Lipid/Lipoprotein Structure and Metabolism (Overview)

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Atherosclerotic Cardiovascular disease
Atherosclerotic Cardiovascular disease
Clinical manifestations of Atherosclerotic Cardiovascular Disease (ASCVD)

- Coronary artery: Myocardial infarction
- Carotid artery: Stroke
- Mesenteric artery: Intestinal gangrene
- Other arteries: Peripheral arterial disease
Modifiable Risk Factors for Atherosclerotic Cardiovascular disease (ASCVD)

- Smoking
- Elevated low density lipoproteins (LDLs)
- Elevated triglyceride-rich lipoproteins
- Reduced high density lipoproteins (HDLs)
- Elevated blood pressure
- Diabetes
- Abdominal obesity
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Plasma lipoproteins

• Why do we have plasma lipoproteins?

• What are plasma lipoproteins?

• What is the metabolism of plasma lipoproteins?

• What is the relationship of plasma lipoproteins to atherosclerosis?
Plasma lipoproteins

- Why do we have plasma lipoproteins?
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Why do we have plasma lipoproteins?

- Main reason for having plasma lipoproteins is to transport triglyceride and cholesterol through plasma between tissues

- Plasma is mainly water and cholesterol and triglyceride are not water-soluble

- Incorporation of cholesterol and triglyceride into lipoproteins allows them to be transported in plasma
Why do we have plasma lipoproteins?

Several other functions of plasma lipoproteins will be covered in other lectures.
Plasma lipoproteins

• Why do we have plasma lipoproteins?

• **What are plasma lipoproteins?**

• What is the metabolism of plasma lipoproteins?

• What is the relationship of plasma lipoproteins to atherosclerosis?
Structure of plasma lipoproteins

Surface monolayer of phospholipids and free cholesterol

Hydrophobic core of triglyceride and cholesteryl esters

apolipoproteins
Lipoprotein fractions in plasma

- Chylomicrons, VLDLs, and their catabolic remnants
  - Pro-atherogenic
- LDLs
- HDLs
  - Anti-atherogenic
Chylomicrons

- Formed in intestinal cells
- Function to transport dietary triglyceride and cholesterol to tissues in the body
- Main core lipid is triglyceride
- Main protein is apoB-48
Very low density lipoproteins (VLDLs)

- Formed in the liver
- Function to transport triglyceride and cholesterol from the liver to tissues in the body
- Main core lipids is triglycerides
- Main protein is apoB-100
Low density lipoproteins (LDLs)

- Formed as end-products of the catabolism of VLDLs
- Function to transport cholesterol from plasma to tissues in the body
- Main core lipids are cholesteryl esters
- Main protein is apoB-100
High density lipoproteins (HDLs)

- Assembled within the plasma from several constituents
- Function to transport intracellular cholesterol into the plasma
- Main core lipids are cholesteryl esters
- Main proteins are apoA-I and apoA-II
Plasma lipoproteins

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Plasma lipid transport: Exogenous pathway
Formation of chylomicrons

Chylomicron

Intestinal cell

Free cholesterol (FC)

Free fatty acid (FFA)

Intestinal lumen

Lymph (thoracic duct)

