B.PHARM SEMESTER II | BP202T

BIOCHEMISTRY (THEORY)

UNIT III

Lipid Metabolism

Short Notes for Quick Revision

What is covered in this unit

UNIT III TOPICS

Part A – Lipids and lipoproteins: classification, functions and properties of lipids; digestion and absorption; lipoproteins (chylomicrons, VLDL, LDL, HDL) and their metabolism.

Part B – Fatty acid metabolism and ketone bodies: β-oxidation, de novo synthesis of fatty acids, synthesis and utilisation of ketone bodies and their clinical significance.

Part C – Cholesterol and lipid profile: biological significance and biosynthesis of cholesterol; lipid profile and its clinical significance.

Part D – Disorders: hyperlipidaemias and hypercholesterolemia, lipid storage diseases, atherosclerosis, fatty liver disease and obesity.

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PART A: LIPIDS AND LIPOPROTEINS

1. Classification, Functions and Properties of Lipids

Lipids are a heterogeneous group of organic compounds that are insoluble in water but soluble in non-polar solvents such as ether, chloroform and benzene. They are actually or potentially **esters of fatty acids** and are used by living organisms. Lipids give the highest energy of all nutrients: **9 kcal per gram**, compared with 4 kcal per gram for carbohydrates and proteins.

Classification

Class	Description	Examples
Simple lipids	Esters of fatty acids with alcohols	**Fats and oils:** triacylglycerols (glycerol esters). **Waxes:** esters with long-chain alcohols (beeswax, lanolin)
Compound (complex) lipids	Esters of fatty acids with alcohol plus another group	**Phospholipids** (phosphate): lecithin, cephalin, sphingomyelin. **Glycolipids** (sugar): cerebrosides, gangliosides. **Lipoproteins** (protein). **Sulpholipids**
Derived lipids	Products of hydrolysis of simple and compound lipids	Fatty acids, glycerol, **steroids** (cholesterol, bile acids, hormones), ketone bodies, fat-soluble vitamins (A, D, E, K), carotenoids, eicosanoids

Fatty acids

- Fatty acids are straight-chain carboxylic acids (R–COOH). In the body most have an **even number of carbons** (usually 16 or 18) because they are built from 2-carbon units.
- **Saturated** fatty acids have no double bond (palmitic 16:0, stearic 18:0). **Unsaturated** fatty acids have one (monounsaturated, oleic 18:1) or more (polyunsaturated, PUFA) double bonds, mostly in the *cis* form.
- **Omega (ω) notation:** counts the first double bond from the methyl end. Linoleic acid is 18:2 ω-6; α-linolenic acid is 18:3 ω-3.
- **Essential fatty acids (EFA):** linoleic and α-linolenic acids cannot be made in humans and must be taken in the diet. They are needed for membranes, for **eicosanoid synthesis** (prostaglandins, thromboxanes, leukotrienes from arachidonic acid) and for brain development (DHA). Deficiency causes scaly dermatitis, poor wound healing and growth retardation.
- **Trans fatty acids** (from partial hydrogenation) raise LDL and lower HDL and are strongly linked to coronary artery disease.

Physical and chemical properties

Property	Details
Amphipathic nature	Phospholipids, fatty acids, bile salts and soaps have a polar head and a non-polar tail. In water they form **micelles, bilayers and liposomes**
Emulsification	Bile salts break fat into fine droplets, increasing the surface for lipase action
Hydrolysis	Lipases or acids split triacylglycerol into glycerol and fatty acids
Saponification	Hydrolysis with alkali gives glycerol and soap. **Saponification number** = mg KOH to saponify 1 g fat (indicates chain length; higher number = shorter chains)
Hydrogenation	Addition of hydrogen to double bonds converts oils to solid fats (margarine); some *trans* fats are formed
Iodine number	g of iodine taken up by 100 g of fat; measures **unsaturation**
Acid number	mg KOH to neutralise the free fatty acids in 1 g fat; indicates rancidity
Rancidity	Spoilage of fat. *Hydrolytic* (lipases, moisture) and *oxidative* (peroxides, aldehydes). Prevented by antioxidants (vitamin E, BHA, BHT)

Functions of lipids

- **Energy:** major fuel and the main long-term energy store as **triacylglycerol in adipose tissue** (an adult has several weeks of energy stored as fat).
- **Structure:** phospholipids, cholesterol and glycolipids form all cell membranes; sphingomyelin forms the myelin sheath.
- **Insulation and protection:** subcutaneous fat prevents heat loss; fat pads protect organs.
- **Precursors:** steroid hormones, bile acids, vitamin D and eicosanoids.
- **Absorption** of fat-soluble vitamins A, D, E and K and essential fatty acids.

