triglycerides

Fatty Acids + Monoglycerides
Cholesterol Absorption

**LYMPH**

**ENTEROCYTE**

**INTESTINAL LUMEN**

- Cholesterol
- Cholesteryl Ester
- ACAT
- ABCG5/G8
Cholesterol Absorption

**LYMPH**

**ENTEROCYTE**

**INTESTINAL LUMEN**

- Cholesterol
- Cholesteryl Ester
- ACAT
- NPC1L1
- ABCG5/G8
Triglyceride Absorption

LYMPH

ENTEROCYTE

INTESTINAL LUMEN

2 Fatty Acid + Monoglyceride

DGAT

Triglyceride
Chylomicron Formation

LYMPH

ENTEROCYTE

Cholesteryl Ester

Triglyceride

CM apoB48

INTESTINAL LUMEN
Overview

• Digestive lipid metabolism

• **Cholesterol balance**

• Inhibitors of cholesterol synthesis and absorption

• Dual inhibition
Enterohepatic Circulation of Bile Salts

- **Synthesis**: 0.4 g/d
- **Secretion**: 24 g/d
- **Portal Venous Return**: (>95% of Biliary Secretion)
- **Fecal Excretion**: 0.4 g/d

**Locations**:
- **Duodenum**
- **Jejunum**
- **Ileum**
- **Colon**
Biliary Cholesterol Secretion

Biliary Cholesterol (2 g/d)

Biliary Transport and Storage

Duodenum
Jejunum
Ileum
Colon
Biliary and Dietary Cholesterol

Dietary Cholesterol (0.4 g/d)

Biliary Cholesterol (2 g/d)

Biliary Transport and Storage

Duodenum

Jejunum

Ileum

Colon
Cholesterol Absorption

Diet

- Low Fat/Low Cholesterol
- High Fat/Low Cholesterol
- High Fat/High Cholesterol

Cholesterol Absorption, %

Modified from Sehayek et al. 1998.
Dietary Cholesterol (0.4 g/d) absorption is approximately 50%. Biliary cholesterol (2 g/d) is transported and stored in the colon. CM apoB48 is involved in the process.
Dietary Cholesterol (0.4 g/d)

Biliary Cholesterol (2 g/d)

Absorption ~50%

CM apoB48

Biliary Transport and Storage

Fecal Excretion (1.2 g/d)

Fecal Cholesterol Excretion

Jejunum

Ileum

Colon
Cholesterol Balance

- Synthesis (1.2 g/d)
- Loss (1.6 g/d) - Dietary Cholesterol (0.4 g/d)

Cholesterol + Bile Salts

Dietary Cholesterol (0.4 g/d)

Loss (1.6 g/d)

Cholesterol (1.2 g/d) + Bile Salts (0.4 g/d)
Overview

• Digestive lipid metabolism
• Cholesterol balance
• Inhibitors of cholesterol synthesis and absorption
• Dual inhibition
Inhibitors of Cholesterol Synthesis: Statins

- Inhibit synthesis of cholesterol by cells
- Lower LDL cholesterol

**Mechanism**: Promote LDL clearance
LDL Receptor

Acetate

HMG-CoA Reductase

Cholesterol

Statins
Statins

Acetate

HMG-CoA Reductase

Cholesterol

LDL Receptor

LDL
Cholesterol Absorption Inhibitors

- Inhibit absorption of dietary cholesterol
- Inhibit reabsorption of biliary cholesterol
- Lower LDL cholesterol

Mechanism: Inhibit LDL formation
Cholesterol Absorption Inhibitors

- Inhibit absorption of dietary cholesterol
- Inhibit reabsorption of biliary cholesterol
- Lower LDL cholesterol

Mechanism: Inhibit LDL formation
Cholesterol Absorption

LYMPH

ENTEROCYTE

NPC1L1

ACAT

INTESTINAL LUMEN

Cholesterol

Cholesteryl Ester

ABCG5/G8
Agents That Interfere With Cholesterol Absorption

- Plant sterols and stanols
- Ezetimibe
Agents That Interfere With Cholesterol Absorption

- Plant sterols and stanols
- Ezetimibe
Cholesterol Absorption

**LYMPH**

**ENTEROCYTE**

**INTESTINAL LUMEN**

- Cholesterol
- NPC1L1
- ACAT
- Cholesteryl Ester
- ABCG5/G8
Plant Sterols and Stanols

