MEDICAL EDUCATION RESOURCE

Cholesterol and Lipoproteins

? Steroids

Steroids are a large family of biologically important molecules derived from a **cyclopentanoperhydrophenanthrene nucleus**, also called the **steroid nucleus** or **sterane nucleus**.

? Basic Features

- Four fused rings: **A, B, C (six-membered)** and **D (five-membered)**
- Rings are numbered from A ? D
- Major natural steroids include:
  - **Cholesterol**
  - **Steroid hormones** (cortisol, aldosterone, estrogen, testosterone)
  - **Bile acids**
  - **Vitamin D**

? Key Functions of Steroids

- Maintain cell membrane structure (cholesterol)
- Act as hormones regulating metabolism, salt-water balance, and reproduction
- Aid in digestion (bile salts)

- Regulate calcium levels (vitamin D)

Cholesterol is the **parent compound** for almost all steroids.

? Structure of Cholesterol

Cholesterol is a **27-carbon steroid alcohol**.
It contains the classic **four-ring steroid structure + hydrocarbon tail**.

? Structural Components

1. **Steroid nucleus**
    - Rings A, B, C, D fused together
    - Provides rigid, planar structure
2. **Hydroxyl group at C-3**
    - Makes cholesterol a **sterol**
    - Allows ester formation (cholesteryl esters)
3. **Double bond between C-5 and C-6**
    - Important for rigidity and membrane behavior
4. **Eight-carbon hydrocarbon side chain attached at C-17**
    - Site needed for conversion to bile acids
5. **Methyl groups at C-10 and C-13**

? Key Properties

- Amphipathic (has both polar and non-polar parts)
- Poorly soluble in water
- Transported in blood via **lipoproteins**
- Precursor for multiple steroid products

? Role in Cell Membranes

- Maintains fluidity at body temperature
- Prevents membranes from becoming too rigid or too fluid
- Interacts with phospholipids and sphingolipids

? Why Cholesterol Is Biologically Important

- Parent molecule for:
  - **Corticosteroids** (cortisol, aldosterone)
  - **Sex hormones** (estrogen, progesterone, testosterone)
  - **Bile acids** (cholic acid, chenodeoxycholic acid)
  - **Vitamin D synthesis** (cholecalciferol)
- Structural component of cell membranes
- Required for lipid raft formation

? Biosynthesis of Cholesterol

Cholesterol is synthesized mainly in the **liver**, and to some extent in **intestine, adrenal cortex, testes, ovaries**.
Synthesis occurs in the **cytosol and smooth endoplasmic reticulum (SER)**.

The entire pathway is built from **Acetyl-CoA**.

? Overview of the Pathway

Cholesterol synthesis occurs in **four major stages**:

1. Formation of **HMG-CoA**
2. Formation of **Mevalonate** (rate-limiting)
3. Formation of **Isoprenoid units ? Squalene**
4. Conversion of **Squalene ? Lanosterol ? Cholesterol**

? Stage 1: Acetyl-CoA ? HMG-CoA

Step 1. Condensation of Acetyl-CoA

2 Acetyl-CoA ? **Acetoacetyl-CoA**
Enzyme: *Thiolase*

Step 2. Addition of 3rd Acetyl-CoA

Acetoacetyl-CoA + Acetyl-CoA ? **HMG-CoA (3-hydroxy-3-methylglutaryl-CoA)**
Enzyme: *HMG-CoA synthase (cytosolic)*

Note: This is NOT the same enzyme used in ketogenesis (mitochondrial isoform).

? Stage 2: HMG-CoA ? Mevalonate (Rate-Limiting Step)

Step 3. Reduction of HMG-CoA

HMG-CoA ? **Mevalonate**
Enzyme: **HMG-CoA reductase**
Requires **2 NADPH**

? Key Point

This is the **rate-limiting**, highly regulated step in the entire pathway.

? Important Clinical Point

Statins (lovastatin, atorvastatin, simvastatin)
? competitively inhibit **HMG-CoA reductase**
? ? cholesterol synthesis in liver.

? Stage 3: Mevalonate ? Isoprenoid Units ? Squalene

Step 4. Phosphorylation Steps

Mevalonate undergoes **three sequential phosphorylations**, forming:

- 5-phosphomevalonate
- 5-pyrophosphomevalonate (activated)

Step 5. Decarboxylation

5-Pyrophosphomevalonate ? **Isopentenyl pyrophosphate (IPP)**
? a 5-carbon “isoprene unit”

Step 6. Isomerization

IPP ? **Dimethylallyl pyrophosphate (DMAPP)**

Step 7. Formation of Geranyl & Farnesyl Units

IPP + DMAPP ? **Geranyl-PP (10-carbon)**
Geranyl-PP + IPP ? **Farnesyl-PP (15-carbon)**

Step 8. Formation of Squalene (30-carbon)

Two farnesyl-PP combine to form:
? **Squalene (30-carbon linear molecule)**

Requires **NADPH**.

? Stage 4: Squalene ? Lanosterol ? Cholesterol

Step 9. Squalene Epoxide Formation

Squalene ? Squalene-2,3-epoxide
(oxygen + NADPH dependent)

Step 10. Cyclization

Squalene epoxide ? **Lanosterol**
This is the first steroid ring structure.

Step 11. Conversion to Cholesterol

Lanosterol undergoes:

- Demethylation (removal of 3 methyl groups)
- Double bond rearrangements
- Side chain modifications

? Final product: **Cholesterol (27-carbons)**

? Energy Requirement for Cholesterol Synthesis

Cholesterol synthesis is energy expensive:

- **18 ATP** used

- **14 NADPH** used

This explains why high-calorie states promote cholesterol synthesis.

? Regulation of Cholesterol Synthesis (Very Important)

? 1. HMG-CoA Reductase (Main Control Point)

Upregulated by:

- **Insulin**
- **Thyroxine**
- High carbohydrate diet
- Low intracellular cholesterol

Downregulated by:

- **Glucagon**
- **Cholesterol (end-product inhibition)**
- **Statin drugs**
- **High intracellular cholesterol ? SREBP suppression**
- **AMP-activated protein kinase (AMPK)**
  (during fasting, exercise, low energy)

? Clinical Correlations

1. Statin therapy

Inhibits HMG-CoA reductase ? ? hepatic cholesterol ? ? LDL receptor expression ? ? plasma LDL.

