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?

• What are 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?

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• 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

LDLs

HDLs

Pro-atherogenic

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

CE
TG

Intestinal cell

CE
TG

Free cholesterol (FC)

Free fatty acid (FFA)

Lymph (thoracic duct)

Blood

Intestinal lumen
Metabolism of chylomicrons

Intestine → Chylomicron

Chylomicron: CE, TG

LPL → FFA

FFA → Adipose and other tissues

Intestine → CETP

CETP → HDL

HDL: CE

Liver → Chylomicron remnant

Chylomicron remnant: CE, TG

Liver → Liver
Plasma lipid transport: Endogenous pathway
Endogenous pathway

Liver

FC → CE → TG

FFA

Adipose tissue
Endogenous pathway

Liver

- FC → CE
- CE → TG

Adipose tissue

FFA

VLDL

TG → CE
Endogenous pathway

Liver

VLDL

LPL

FFA

Adipose and other tissues

FFA

Adipose tissue

FC → CE

CE → TG

TG → VLDL

TG → CE

FFA
Endogenous pathway

Liver

VLDL

FFA

Adipose and other tissues

LPL

LDL

Adipose tissue
Endogenous pathway

Liver

FC → CE → TG → FFA

Adipose tissue

FFA

Adipose and other tissues

Liver

VLDL

TG → CE

LPL

FFA

LDL

TG → CE

LDL receptor

Endogenous pathway
Endogenous pathway

Liver

FC → CE → TG

FFA → Adipose tissue

Liver

VLDL

TG → CE

LPL → FFA

Adipose and other tissues

LDL

TG → CE

LDL receptor → Liver

Cell in peripheral tissue

LDL receptor
Endogenous pathway

Liver

TC \rightarrow CE \rightarrow TG

FFA

Adipose tissue

VLDL

TG

CE

FFA

Adipose and other tissues

LDL

LPL

LDL receptor

Liver

New synthesis

Cell in peripheral tissue
Endogenous pathway

Liver

FD → CE → TG

FFA
Adipose tissue

VLDL

TG → CE

LPL

FFA
Adipose and other tissues

LDL receptor

LDL

TG → CE

LDL receptor

Liver

HDL

TG → CE

LCAT
ABCA1

Cell in peripheral tissue

New synthesis

Cell in peripheral tissue

FC → CE → TG

LDL receptor
Endogenous pathway

Liver

FC ➔ CE ➔ TG

↑ CE

FFA ➔ Adipose tissue

VLDL

TG ➔ CE

LPL ➔ FFA ➔ Adipose and other tissues

LDL ➔ LDL receptor ➔ Liver

LDL receptor ➔ New synthesis ➔ Cell in peripheral tissue

HDL

TG ➔ CE

LCAT ➔ ABCA1 ➔ FC
Endogenous pathway

Liver

FC ➔ CE ➔ TG

VLDL

TG ➔ CE

LPL ➔ FFA ➔ Adipose and other tissues

FFA ➔ Adipose tissue

Bile

HDL

TG ➔ CE

LDL receptor

LDL

TG ➔ CE

LDL receptor ➔ Liver

Cell in peripheral tissue

New synthesis

FC ➔ CE ➔ TG

LCAT ➔ ABCA1
Endogenous pathway

Liver

VLDL

LPL

FFA

Adipose and other tissues

LDL receptor

LDL

CETP

LCAT

ABCA1

HDL

Bile

FFA

Adipose tissue

New synthesis

Cell in peripheral tissue
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

Prebeta mobility

Spherical

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

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

Liver
Intestine

apoA-I

Discoidal HDL

free cholesterol

LCAT

cholesteryl esters

Spherical HDL

CE
Role of CETP and SRB1 in HDL metabolism
Plasma lipoproteins

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ATHEROSCLEROSIS
Adhesion Molecule

Monocyte

MCP-1

Endothelium

Vessel Lumen

Intima

Foam Cell

Macrophage

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

Adhesion Molecule

Monocyte

Vessel Lumen

Endothelium

LDL

MCP-1

MODIFIED LDL

Cytokines

Macrophage

Intima

Foam Cell
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.
Lipoprotein classes and atherosclerosis

Non-HDL

Chylomicrons, VLDL, and their catabolic remnants

Pro-atherogenic

LDL

HDL

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

Monocyte

Adhesion Molecule

Cytokines

MCP-1

Modified TRL remnants

TRL remnants

Foam Cell

Intima

Vessel Lumen

Endothelium

Macrophage
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 inhibit MCP-1 expression
- HDL promote cholesterol efflux

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

LDL

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