Blood
Metabolism of chylomicrons

Intestine → Chylomicron

Chylomicron

Intestine

CE

TG

LPL

FFA

Adipose and other tissues

CETP

HDL

CE

Liver

Chylomicron remnant

CE

TG
Plasma lipid transport: Endogenous pathway
Endogenous pathway

Liver

FC ➔ CE
TG

FFA

Adipose tissue
Endogenous pathway

Liver

FC → CE → TG

FFA → Adipose tissue

VLDL

TG

CE
Endogenous pathway

Liver

FC → CE → TG

Adipose tissue

FFA

VLDL

LPL

TG

CE

FFA

Adipose and other tissues
Liver

- FC → CE
- CE → TG

VLDL
- TG → CE
- TG → LPL → FFA
- FFA → Adipose tissue

Adipose and other tissues

LDL
- TG → CE
Endogenous pathway

Liver

VLDL

TG

CE

FFA

Adipose tissue

Adipose and other tissues

LDL

LPL

FFA

LDL receptor

Liver
Endogenous pathway

Liver

FC → CE → TG

FFA

Adipose tissue

VLDL

TG → CE

LPL → FFA

Adipose and other tissues

LDL

TG → CE

LDL receptor → Liver

LDL receptor → Cell in peripheral tissue
Endogenous pathway

Liver

FC → CE → TG

FFA → Adipose tissue

VLDL

TG → CE

LPL

FFA → FFA

Adipose and other tissues

LDL

TG → CE

LDL receptor

Liver

FC → CE → TG

New synthesis

Cell in peripheral tissue
Endogenous pathway

Liver → VLDL → LDL → Liver

Adipose and other tissues

FFA

LDL receptor

Cell in peripheral tissue

New synthesis

HDL

VLDL

LCAT

ABCA1
Endogenous pathway

Liver

VLDL

FFA

Adipose and other tissues

LDL receptor

Liver

FFA

Adipose tissue

HDL

LDL

TGL

LDL receptor

Cell in peripheral tissue

New synthesis

LCAT

ABCA1

FC

CE

TGL

TG

CE
Endogenous pathway

Liver

FC → CE → TG

FFA → Adipose tissue

VLDL

TG → CE

LPL

FFA → LDL

Adipose and other tissues

LDL receptor

LDL

TG → CE

LPL

FFA → LDL receptor

Liver

LDL receptor

LDL

New synthesis

Cell in peripheral tissue

HDL

TG → CE

LCAT

ABCA1

FC
Endogenous pathway

Liver

FC → CE → TG

CE ↑

FC

FFA → Adipose tissue

VLDL

TG → CE

LPL

FFA → Adipose and other tissues

LDL

LDL receptor

LDL

TG → CE

CETP

LDL receptor

LDL receptor

New synthesis

HDL

TG → CE

FFA

Bile

FC

HDL

CE

LPL

FFA

Adipose and other tissues

Cell in peripheral tissue

LCAT

ABCA1

FC

Endogenous pathway
Formation and metabolism of HDL
Structure of HDL

Surface monolayer of phospholipids and free cholesterol

Hydrophobic core of triglyceride and cholesteryl esters

apoA-I

apoA-II
HDL Charge and shape

Lipid-poor apoA-I

Discoidal

Spherical

Prebeta mobility

Prebeta mobility

Alpha mobility
HDL Subpopulations

PARTICLE SHAPE
- Discoidal
- Spherical

APOLIPOPROTEIN COMPOSITION
- A-I HDL
- A-I/A-II HDL

PARTICLE SIZE
- HDL$_{2b}$
- HDL$_{2a}$
- HDL$_{3a}$
- HDL$_{3b}$
- HDL$_{3c}$

Lipid-poor apoA-I
Formation of HDL

LIVER
Lipid-poor apoA-I

INTESTINE
Chylomicrons
Lipoplysis
Lipidation of apoA-I to form discoidal HDL

Lipid-poor apoA-I

Cell membrane

ABCA-1

phospholipid, cholesterol

Discoidal HDL
Role of LCAT in formation of spherical HDL

Liver
Intestine

apoA-I

Discoidal HDL

Free cholesterol transferred from cell membranes (including liver and intestine)

Free cholesterol transferred from cell membranes (including liver and intestine)

LCAT

cholesteryl esters

Spherical HDL
Role of CETP and SRB1 in HDL metabolism

Liver

LDL-R

CE

SR-B1

FC

SR-B1

Bile

HDL

Extrahepatic Tissues (including the artery wall)

Free Cholesterol

CETP

VLDL/LDL

LDL-R

CE

SR-B1

Bile

FC

HDL

CE

LCAT
Plasma lipoproteins

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ATHEROSCLEROSIS
Monocyte

Adhesion Molecule

MCP-1

Macrophage

Intima

Foam Cell

Vessel Lumen

Endothelium

ATHEROSCLEROSIS
Lipoprotein classes and atherosclerosis

Non-HDL

Chylomicrons, VLDL, and their catabolic remnants

Pro-atherogenic

LDL

Anti-atherogenic

HDL
ROLE OF LDLs IN CAUSING ATHEROSCLEROSIS

- Monocyte
- Adhesion Molecule
- Cytokines
- MCP-1
- Modified LDL
- Vessel Lumen
- Endothelium
- Intima
- Foam Cell

Monocyte binds to Adhesion Molecule on the endothelium, secreting MCP-1. MCP-1 attracts Macrophages which engulf Modified LDLs, becoming Foam Cells in the Intima.
It has been proven beyond all doubt in many large clinical trials that reducing level of LDL cholesterol reduces the risk of having a cardiovascular event.
REDUCTION IN MCVE EVENTS (%)

REDUCTION IN LDL CHOLESTEROL (mg/dL)

CLINICAL INTERVENTION TRIALS

SEARCH
IMPROVE-IT
ALLHAT
IDEAL
LRC
TNT
HPS
LIPID
CARE
AFCAPS
ASCOT
WOS
CARDS
Posch
4S
JUPITER
Lipoprotein classes and atherosclerosis

Non-HDL

Chylomicrons, VLDL, and their catabolic remnants

LDL

HDL

Pro-atherogenic

Anti-atherogenic
ROLE OF TRIGLYCERIDE-RICH LIPOPROTEINS (TRLs) IN CAUSING ATHEROSCLEROSIS

- **Monocyte**
- **Adhesion Molecule**
- **Cytokines**
- **Macrophage**
- **MCP-1**
- **Modified TRL remnants**
- **Foam Cell**
- **Intima**
- **Endothelium**
- **Vessel Lumen**
It is likely (but still not proven) that reducing levels of triglyceride-rich lipoproteins will reduce the risk of having a cardiovascular event.
INHIBITION OF ATHEROSCLEROSIS BY HDLs

HDL INHIBIT ADHESION MOLECULE EXPRESSION

HDL INHIBIT MCP-1 EXPRESSION

HDL INHIBIT OXIDATION OF LDL

HDL PROMOTE CHOLESTEROL EFFLUX
It is possible (but not proven) that increasing levels of HDLs will reduce the risk of having a cardiovascular event
Conclusions

• Plasma lipoproteins transport triglyceride and cholesterol through plasma between tissues

• LDLs and the remnants of triglyceride-rich lipoproteins cause atherosclerosis, while HDLs protect

• Reducing plasma levels of LDL cholesterol reduces the risk of having a cardiovascular event

• It is still not known whether decreasing triglyceride-rich lipoproteins or increasing HDL levels reduce cardiovascular risk