2. Smith–Lemli–Opitz Syndrome

Deficiency of **7-dehydrocholesterol reductase**
? low cholesterol ? multiple congenital anomalies.

3. Genetic Hypercholesterolemias

Due to defective LDL receptor or ApoB ? high LDL ? early atherosclerosis.

? Quick Revision Points

- Cholesterol synthesized in **cytosol + SER**
- **HMG-CoA reductase** is rate limiting
- **Statins inhibit HMG-CoA reductase**
- NADPH from **HMP shunt** is required
- Final structure formed through **lanosterol**

? Plasma Lipids

Plasma lipids circulate in blood in association with proteins as **lipoproteins**.
The major plasma lipids are:

1. Triacylglycerols (TAGs)

- Main storage form of fat

- Present in chylomicrons and VLDL
- Hydrophobic ? require transport in lipoproteins

2. Cholesterol

- Exists as **free cholesterol** and **cholesteryl esters**
- Precursor of bile acids, steroid hormones, vitamin D
- Excess ? atherosclerosis

3. Phospholipids

- Amphipathic
- Form structural component of lipoprotein surface
- Essential for cell membrane integrity

4. Free Fatty Acids (Non-Esterified Fatty Acids)

- Released from adipose tissue during fasting
- Carried by **albumin**
- Quickly taken up by liver & muscle for oxidation

? Transport of Lipids

Since lipids are hydrophobic, they cannot travel freely in blood.
They are transported in two major ways:

? 1. Lipoprotein-Mediated Transport

This is the major mechanism.
Dietary and endogenous lipids are packaged into **lipoproteins**, which circulate in plasma.

Functions:

- Deliver dietary fat ? tissues
- Deliver liver-synthesized TAG ? tissues
- Return cholesterol ? liver
- Maintain lipid homeostasis

? 2. Albumin-Mediated Transport

Free fatty acids are transported bound to **serum albumin** after lipolysis during fasting.

? Lipoproteins

Lipoproteins are **spherical particles** that transport lipids in blood.
They contain:

- **Core:** TAGs + cholesteryl esters
- **Surface:** phospholipids + free cholesterol + apolipoproteins

They differ in:

- Density
- Size

- Lipid composition
- Function
- Apolipoprotein content

? Classification of Lipoproteins

From largest ? smallest (lowest ? highest density):

1. Chylomicrons

- Largest, least dense
- Highest TAG content
- Transport **dietary TAGs** from intestine to tissues

2. VLDL (Very-Low-Density Lipoprotein)

- Produced by liver
- Transports **endogenous TAGs** to tissues

3. IDL (Intermediate-Density Lipoprotein)

- Intermediate remnant of VLDL metabolism

4. LDL (Low-Density Lipoprotein)

- Rich in cholesterol

- Delivers cholesterol to tissues
- “Bad cholesterol” because high LDL ? atherosclerosis

5. HDL (High-Density Lipoprotein)

- Smallest, most dense
- Rich in proteins
- Responsible for **reverse cholesterol transport**
- “Good cholesterol”

? Functions of Each Lipoprotein

Chylomicrons

- Carry dietary TAGs from intestine ? muscle & adipose
- Remnants are taken up by liver

VLDL

- Carry liver-synthesized TAGs ? peripheral tissues

IDL

- Transitional form ? converted to LDL

LDL

- Supplies cholesterol to all cells
- Taken up by LDL receptors

HDL

- Collects cholesterol from tissues
- Transfers cholesterol to liver for disposal
- Contains LCAT (lecithin:cholesterol acyltransferase)

? Apolipoproteins (Apos)

Apolipoproteins are **protein components** of lipoproteins.
They serve as:

- Structural components
- Enzyme activators
- Ligands for receptors

? Major Apolipoproteins & Their Functions

? Apo A-I

- Found mainly in **HDL**
- Activates **LCAT**
- Essential for reverse cholesterol transport

? Apo B-48

- Found in **chylomicrons**
- Required for their assembly in intestine

? Apo B-100

- Present in **VLDL, IDL, LDL**
- Ligand for **LDL receptor**
- Needed for hepatic lipoprotein secretion

? Apo C-II

- Activator of **Lipoprotein Lipase (LPL)**
- Required for TAG breakdown in chylomicrons & VLDL

? Apo C-III

- Inhibits LPL
- Delays TAG clearance ? high triglycerides

? Apo E

- Present on chylomicron remnants, VLDL remnants, HDL

- Ligand for **ApoE receptor / remnant receptor**
- Required for hepatic uptake of remnants

? Apo(a)

- Present in **Lipoprotein(a)**
- Structural analog of plasminogen
- High levels ? increased risk of atherosclerosis & thrombosis

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? Distribution Summary (Easy Memory Aid)

- **Chylomicrons:** Apo B-48, A, C, E
- **VLDL:** Apo B-100, C, E
- **LDL:** Apo B-100
- **HDL:** Apo A-I, A-II, C, E

? Clinical Correlations (Important)

1. Familial Hypercholesterolemia

- Defective LDL receptor or Apo B-100
- Very high LDL
- Early atherosclerosis, xanthomas

2. Familial Apo E Deficiency

- Remnant accumulation
- High chylomicron remnants & IDL
- Palmar xanthomas

3. Abetalipoproteinemia

- No Apo B ? no chylomicrons/VLDL
- Fat malabsorption, acanthocytosis, neurological defects

4. Apo C-II deficiency

- No LPL activation
- Severe hypertriglyceridemia

? Short Summary

- Plasma lipids = TAG, cholesterol, cholesteryl ester, phospholipids, FFAs
- Lipoproteins transport insoluble lipids
- Chylomicrons ? dietary TAGs
- VLDL ? endogenous TAGs
- LDL ? cholesterol to tissues

- HDL ? cholesterol back to liver
- Apolipoproteins regulate metabolism & receptor interaction

? Chylomicrons

Chylomicrons are the **largest**, **least dense** lipoproteins.
Their main function is to transport **dietary triacylglycerols (TAGs)** from the intestine to peripheral tissues.

