Metabolism of Triglycerides and Cholesterol: Regulation and Clinical Significance

Triglycerides (TAG) are the major **storage form of energy**, while cholesterol is an essential structural component of cell membranes and a precursor of **bile acids, steroid hormones and vitamin D**.

I. Triglyceride metabolism

1. Digestion and absorption

Dietary triglycerides are:

TAG → fatty acids + monoacylglycerol

by pancreatic lipase.

They form micelles with bile salts and enter intestinal mucosal cells.

Inside enterocytes:

Fatty acids + monoacylglycerol → TAG

TAG is incorporated with cholesterol, phospholipids and **apo B-48** into **chylomicrons**.

Chylomicrons → lymph → thoracic duct → blood

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2. Transport of triglycerides

The major triglyceride-rich lipoproteins are:

- **Chylomicrons** – transport dietary/exogenous TAG.
- **VLDL** – transport endogenous TAG synthesized mainly in the liver.

Lipoprotein lipase (LPL)

LPL is present on the endothelial surface of adipose tissue, skeletal muscle and cardiac muscle.

It hydrolyses:

TAG in chylomicrons/VLDL → free fatty acids + glycerol

- Fatty acids enter adipose tissue → storage.
- Fatty acids enter muscle → oxidation for energy.
- Glycerol returns mainly to the liver.

LPL requires **apo C-II** for activation.

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3. Endogenous triglyceride synthesis

The liver synthesizes TAG from:

- Fatty acids
- Glycerol-3-phosphate

Fatty acids are activated to fatty acyl-CoA and esterified with glycerol-3-phosphate.

TAG is incorporated into **VLDL**, containing **apo B-100**, and secreted into the blood.

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4. Storage and mobilization of triglycerides

Fed state

High insulin promotes:

- Glucose uptake into adipocytes
- Fatty acid synthesis
- TAG synthesis
- LPL activity in adipose tissue

Therefore:

Insulin → storage of TAG

Fasting state

Low insulin and increased catecholamines activate adipose lipolysis.

The major enzymes are:

- **Adipose triglyceride lipase (ATGL)**
- **Hormone-sensitive lipase (HSL)**
- Monoglyceride lipase

TAG → fatty acids + glycerol

Free fatty acids travel bound to **albumin** and are oxidized by tissues.

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5. Regulation of triglyceride metabolism

State	Hormonal effect	Result
Fed/high insulin	↑ TAG synthesis	Fat storage
Fasting/low insulin	↑ lipolysis	Fat mobilization
Catecholamines	↑ lipolysis	↑ free fatty acids
Glucagon	Promotes fasting metabolism	↑ fat mobilization
Malonyl-CoA	Inhibits CPT-I	↓ fatty acid oxidation

II. Cholesterol metabolism

Functions of cholesterol

Cholesterol is required for:

1. Cell membranes
2. Bile acids and bile salts
3. Steroid hormones
4. Vitamin D
5. Lipoprotein structure

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1. Sources of cholesterol

Cholesterol comes from:

Exogenous source

Dietary cholesterol absorbed from the intestine.

Endogenous source

Synthesized mainly in:

- Liver
- Intestine
- Adrenal cortex
- Gonads and other tissues

The liver is a major site of synthesis.

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2. Cholesterol synthesis

Cholesterol is synthesized from **acetyl-CoA**.

Major pathway

Acetyl-CoA
↓
Acetoacetyl-CoA
↓
HMG-CoA
↓
Mevalonate
↓
Isoprenoid units
↓
Squalene
↓
Lanosterol
↓
Cholesterol

Rate-limiting enzyme

HMG-CoA reductase

It converts:

HMG-CoA → Mevalonate

This enzyme is the major regulatory point in cholesterol synthesis.

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3. Regulation of cholesterol synthesis

HMG-CoA reductase is stimulated by

- Low intracellular cholesterol
- Insulin
- Thyroid hormone

HMG-CoA reductase is inhibited by

- High intracellular cholesterol
- Glucagon
- Phosphorylation
- **Statins**

Statins are competitive inhibitors of HMG-CoA reductase and reduce hepatic cholesterol synthesis.

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4. Cholesterol transport

Because cholesterol is poorly soluble in plasma, it is transported in **lipoproteins**.

Major lipoproteins

Lipoprotein	Major function	Major apoprotein
Chylomicron	Dietary TAG	Apo B-48
VLDL	Hepatic TAG	Apo B-100
IDL	VLDL remnant	Apo B-100
LDL	Delivers cholesterol to tissues	Apo B-100
HDL	Reverse cholesterol transport	Apo A-I

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5. LDL metabolism

VLDL loses triglycerides through LPL:

VLDL → IDL → LDL

LDL is cholesterol-rich.