- **Signalling:** phosphatidylinositol gives IP_3 and DAG; eicosanoids act as local mediators.
- **Lung surfactant:** dipalmitoyl phosphatidylcholine prevents alveolar collapse.

2. Digestion and Absorption of Dietary Lipids

A normal diet has 60–100 g of fat per day, mostly **triacylglycerol (TAG)**, with small amounts of cholesterol, cholesterol esters and phospholipids. Digestion begins in the mouth and stomach (lingual and gastric lipases, minor in adults) but takes place mainly in the **small intestine**.

Step	What happens
Emulsification	Bile salts from the gallbladder break fat into small droplets
Digestion	**Pancreatic lipase** with its cofactor **colipase** splits TAG at positions 1 and 3 to give **2-monoacylglycerol + 2 free fatty acids**. **Phospholipase A_2** digests phospholipids; **cholesterol esterase** splits cholesterol esters
Micelle formation	Bile salts, monoacylglycerol, fatty acids, cholesterol and fat-soluble vitamins form **mixed micelles**
Absorption	Micelles bring the products to the brush border of **enterocytes**, where they diffuse in. Short- and medium-chain fatty acids (below 12 carbons) enter the portal blood directly
Re-esterification	Inside enterocytes, TAG is resynthesised (monoacylglycerol pathway)
Chylomicron formation	TAG, cholesterol esters, phospholipid and **apo B-48** are packed into **chylomicrons**, which leave through the **lymph (lacteals)** and enter the blood through the thoracic duct

CLINICAL CORRELATION

Steatorrhoea (fatty, bulky, pale, foul-smelling stool) occurs in pancreatic insufficiency (lack of lipase), obstructive jaundice or bile salt deficiency, and celiac disease. **Orlistat**, an anti-obesity drug, blocks pancreatic and gastric lipase and reduces fat absorption by about 30%; it can reduce absorption of fat-soluble vitamins.

3. Lipoproteins

Lipids are insoluble in plasma, so they travel as **lipoproteins**: spherical particles with a **core of non-polar lipids** (TAG and cholesteryl esters) surrounded by a **shell of phospholipid, free cholesterol and apolipoproteins**. Apolipoproteins give structure, direct the particle to receptors and activate enzymes.

Classification of lipoproteins

Property	Chylomicron	VLDL	LDL	HDL
Density (g/mL)	Below 0.95 (lowest)	0.95–1.006	1.019–1.063	1.063–1.21 (highest)
Size	Largest	Large	Medium	Smallest
Electrophoretic band	Origin	Pre-β	β	α
Main lipid	Dietary TAG (about 85–90%)	Endogenous TAG (about 55%)	**Cholesterol and its esters (about 50%)**	**Protein (about 50%)** and phospholipid
Main apoproteins	B-48, C-II, E, A-I	B-100, C-II, E	B-100	A-I, A-II, C-II, E
Origin	Intestine	Liver	From VLDL in blood	Liver and intestine
Function	Carries dietary fat to tissues	Carries liver-made TAG to tissues	Carries cholesterol to tissues; **atherogenic**	Removes cholesterol from tissues to the liver; **protective**

IDL (intermediate-density lipoprotein) is a short-lived product of VLDL that is either taken up by the liver or converted to LDL. **Lp(a)** is an LDL-like particle with an extra protein, apo(a), that resembles plasminogen; a high level is an independent risk factor for coronary disease and thrombosis.