? Composition

- **Very high TAG (85–90%)**
- Small amounts of cholesterol & phospholipids
- Major apolipoproteins:
  - **Apo B-48** (structural; unique to intestine)
  - **Apo C-II** (activates LPL)
  - **Apo E** (required for remnant uptake by liver)

? Formation

- Synthesized in **intestinal mucosal cells**
- Assembled by microsomal triglyceride transfer protein (MTP)

? Metabolism

1. Chylomicrons enter lymph ? blood
2. **Apo C-II activates LPL** in adipose & muscle
3. TAGs are hydrolyzed ? FFAs + glycerol
4. Particle shrinks ? **chylomicron remnant**
5. Remnant taken up by **liver via Apo E receptor**

? Clinical Points

- **Type I Hyperlipoproteinemia:**
  LPL deficiency or Apo C-II deficiency ? huge chylomicron accumulation ? pancreatitis
- **Abetalipoproteinemia:**
  No Apo B ? no chylomicrons.

? VLDL (Very-Low-Density Lipoprotein)

VLDL transports **endogenously synthesized TAGs** from the liver to peripheral tissues.

? Composition

- TAG-rich (but less than chylomicrons)
- Contains:
  - **Apo B-100**
  - **Apo C-II**
  - **Apo E**

? Function

- Deliver liver TAG to adipose & muscle
- After TAG removal by LPL ? becomes **IDL**

? Metabolism

1. Liver secretes VLDL
2. LPL removes TAG ? particle becomes IDL
3. IDL has two fates:
    - Taken up by liver (via Apo E)
    - Converted to LDL (by losing Apo E & TAG)

? Clinical Points

- Increased in obesity, diabetes, alcohol excess
- High VLDL ? high triglycerides
- **Type IV Hyperlipoproteinemia:** VLDL excess.

? LDL (Low-Density Lipoprotein)

LDL is the **major cholesterol-carrying lipoprotein** in blood.
It delivers cholesterol to all tissues.

? Composition

- High cholesterol & cholesteryl esters
- Apo B-100 only

? Function

- Supply cholesterol for:
  - Membranes
  - Steroid hormones
  - Bile acids

? Metabolism

- Formed from IDL
- Taken up by **LDL receptors** via Apo B-100
- Degraded in lysosomes

? Clinical Points

- “**Bad cholesterol**”
- High LDL ? atherosclerosis
- Familial hypercholesterolemia (LDL receptor defect):
  - Very high LDL
  - Premature coronary artery disease

- Tendon xanthomas

? Statins effect

- Inhibit HMG-CoA reductase ? ? hepatic cholesterol
- ? LDL receptor expression ? ? LDL levels.

? HDL (High-Density Lipoprotein)

HDL is the **smallest, densest, most protein-rich** lipoprotein.

? Function

- **Reverse cholesterol transport**
  - Collects free cholesterol from tissues
  - Esterifies it via **LCAT (activated by Apo A-I)**
  - Transfers cholesteryl esters to VLDL/LDL or transports to liver

? Composition

- High protein
- Apo A-I (main), Apo A-II, Apo C, Apo E

? Clinical Points

- "**Good cholesterol**"
- High HDL ? protective against heart disease

- Low HDL seen in metabolic syndrome, smoking, diabetes.

? Lipoprotein(a) — Lp(a)

Lp(a) is an LDL-like particle with an additional protein called **Apo(a)** attached to Apo B-100.

? Structure

- LDL particle + **Apo(a)**
- Apo(a) resembles **plasminogen**

? Function

- Not fully understood
- Associated with:
  - Atherosclerosis
  - Thrombosis (because Apo(a) competes with plasminogen ? inhibits fibrinolysis)

? Clinical Importance

- High Lp(a) = **strong independent risk factor** for:
  - Myocardial infarction
  - Stroke
- Levels genetically determined
- Niacin reduces Lp(a) levels; statins do not.

? Free Fatty Acids (FFA)

FFAs are **non-esterified fatty acids** released from adipose tissue during fasting.

? Origin

- Breakdown of TAGs in adipose tissue by **Hormone-Sensitive Lipase (HSL)**

? Transport

- Circulate in blood bound to **albumin**

? Function

- Important fuel during fasting
- Used by liver, muscle, heart
- Liver converts excess FFAs to:
  - Acetyl-CoA
  - Ketone bodies (fasting state)

? Clinical Points

- Elevated FFAs ? insulin resistance
- Very high FFAs in uncontrolled diabetes due to ? lipolysis
- FFAs are the main substrate for **ketogenesis**

? Ultra-Short Summary

- **Chylomicrons** ? dietary TAGs (Apo B48, C-II, E)
- **VLDL** ? endogenous TAGs (Apo B100, C-II, E)
- **IDL** ? intermediate, remnant form
- **LDL** ? cholesterol to tissues (Apo B100)
- **HDL** ? reverse cholesterol transport (Apo A-I)
- **Lp(a)** ? LDL + Apo(a) ? thrombosis risk
- **Free fatty acids** ? transported by albumin, used in fasting

? Non-Esterified Fatty Acids (NEFA)

(Also called **Free Fatty Acids — FFA**)

Non-esterified fatty acids are fatty acids **not bound to glycerol**. They circulate directly in the bloodstream, especially during fasting.

? Origin

They are produced when **adipose tissue TAGs break down** via **Hormone-Sensitive Lipase (HSL)**.

Triggered by:

- Low insulin
- High glucagon

- Epinephrine
- Cortisol

? Transport

NEFAs are **hydrophobic**, so they circulate **bound to albumin**.

- One molecule of albumin can bind multiple FFAs.
- During fasting or uncontrolled diabetes, FFAs in blood rise sharply.

? Fate of NEFA

After entering tissues:

1. Oxidation for ATP

- Liver
- Muscle
- Heart

? undergo ?-oxidation ? acetyl-CoA ? TCA or ketogenesis.

2. Re-esterification

In fed states or in liver ? converted back to TAGs and packed into **VLDL**.