It binds to the **LDL receptor** through **apo B-100** and is taken up by cells by receptor-mediated endocytosis.

Functions

LDL delivers cholesterol to peripheral tissues and the liver.

Excess LDL promotes cholesterol accumulation in arterial walls.

Hence LDL is commonly referred to clinically as **atherogenic cholesterol**.

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6. HDL and reverse cholesterol transport

HDL removes excess cholesterol from peripheral tissues and transports it toward the liver.

This is called:

Reverse cholesterol transport

Important enzyme:

LCAT (lecithin-cholesterol acyltransferase)

It esterifies free cholesterol on HDL.

A major apoprotein of HDL is:

Apo A-I

HDL-cholesterol can ultimately be delivered to the liver for disposal or reutilization.

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7. Excretion of cholesterol

Humans cannot completely degrade the cholesterol nucleus into CO_2 and water.

The major route of elimination is:

Cholesterol → bile acids/bile salts → bile → intestine → faeces

Some free cholesterol is also secreted directly into bile.

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8. Conversion to bile acids

Cholesterol is converted in the liver into **primary bile acids**:

- Cholic acid
- Chenodeoxycholic acid

These are conjugated with glycine or taurine and secreted into bile.

Bile acids facilitate intestinal lipid digestion and absorption.

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9. Clinical significance

A. Hypertriglyceridaemia

Causes include:

- Obesity
- Diabetes mellitus
- Alcohol excess
- Hypothyroidism
- Genetic disorders
- Some medications

Severe hypertriglyceridaemia can cause **acute pancreatitis**.

B. Hypercholesterolaemia

Raised LDL cholesterol is associated with increased risk of:

- Atherosclerosis
- Coronary artery disease
- Myocardial infarction
- Ischaemic stroke
- Peripheral arterial disease

Familial hypercholesterolaemia

Usually caused by abnormalities involving:

- **LDL receptor**
- Apo B
- PCSK9 pathway

This causes markedly elevated LDL cholesterol and premature atherosclerotic cardiovascular disease.

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10. Atherosclerosis — metabolic basis

↑ **LDL / apo B-containing lipoproteins**
↓
Entry into arterial intima
↓
Lipoprotein modification/oxidation
↓
Macrophage uptake
↓
Foam cells
↓
Fatty streak
↓
Atherosclerotic plaque
↓
Possible plaque rupture/thrombosis
↓
Cardiovascular events

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11. Important clinical correlations

Statins

Inhibit **HMG-CoA reductase** → ↓ hepatic cholesterol synthesis → ↑ hepatic LDL receptors → ↓ plasma LDL.

Diabetes mellitus

Insulin deficiency/resistance may produce:

- ↑ lipolysis
- ↑ hepatic VLDL production
- ↑ triglycerides
- Low HDL
- Increased atherogenic lipoproteins

This pattern is often called **diabetic dyslipidaemia**.

Obesity/metabolic syndrome

Commonly associated with:

↑ **triglycerides +** ↓ **HDL + increased small dense LDL particles**

Integrated overview

Exogenous lipid pathway

Dietary TAG/cholesterol
↓
Intestine
↓
Chylomicrons (Apo B-48)
↓
LPL
↓
Fatty acids → tissues
↓
Chylomicron remnants → liver

Endogenous pathway

Liver
↓
VLDL (Apo B-100)
↓ LPL

IDL
↓
LDL
↓
Cholesterol delivered to tissues/liver

Reverse cholesterol transport

Peripheral tissues
↓
HDL (Apo A-I)
↓
Cholesterol → liver
↓
Bile acids/free cholesterol → bile → faeces

High-yield examination points

- **Major storage form of fat:** triglyceride.
- **Dietary TAG transport:** chylomicrons.
- **Hepatic TAG transport:** VLDL.
- **LPL activator:** Apo C-II.
- **LDL receptor ligand:** Apo B-100.
- **Major HDL apoprotein:** Apo A-I.
- **Rate-limiting enzyme of cholesterol synthesis:** HMG-CoA reductase.
- **Statins:** inhibit HMG-CoA reductase.
- **LCAT:** esterifies cholesterol in HDL.
- **Main route of cholesterol elimination:** bile → faeces.
- **Excess LDL:** promotes atherosclerosis.
- **Severe hypertriglyceridaemia:** risk of acute pancreatitis.