Chemical composition (% by weight, approximate)

Lipoprotein	Triacylglycerol	Cholesterol (free + ester)	Phospholipid	Protein
Chylomicron	85–90	3–5	7–8	1–2

Lipoprotein	Triacylglycerol	Cholesterol (free + ester)	Phospholipid	Protein
VLDL	50–55	18–22	15–20	8–10
IDL	25–30	30–35	20–25	10–12
LDL	5–10	45–50	20–22	20–25
HDL	3–5	18–25	25–30	45–55

Particle size and density depend on the lipid-to-protein ratio: **more lipid means a larger, lighter particle**. This is why chylomicrons float at the top of a plasma sample, and HDL, which is half protein, is the densest.

Important apolipoproteins

Apolipoprotein	Present in	Function
Apo A-I	HDL, chylomicrons	Activates **LCAT**; main structural protein of HDL; binds ABCA1
Apo B-48	Chylomicrons	Structural; made in the intestine; no LDL receptor binding
Apo B-100	VLDL, IDL, LDL	Structural; **ligand for the LDL receptor**; made in the liver
Apo C-II	Chylomicron, VLDL, HDL	**Activates lipoprotein lipase** (LPL)
Apo E	Chylomicron remnants, VLDL, IDL, HDL	Ligand for remnant and LDL receptors; the apo E4 form increases risk of Alzheimer's disease

Metabolism of lipoproteins

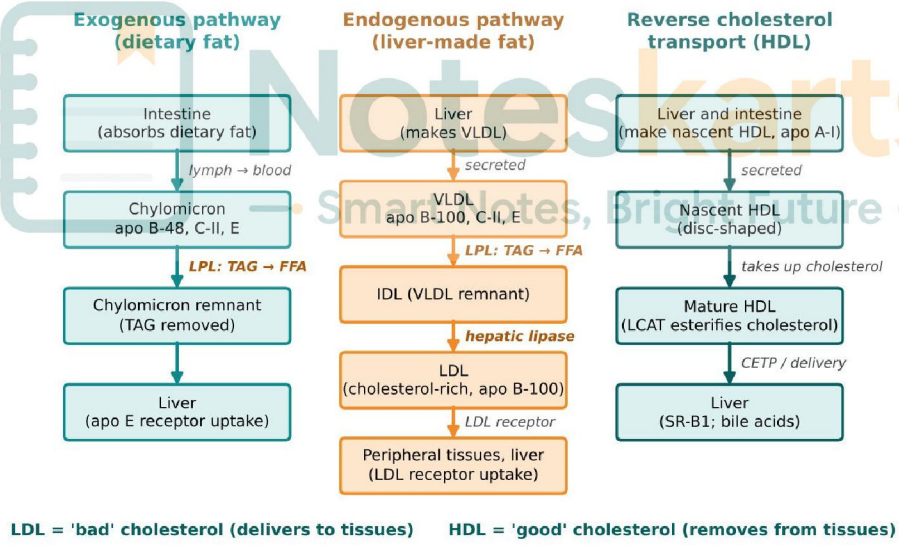

Figure 1: Overview of lipoprotein metabolism

1. Exogenous pathway (chylomicrons)

- Chylomicrons enter the blood by lymph and pick up apo C-II and apo E from HDL.
- **Lipoprotein lipase (LPL)**, on the endothelium of capillaries in adipose tissue, muscle and heart, splits the TAG, releasing free fatty acids and glycerol for the tissues. Insulin increases LPL in adipose tissue; **heparin** releases LPL into the blood (the clearing factor).
- The **chylomicron remnant** (TAG-depleted, cholesterol-rich, with apo E) is removed by the liver through the remnant (apo E) receptor.

2. Endogenous pathway (VLDL → IDL → LDL)

- The liver makes **VLDL** from TAG (from de novo synthesis and free fatty acids) and secretes it. LPL again removes TAG and VLDL becomes **IDL**.
- About half of IDL goes back to the liver; the rest loses more TAG (hepatic lipase) and becomes **LDL**.

- **LDL receptor pathway:** LDL binds to the **LDL receptor** (recognising apo B-100) in coated pits, is taken in by endocytosis and broken down in lysosomes. The released cholesterol (i) suppresses HMG-CoA reductase, (ii) is esterified by **ACAT**, and (iii) reduces the number of LDL receptors. About 70% of LDL is removed by the liver.