? Clinical Points

- Elevated NEFA in **uncontrolled diabetes** ? increased ketone body production.
- High FFAs contribute to **insulin resistance** in metabolic syndrome.
- High NEFA in prolonged fasting ? liver shifts to **ketogenesis**.

? Bile Salts

Bile salts are **amphipathic derivatives of cholesterol** that aid digestion and absorption of lipids.

? Synthesis of Bile Acids

Cholesterol ? **Primary bile acids**

- **Cholic acid**
- **Chenodeoxycholic acid**

These combine with:

- **Glycine** ? glycocholic acid
- **Taurine** ? taurocholic acid

? forming **bile salts** (more water-soluble than acids).

? Functions of Bile Salts

1. Emulsification of dietary fat

- Break large fat droplets into smaller ones
- Increase surface area for pancreatic lipase

2. Micelle formation

- Essential for absorption of:
  - Fatty acids
  - Monoglycerides
  - Cholesterol
  - Fat-soluble vitamins (A, D, E, K)

3. Cholesterol excretion

- Major pathway for removing cholesterol from the body.

? Enterohepatic Circulation

- 95% of bile salts are reabsorbed from the ileum
- Returned to liver

- Re-secreted in bile
  This cycle repeats multiple times per meal.

? Clinical Points

- **Cholestyramine** (bile acid binding resin) increases fecal loss of bile salts ? lowers cholesterol.
- Ileal disease (Crohn's) ? bile salt malabsorption ? steatorrhea, fat-soluble vitamin deficiency.
- Gallstones form when cholesterol exceeds bile salt capacity.

? Steroid Hormones

Steroid hormones are **cholesterol-derived hormones** produced by the adrenal cortex, gonads, and placenta.

All share the **cyclopentanoperhydrophenanthrene (steroid) nucleus**.

? Classification & Functions

? 1. Glucocorticoids

Example: Cortisol

- Produced in **adrenal cortex (zona fasciculata)**
- Functions:

- Raises blood glucose (gluconeogenesis)
- Anti-inflammatory
- Catabolic effects on muscle
- Maintains vascular tone

? 2. Mineralocorticoids

Example: Aldosterone

- Produced in **adrenal cortex (zona glomerulosa)**
- Functions:
  - Increases **Na? reabsorption**
  - Increases **K? & H? excretion**
  - Regulates blood pressure & fluid balance

? 3. Sex Hormones

Androgens

- Testosterone (testes)
- Dihydrotestosterone (DHT — more potent)

Estrogens

- Estradiol, estrone (ovaries)

Progesterone

- Prepares uterus for implantation
- Maintains pregnancy

? Synthesis Pathway Overview (Simplified)

Cholesterol ? Pregnenolone ?
? Progesterone (branch point)

From Progesterone:

- **Glucocorticoids** (cortisol)
- **Mineralocorticoids** (aldosterone)
- **Androgens ? Estrogens**

Occurs in mitochondrial + ER enzymes.

? Mechanism of Action

Steroid hormones bind to **intracellular receptors** ? receptor-hormone complex binds DNA ? regulates gene transcription.

Slow onset, long duration.

? Clinical Points

- **Cushing syndrome** ? excess cortisol
- **Addison disease** ? deficiency of adrenal steroids
- **Hyperaldosteronism** ? hypertension, hypokalemia
- **Polycystic ovary syndrome (PCOS)** ? increased androgens
- Aromatase inhibitors used in estrogen-dependent breast cancer therapy.

? Ultra-Short Revision Table

TOPIC	KEY FACTS
NEFA	Released from adipose by HSL, transported by albumin, used in fasting
Bile salts	Derived from cholesterol, emulsify fat, form micelles, enterohepatic recycling
Steroid hormones	Cholesterol-derived; include cortisol, aldosterone, estrogen, progesterone, testosterone

? Important Points to Remember — Entire Chapter

? Cholesterol & Steroids

- All steroids share the **cyclopentanoperhydrophenanthrene nucleus**.

- Cholesterol is a **27-carbon sterol** with a hydroxyl group at C-3.
- Cholesterol is precursor of **bile acids, steroid hormones, vitamin D**.
- Cholesterol is an **essential membrane component** (regulates fluidity).
- Cholesterol synthesis occurs in **cytosol + SER** of liver.

? Biosynthesis of Cholesterol

- Begins with **acetyl-CoA**.
- Rate-limiting enzyme = **HMG-CoA reductase**.
- Statins **competitively inhibit HMG-CoA reductase** ? ? hepatic cholesterol.
- Mevalonate ? isoprenoids ? squalene ? lanosterol ? cholesterol.
- Requires **18 ATP + 14 NADPH**.
- Activated by **insulin**, inhibited by **glucagon & cholesterol**.

? Plasma Lipids

- Plasma lipids include **TAG, cholesterol, cholesteryl esters, phospholipids, FFAs**.
- They are transported in blood mainly as **lipoproteins**.

? Transport of Lipids

- TAGs & cholesterol are transported via **lipoproteins** (chylomicrons, VLDL, LDL, HDL).
- Free fatty acids travel **bound to albumin**.
- Bile salts are essential for absorption of dietary lipids.

? Lipoprotein Overview

- **Larger lipoprotein ? lower density** (more TAG, less protein).
- **Smaller lipoprotein ? higher density** (more protein, less TAG).

Order:
Chylomicron > VLDL > IDL > LDL > HDL

? Chylomicrons

- Transport **dietary TAGs** from intestine to tissues.
- Contain **Apo B-48, Apo C-II, Apo E**.
- Hydrolyzed by **LPL** (activated by Apo C-II).
- Remnants taken up by **liver via Apo E**.
- LPL or Apo C-II deficiency ? **Type I hyperlipoproteinemia**.

? VLDL

- Transport **endogenous TAGs** from liver to tissues.

- Contain **Apo B-100, C-II, E**.
- Converted ? IDL ? LDL.
- High VLDL = high triglycerides (seen in obesity, diabetes, alcohol use).