Dietary Cholesterol

Sterol/Stanol
Plant Sterols and Stanols

Dietary Cholesterol

Sterol/Stanol
Plant Sterols and Stanols

**LYMPH**

**ENTEROCYTE**

**INTESTINAL LUMEN**

- Cholesterol
- ACAT
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Plant Sterols and Stanols

LYMPH

ENTEROCYTE

INTESTINAL LUMEN

Cholesterol

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Plant Sterols and Stanols

**LYMPH**

**ENTEROCYTE**

- Cholesterol
- ACAT
- Cholesteryl Ester
- NPC1L1

**INTESTINAL LUMEN**

- ABCG5/G8
Cholesterol Absorption Inhibitors

- Plant sterols and stanols
- Ezetimibe
Ezetimibe

LYMPH

ENTEROCYTE

INTESTINAL LUMEN

Cholesterol

Ezetimibe

NPC1L1

ACAT

Cholesteryl Ester

ABCG5/G8
Mechanism of Ezetimibe Action: Role of NPC1L1

Cholesterol Absorption in NPC1L1 Knockout Mice

% Cholesterol absorption

+/- Heterozygous
-/- Homozygous

+/- Wild type

†$P<0.001$ compared with wild-type mice (+/+ ) and heterozygous (+/-) mice.

Cholesterol Absorption Inhibitors

LYMPH

ENTEROCYTE

INTESTINAL LUMEN

CM apoB48

Triglyceride

Cholesteryl Ester
Cholesterol Absorption Inhibitors

LYMPH

ENTEROCYTE

INTESTINAL LUMEN

CM
apoB48

Triglyceride

Cholesteryl Ester
Cholesterol Absorption Inhibitors

**LYMPH**

**ENTEROCYTE**

**INTESTINAL LUMEN**

- CM apoB48
- Triglyceride
- Cholesteryl Ester
Cholesterol Absorption Inhibitors

- LDL apoB100
- VLDL apoB100
- CM Remnant apoB48
- CM apoB48
- Ezetimibe

Liver → Duodenum
Jejunum
Ileum
Colon
Overview

• Digestive lipid metabolism
• Cholesterol balance
• Inhibitors of cholesterol synthesis and absorption
• Dual inhibition
Assembly and Secretion of VLDL

Endoplasmic Reticulum

Presence of Triglycerides

ApoB

MTP

MTP
Assembly and Secretion of VLDL

Presence of Triglycerides

MTP

Cholesteryl Esters

Cholesterol

Dietary/Biliary

Synthesis

ApoB
Effect of Ezetimibe

Presence of Triglycerides

MTP

ApoB

Cholesteryl Esters

Cholesterol

Dietary/Biliary

Synthesis

Ezetimibe

X
Effect of Ezetimibe

Presence of Triglycerides

ApoB

MTP

Cholesteryl Esters

Cholesterol

Dietary/Biliary

Ezetimibe

Synthesis
Compensatory Upregulation of Cholesterol Synthesis

Presence of Triglycerides

MTP

ApoB

Cholesteryl Esters

Cholesterol

Dietary/Biliary

Ezetimibe

X

Synthesis
Compensatory Upregulation of Cholesterol Synthesis
Addition of Statin Therapy Blocks the Compensatory Response

Presence of Triglycerides

ApoB

Cholesteryl Esters

Cholesterol

Ezetimibe

Dietary/Biliary

Statin

Synthesis
Addition of Statin Therapy Blocks the Compensatory Response

- Presence of Triglycerides
- MTP
- Cholesteryl Esters
- Cholesterol
- Ezetimibe
- Dietary/Biliary Synthesis
- Statin
- Synthesis
**Cholesterol Absorption Inhibitors**

- LDL apoB100
- VLDL apoB100
- CM Remnant apoB48
- CM apoB48
- Ezetimibe

**Locations:**
- Duodenum
- Jejunum
- Ileum
- Colon
Dual Inhibition

- LDL apoB100
- VLDL apoB100
- CM Remnant apoB48
- CM apoB48
- Ezetimibe
- Duodenum
- Jejunum
- Ileum
- Colon

Liver

- Dual Inhibition
- Statin
- Ezetimibe
Benefits of Managing Dual Pathways

- Cholesterol balance is regulated by both synthesis and absorption
- Each pathway may compensate for changes in the other
- Optimal LDL lowering may best be achieved by inhibiting both pathways