? LDL

- Carries **70% of plasma cholesterol**.
- Contains **Apo B-100**.
- Delivers cholesterol to tissues via **LDL receptor**.
- High LDL ? **atherosclerosis** (“bad cholesterol”).
- Familial hypercholesterolemia = **defective LDL receptor**.

? HDL

- Smallest, densest lipoprotein; very high protein content.
- Contains **Apo A-I, A-II, C, E**.
- Performs **reverse cholesterol transport**.
- LCAT activated by **Apo A-I** esterifies cholesterol.
- High HDL = protective against heart disease.

? Lipoprotein(a) — Lp(a)

- LDL particle with **Apo(a)** attached.
- Apo(a) is similar to **plasminogen** ? inhibits fibrinolysis.
- High Lp(a) = **independent risk factor for heart attack & stroke**.
- Genetically determined; statins DO NOT lower Lp(a).

? Apolipoproteins — Key Points

- **Apo B-48** ? chylomicron assembly.
- **Apo B-100** ? VLDL/LDL secretion + LDL receptor binding.
- **Apo C-II** ? activates LPL (TAG hydrolysis).
- **Apo C-III** ? inhibits LPL (? triglycerides).
- **Apo E** ? remnant uptake by liver.
- **Apo A-I** ? activates LCAT (HDL maturation).

? Free Fatty Acids (NEFA)

- Released from adipose by **Hormone-Sensitive Lipase** during fasting.
- Transported in blood **bound to albumin**.
- Oxidized via **?-oxidation** ? ATP or ketone body formation.
- High FFAs ? **insulin resistance** in metabolic syndrome.

? Bile Salts

- Synthesized from cholesterol in the liver.
- Primary bile acids = **cholic acid & chenodeoxycholic acid**.
- Conjugated with **glycine/taurine** ? bile salts.
- Functions:
  - **Emulsify fats**
  - Form **micelles**
  - Absorb fat-soluble vitamins
- Recycled via **enterohepatic circulation**.

? Steroid Hormones

All steroid hormones are derived from **cholesterol** through **pregnenolone**.

Categories:

- **Glucocorticoids** (cortisol) ? gluconeogenesis, stress response
- **Mineralocorticoids** (aldosterone) ? Na? retention, K? excretion
- **Sex steroids**
  - Androgens ? testosterone, DHT
  - Estrogens ? estradiol

- Progesterone ? pregnancy maintenance

Key facts:

- Synthesized in adrenal cortex, gonads, placenta.
- Act via **intracellular receptors** ? regulate gene expression.
- Slow onset, long duration of action.

? Ultra-High-Yield 10 One-Liners (Exam Favorites)

1. **Apo C-II activates LPL** — essential for TAG breakdown.
2. **Apo A-I activates LCAT** — cholesterol esterification in HDL.
3. **Apo B-48 = chylomicrons**, **Apo B-100 = VLDL/LDL**.
4. **LDL delivers cholesterol; HDL removes cholesterol.**
5. **Statins inhibit HMG-CoA reductase** ? ? cholesterol synthesis.
6. **Lp(a) resembles plasminogen ? thrombosis risk.**
7. **Chylomicron remnants enter liver via Apo E receptor.**
8. **HDL performs reverse cholesterol transport.**
9. **Free fatty acids travel with albumin during fasting.**
10. **Bile salts are essential for fat digestion & absorption.**

? FAQs — Cholesterol & Lipoprotein Metabolism (Complete Chapter)

1. What is the basic nucleus of all steroids?

The **cyclopentanoperhydrophenanthrene nucleus**.

2. What is cholesterol chemically?

A **27-carbon sterol** with a hydroxyl group at C-3.

3. Where does cholesterol synthesis occur?

In the **cytosol and smooth ER**, mainly in the **liver**.

4. What is the rate-limiting enzyme of cholesterol synthesis?

HMG-CoA reductase.

5. Which drugs inhibit HMG-CoA reductase?

Statins (e.g., atorvastatin, simvastatin).

6. What are the major functions of cholesterol?

- Membrane fluidity

- Precursor of **bile acids**, **steroid hormones**, **vitamin D**
- Component of lipoproteins

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7. What are the primary bile acids?

Cholic acid and **chenodeoxycholic acid**.

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8. What is the function of bile salts?

Emulsification of fats and **micelle formation** for lipid absorption.

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9. What is enterohepatic circulation?

Reabsorption of **95% of bile salts** from the ileum back to the liver.

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10. What are plasma lipids?

TAGs, cholesterol, cholesteryl esters, phospholipids, and free fatty acids.

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11. Why do lipids need lipoproteins?

Because they are **hydrophobic**; require transport in soluble particles.

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12. Which lipoprotein transports dietary TAGs?

Chylomicrons.

13. Which apolipoprotein is essential for chylomicron formation?

Apo B-48.

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14. Which enzyme hydrolyzes TAGs in chylomicrons and VLDL?

Lipoprotein lipase (LPL).

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15. Which apolipoprotein activates LPL?

Apo C-II.

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16. What does Apo E do?

Mediates uptake of **remnants** by the liver.

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17. What is the main lipid transported by VLDL?

Endogenous TAGs synthesized in the liver.

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18. What is IDL?

Intermediate-density lipoprotein; remnant of VLDL.

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19. What is LDL?

The **major cholesterol-carrying** lipoprotein in plasma.

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20. Which apolipoprotein is found in LDL?

Apo B-100.

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21. Why is LDL called “bad cholesterol”?

High LDL ? **atherosclerosis** due to cholesterol deposition.

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22. What is the function of HDL?

Reverse cholesterol transport from tissues back to liver.

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23. Which enzyme does Apo A-I activate in HDL?

LCAT (lecithin–cholesterol acyltransferase).

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24. Why is HDL called “good cholesterol”?

High HDL ? protective against cardiovascular disease.

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25. What is Lipoprotein(a) [Lp(a)]?

An LDL particle attached to **Apo(a)**.

26. Why is Lp(a) dangerous?

Apo(a) resembles **plasminogen** ? inhibits fibrinolysis ? ? thrombosis risk.

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27. What carries free fatty acids in blood?

Albumin.

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28. When do NEFAs increase?

During **fasting**, **exercise**, and **uncontrolled diabetes** (? lipolysis).

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29. Which enzyme releases NEFAs from adipose tissue?

Hormone-Sensitive Lipase (HSL).

---

30. What stimulates HSL?

Glucagon & epinephrine (via cAMP).

---

31. What inhibits HSL?

Insulin.

---

32. Name the three major classes of steroid hormones.

Glucocorticoids, **mineralocorticoids**, **sex steroids**.

---

33. What is the immediate precursor for all steroid hormones?

Pregnenolone, derived from cholesterol.

---

34. Where are steroid hormones synthesized?

Adrenal cortex, gonads, placenta.

---

35. How do steroid hormones act?

Bind intracellular receptors ? **gene transcription** ? protein synthesis.

---

36. Why do statins reduce LDL levels?

? hepatic cholesterol ? ? LDL receptors ? ? LDL clearance.

---

37. What happens in familial hypercholesterolemia?

Defective **LDL receptor** ? very high LDL ? premature atherosclerosis.

---

38. Which lipoprotein rises in Type I hyperlipoproteinemia?

Chylomicrons (due to LPL or Apo C-II deficiency).

39. Which lipoprotein rises in Type IV hyperlipoproteinemia?

VLDL (endogenous hypertriglyceridemia).

---

40. Which lipoprotein is formed only in the intestine?

Chylomicrons.

? MCQs — Cholesterol & Lipoproteins (Full Chapter)

---

1. The basic structural nucleus of all steroids is called:

A. Acyl-CoA nucleus
B. Cyclopentanoperhydrophenanthrene nucleus
C. Cholesteryl nucleus
D. Pyridine nucleus

Answer: B
Explanation: All steroids share this four-ring nucleus.

---

2. The rate-limiting step of cholesterol synthesis is catalyzed by:

A. HMG-CoA synthase
B. Squalene epoxidase
C. HMG-CoA reductase
D. Lanosterol demethylase

Answer: C

Explanation: Converts HMG-CoA ? mevalonate; target of statins.

---

3. The major site of cholesterol synthesis is:

A. Kidney
B. Brain
C. Liver
D. Pancreas

Answer: C

---

4. Statins lower cholesterol by inhibiting:

A. Squalene synthase
B. HMG-CoA reductase
C. LCAT
D. LDL receptor

Answer: B

---

5. Which lipoprotein transports *dietary* triacylglycerols?

A. LDL
B. HDL
C. Chylomicrons
D. VLDL

Answer: C

---

6. Apo B-48 is present in:

A. Chylomicrons
B. LDL
C. HDL
D. Lp(a)

Answer: A

---

7. The apolipoprotein required for activation of lipoprotein lipase (LPL) is:

A. Apo A-I
B. Apo C-II
C. Apo B-100
D. Apo E

Answer: B

---

8. VLDL is secreted by:

A. Adipose tissue
B. Liver
C. Intestine
D. Pancreas

Answer: B

---

9. LDL contains which apolipoprotein?

A. Apo B-48
B. Apo A-I
C. Apo C-II

D. Apo B-100

Answer: D

---

10. Which lipoprotein delivers cholesterol to peripheral tissues?

A. HDL
B. LDL
C. Chylomicrons
D. VLDL

Answer: B

---

11. Which enzyme esterifies cholesterol in HDL?

A. LPL
B. ACAT
C. LCAT
D. CETP

Answer: C
Explanation: Activated by Apo A-I.

---

12. Reverse cholesterol transport is carried out by:

A. LDL
B. HDL
C. VLDL
D. Chylomicrons

Answer: B

---

13. Free (non-esterified) fatty acids are transported in plasma by:

A. HDL
B. LDL
C. Albumin
D. VLDL

Answer: C

---

14. Bile salts are synthesized from:

A. TAG
B. Phospholipids
C. Cholesterol
D. Free fatty acids

Answer: C

---

15. Major primary bile acids in humans include:

A. Deoxycholic acid
B. Lithocholic acid
C. Cholic acid
D. Stearic acid

Answer: C
Explanation: Cholic & chenodeoxycholic = primary bile acids.

---

16. Lp(a) is structurally similar to:

A. Apo C-II
B. Albumin

C. Plasminogen
D. Ferritin

Answer: C
Explanation: Apo(a) resembles plasminogen ? thrombotic risk.

---

17. High Lp(a) levels are associated with increased risk of:

A. COPD
B. Pancreatitis
C. Atherosclerosis & thrombosis
D. Liver cirrhosis

Answer: C

---

18. Which hormone stimulates Hormone-Sensitive Lipase (HSL)?

A. Insulin
B. Cortisol
C. Glucagon
D. Thyroxine

Answer: C
Explanation: Fasting ? glucagon ? cAMP ? HSL activation.

---

19. Which enzyme is inhibited by insulin?

A. LCAT
B. HSL
C. LPL
D. CETP

Answer: B

Explanation: Insulin inhibits lipolysis.

---

20. Which apolipoprotein is required for hepatic uptake of remnants?

A. Apo A-I

B. Apo C-III

C. Apo E

D. Apo B-48

Answer: C

---

21. “Bad cholesterol” refers to:

A. HDL

B. Chylomicron remnants

C. LDL

D. VLDL

Answer: C

---

22. Which lipoprotein is smallest and densest?

A. HDL

B. LDL

C. VLDL

D. Chylomicron

Answer: A

---

23. Familial hypercholesterolemia is due to defect in:

A. Apo A-I
B. LDL receptor
C. LCAT
D. CETP

Answer: B

---

24. Which apolipoprotein inhibits lipoprotein lipase?

A. Apo A-I
B. Apo C-II
C. Apo C-III
D. Apo E

Answer: C

---

25. Cholesterol is a precursor for all EXCEPT:

A. Steroid hormones
B. Bile salts
C. Vitamin D
D. Catecholamines

Answer: D
Explanation: Catecholamines come from tyrosine.

? Clinical Case–Based Problems (Complete Chapter)

---

1. Severe abdominal pain + creamy supernatant in blood sample

A 7-year-old child presents with recurrent abdominal pain and eruptive xanthomas. A blood sample left overnight forms a thick creamy layer on top.
TAG levels = **>2000 mg/dL**

Most likely diagnosis:

Type I Hyperlipoproteinemia

Biochemical defect:

- **LPL deficiency** *or*
- **Apo C-II deficiency**

Key finding:

Marked accumulation of **chylomicrons**.

---

2. Early heart attack in 25-year-old with tendon xanthomas

A 25-year-old man presents with MI. Physical exam shows **tendon xanthomas** over Achilles tendon. LDL > 300 mg/dL.

Most likely diagnosis:

Familial Hypercholesterolemia (Type IIa)

Defect:

- **LDL receptor deficiency**
- Or **Apo B-100 defect**

Result:

Markedly high **LDL** ? premature atherosclerosis.

---

3. After a fatty meal, plasma appears milky; VLDL normal

A patient has milky plasma after a high-fat meal. Fasting sample returns to normal.
TAG after meal = very high.
VLDL = normal.

Diagnosis:

Accumulation of chylomicrons (post-prandial)

Likely issue:

Delayed or insufficient **LPL activity**.

---

4. High LDL, normal VLDL, normal chylomicrons

A 40-year-old non-obese man has LDL = 240 mg/dL but triglycerides normal.

Diagnosis:

Type IIa Hyperlipoproteinemia

Defect:

LDL receptor ? impaired LDL clearance.

---

5. Diabetic patient with fasting for 16 hr—high NEFA & ketones

A 50-year-old diabetic man comes after prolonged fasting. He has dehydration, fruity breath, and Kussmaul breathing.

Diagnosis:

Diabetic ketoacidosis

Biochemical basis:

- Low insulin ? ? HSL
- ? NEFA to liver
- Excess acetyl-CoA ? **ketogenesis**

---

6. Defective Apo E ? accumulation of IDL & chylomicron remnants

A 35-year-old has palmar xanthomas and tuberoeruptive xanthomas. TAG moderately elevated.

Diagnosis:

Type III Hyperlipoproteinemia (Familial dysbetalipoproteinemia)

Defect:

Apo E deficiency

Result:

Accumulation of **IDL + chylomicron remnants**

---

7. Child with steatorrhea, fat malabsorption, no chylomicrons

5-year-old child has chronic diarrhea, acanthocytosis on blood smear, absence of chylomicrons after meals.

Diagnosis:

Abetalipoproteinemia

Defect:

Absence of **Apo B** (both B-48 and B-100)

Result:

- No chylomicrons
- No VLDL
- Fat malabsorption

---

8. High triglycerides + pancreatitis in uncontrolled diabetic

A 35-year-old uncontrolled diabetic has abdominal pain.
TAG = **900 mg/dL**, ketones present.

Diagnosis:

Hypertriglyceridemia (Type IV) due to ? VLDL

Cause:

Insulin deficiency ? ? HSL ? ? NEFA ? liver converts to **VLDL**.

---

9. Low HDL in a smoker with metabolic syndrome

A 48-year-old man with central obesity and insulin resistance shows HDL = 28 mg/dL.

Diagnosis:

Low HDL due to metabolic syndrome

Mechanism:

- Chronic inflammation
- Increased TAG exchange ? HDL depletion
- Reduced Apo A-I synthesis

---

10. Bile salt deficiency after ileal resection

A patient who underwent ileal surgery develops bulky, oily stools.

Diagnosis:

Bile salt malabsorption ? steatorrhea

Cause:

Ileum is site of bile salt reabsorption (enterohepatic circulation).

---

11. High Lp(a) levels in middle-aged man

A 45-year-old man with no diabetes or obesity presents with MI.
Lipid profile:

- LDL: 115 mg/dL (near normal)
- HDL: 55 mg/dL
- Lp(a): **very high**

Diagnosis:

Lp(a)-associated premature atherosclerosis

Mechanism:

Apo(a) competes with plasminogen ? ? fibrinolysis ? ? thrombosis.

---

12. Infant with very low cortisol & aldosterone

A 3-month-old infant has salt-wasting, dehydration, low cortisol, low aldosterone.

Diagnosis:

Defect in steroid hormone synthesis

Importance:

Cholesterol ? precursor for all steroid hormones.

---

13. Statin therapy reduces LDL effectively—why?

A 55-year-old with high LDL is started on a statin. LDL decreases significantly after 6 weeks.

Mechanism:

- Statins ? HMG-CoA reductase
- ? hepatic cholesterol
- ? LDL receptor expression
- ? LDL clearance

---

14. Alcoholic patient with fatty liver

A 42-year-old alcoholic develops fatty liver.
Liver biopsy: fat accumulation within hepatocytes.

Mechanism:

- Alcohol ? ? NADH
- NADH inhibits ?-oxidation
- Leads to ? TAG synthesis and accumulation

---

15. Patient with cholesterol gallstones

A 40-year-old woman develops right-upper-quadrant pain. Ultrasound shows gallstones.

Mechanism:

- Excess cholesterol in bile
- Insufficient bile salts ? precipitation
- Causing **cholesterol stones**

---

16. Patient with high LDL despite statins—suspect receptor defect

A 30-year-old with persistently high LDL despite maximal statin therapy.

Diagnosis:

Familial hypercholesterolemia (receptor-negative subtype)

Mechanism:

Statins do not work well when LDL receptors are absent.

---

17. Increased NEFA in chronic stress

A stressed individual has elevated cortisol levels.
TAG breakdown increases.

Mechanism:

Cortisol enhances **HSL activity** ? ? NEFA release ? ? VLDL synthesis.

---

18. Infant with vitamin D deficiency despite sunlight exposure

Likely cause: **cholesterol synthesis disorder** (7-dehydrocholesterol defect).

Importance:

Vitamin D precursor is derived from cholesterol in skin.

? Viva Voce — Cholesterol & Lipoproteins (Full Chapter)

---

1. What is the basic nucleus of all steroid compounds?

The **cyclopentanoperhydrophenanthrene nucleus**.

---

2. How many carbons does cholesterol contain?

27 carbons.

---

3. What functional group makes cholesterol a sterol?

A **hydroxyl group at carbon 3 (C-3)**.

---

4. Where does cholesterol synthesis occur?

In the **cytosol and smooth endoplasmic reticulum**, mainly in the **liver**.

---

5. What is the rate-limiting enzyme of cholesterol synthesis?

HMG-CoA reductase.

---

6. Which step in cholesterol synthesis do statins inhibit?

Conversion of **HMG-CoA to mevalonate**.

---

7. What is the immediate precursor of all steroid hormones?

Pregnenolone (from cholesterol).

---

8. Name the primary bile acids.

Cholic acid and **chenodeoxycholic acid**.

9. What is the function of bile salts?

They **emulsify fats** and help form **micelles** for lipid absorption.

---

10. What is enterohepatic circulation?

Recycling of bile salts from the **ileum ? portal blood ? liver**.

---

11. What are the major plasma lipids?

TAGs, cholesterol, cholesteryl esters, phospholipids, and **free fatty acids**.

---

12. Why do lipids need lipoproteins?

Because they are **hydrophobic** and cannot circulate freely.

---

13. Which lipoprotein transports dietary triacylglycerols?

Chylomicrons.

---

14. Which apolipoprotein is unique to chylomicrons?

Apo B-48.

---

15. Which apolipoprotein activates lipoprotein lipase (LPL)?

Apo C-II.

---

16. What is the function of LPL?

Hydrolyses **TAGs** in chylomicrons and VLDL into FFAs + glycerol.

---

17. Which lipoprotein carries endogenous TAGs?

VLDL.

---

18. What is IDL?

Intermediate-density lipoprotein; VLDL remnant.

---

19. Which lipoprotein delivers cholesterol to tissues?

LDL.

---

20. Which apolipoprotein does LDL contain?

Apo B-100.

---

21. Why is LDL considered “bad cholesterol”?

Because high LDL leads to **cholesterol deposition** in arteries ? atherosclerosis.

22. Which lipoprotein is called “good cholesterol”?

HDL.

---

23. What is the main function of HDL?

Reverse cholesterol transport (from tissues ? liver).

---

24. Which enzyme does Apo A-I activate?

LCAT.

---

25. What is the composition of Lp(a)?

LDL + **Apo(a)**.

---

26. Why is Lp(a) harmful?

Apo(a) resembles **plasminogen** ? inhibits fibrinolysis ? ? thrombosis.

---

27. How are free fatty acids transported in blood?

Bound to **albumin**.

---

28. When do plasma free fatty acids increase?

During **fasting**, exercise, and uncontrolled diabetes due to ? HSL activity.

---

29. Which enzyme releases free fatty acids from adipose tissue?

Hormone-Sensitive Lipase (HSL).

---

30. Which hormone inhibits HSL?

Insulin.

---

31. Which hormone group is derived from cholesterol?

Steroid hormones.

---

32. Name the three major classes of steroid hormones.

Glucocorticoids, mineralocorticoids, and sex steroids.

---

33. What is the main glucocorticoid in humans?

Cortisol.

---

34. What is the function of aldosterone?

Regulates **Na? retention**, **K? excretion**, and **blood pressure**.

35. How do steroid hormones act at the cellular level?

Bind **intracellular receptors**, then alter **gene transcription**.

---

36. What is the major lipoprotein abnormality in Type I hyperlipoproteinemia?

Accumulation of **chylomicrons**.

---

37. What is the key defect in familial hypercholesterolemia?

Defective **LDL receptor** or **Apo B-100**.

---

38. Which lipoprotein is lowest in density and largest in size?

Chylomicrons.

---

39. Which lipoprotein is highest in density?

HDL.

---

40. Why do statins increase LDL receptor expression?

They reduce hepatic cholesterol ? liver pulls more LDL from blood.

Flowchart 1: Chylomicron Metabolism

Dietary Fat ? Intestinal Lumen

? (Bile salts emulsify)

Fatty acids + 2-MAG absorbed by enterocytes

?

Re-esterified ? TAG

?

Chylomicron Assembly (Apo B-48)

?

Chylomicrons enter lymph ? blood

?

HDL donates Apo C-II + Apo E

?

Apo C-II activates LPL on capillary endothelium

?

LPL hydrolyses TAG ? FFA + Glycerol

?

FFA go to muscle (energy) or adipose (storage)

?

Chylomicron shrinks ? becomes Chylomicron Remnant

?

Apo C-II is returned to HDL

?

Remnant (with Apo E + B-48) taken up by liver

?

Hepatic uptake via Apo E receptor

? Flowchart 2: VLDL ? IDL ? LDL Metabolism

Liver synthesizes TAG

?

VLDL Assembly (Apo B-100)

?

VLDL secreted into blood

?

HDL donates Apo C-II + Apo E

?

Apo C-II activates LPL ? hydrolyses TAG

?

FFAs taken up by muscle & adipose

?

VLDL loses TAG ? becomes IDL (VLDL remnant)

?

Two possible pathways:

PATHWAY A:

IDL (with Apo E) taken up by liver

?

Hepatic remnant receptor clears IDL

PATHWAY B:

IDL loses Apo E + more TAG via hepatic lipase

?

IDL becomes LDL (rich in cholesterol)

?

LDL delivers cholesterol to tissues via Apo B-100

?

LDL taken up by LDL receptors

?

Excess LDL ? atherosclerosis

? Flowchart 3: Reverse Cholesterol Transport (HDL Pathway)

HDL synthesized in liver & intestine

?

Nascent HDL (discoid shape; Apo A-I) enters blood

?

HDL picks up free cholesterol from peripheral tissues

?

Apo A-I activates LCAT

?

LCAT esterifies cholesterol ? cholesteryl esters

?

HDL matures (spherical HDL3 ? HDL2)

?

Two pathways:

PATHWAY A:

HDL2 delivers cholesteryl esters directly to liver

?

SR-B1 receptor mediates uptake

PATHWAY B:

HDL transfers cholesteryl esters to VLDL/LDL

?

Mediated by CETP

?

VLDL/LDL carry CE to liver

Ultimately:

Liver excretes cholesterol as ? Bile acids & bile salts

?

Removal from the body