3. Reverse cholesterol transport (HDL)

- **Nascent HDL** is made as a disc by the liver and intestine (apo A-I) and takes up free cholesterol from tissues and from macrophages (through **ABCA1**).
- **LCAT** (lecithin–cholesterol acyltransferase, activated by apo A-I) converts the cholesterol to cholesteryl ester, which moves into the core, giving **mature (spherical) HDL**.
- **CETP** (cholesteryl ester transfer protein) exchanges HDL cholesteryl esters for TAG of VLDL and LDL. The liver takes up HDL cholesterol through **SR-B1** and converts it to bile acids or excretes it.

Key enzymes and proteins in lipoprotein metabolism

Enzyme / protein	Site	Function
Lipoprotein lipase (LPL)	Capillary endothelium of adipose tissue, muscle, heart	Hydrolyses TAG of chylomicrons and VLDL; needs **apo C-II**; deficiency causes type I hyperlipoproteinemia
Hepatic lipase	Liver sinusoids	Converts IDL to LDL; removes TAG and phospholipid from HDL
LCAT	Plasma, on HDL	Esterifies cholesterol using fatty acid from lecithin; activated by apo A-I
CETP	Plasma	Moves cholesteryl esters from HDL to VLDL and LDL, TAG in the opposite direction
ACAT	Inside cells	Esterifies cholesterol for storage
Hormone-sensitive lipase	Adipose tissue	Releases fatty acids from stored TAG in fasting

WHY LDL IS 'BAD' AND HDL IS 'GOOD'

LDL carries cholesterol into tissues and arteries, where oxidised LDL is taken up by macrophages to give foam cells (atherosclerosis). HDL removes cholesterol from tissues and artery walls and carries it to the liver. A **high HDL and a low LDL** lower the risk of heart disease.

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PART B: FATTY ACID METABOLISM AND KETONE BODIES

4. Mobilisation of Fat and Activation of Fatty Acids

Between meals and in fasting, the TAG stored in adipose tissue is broken down (**lipolysis**) and the fatty acids are used as fuel by most tissues, except the brain and red cells (which cannot use fatty acids).

- **Hormone-sensitive lipase (HSL)** is the rate-limiting enzyme. It is activated by **glucagon, adrenaline, noradrenaline, ACTH, cortisol and growth hormone** (through cAMP and protein kinase A, which phosphorylates HSL) and inhibited by **insulin** (the main anti-lipolytic hormone).
- HSL and other lipases release **free fatty acids (FFA)**, which bind **albumin** in blood and are carried to tissues, and **glycerol**, which goes to the liver (glycerol kinase) for glycolysis or gluconeogenesis. Adipose tissue lacks glycerol kinase.
- **Activation:** in the cytosol, fatty acids are activated to **fatty acyl-CoA** by **acyl-CoA synthetase (thiokinase)**: Fatty acid + CoA + ATP → Acyl-CoA + AMP + PPi. Two high-energy bonds are used (ATP → AMP).

Carnitine shuttle

Long-chain acyl-CoA cannot cross the inner mitochondrial membrane, where β-oxidation takes place. It is carried across by **carnitine** (β-hydroxy-γ-trimethylammonium butyrate), made from lysine and methionine, with vitamin C needed in its synthesis.

- **CPT-I (carnitine palmitoyltransferase I)** on the outer membrane converts acyl-CoA + carnitine to **acylcarnitine**.
- A **translocase** carries acylcarnitine in and carnitine out. **CPT-II** inside the matrix changes acylcarnitine back to acyl-CoA.
- **CPT-I is the regulatory step.** It is inhibited by **malonyl-CoA** (the first intermediate of fatty acid synthesis), so synthesis and oxidation cannot go on together. Short- and medium-chain acids do not need carnitine.

5. β-Oxidation of Fatty Acids

β-Oxidation is the main pathway for breaking down fatty acids. It occurs in the **mitochondrial matrix** (liver, heart, skeletal muscle and kidney). Two carbons are removed as **acetyl-CoA** from the carboxyl end in each cycle by oxidation of the β-carbon (carbon 3). It is called the **fatty acid spiral** because the same four reactions repeat.

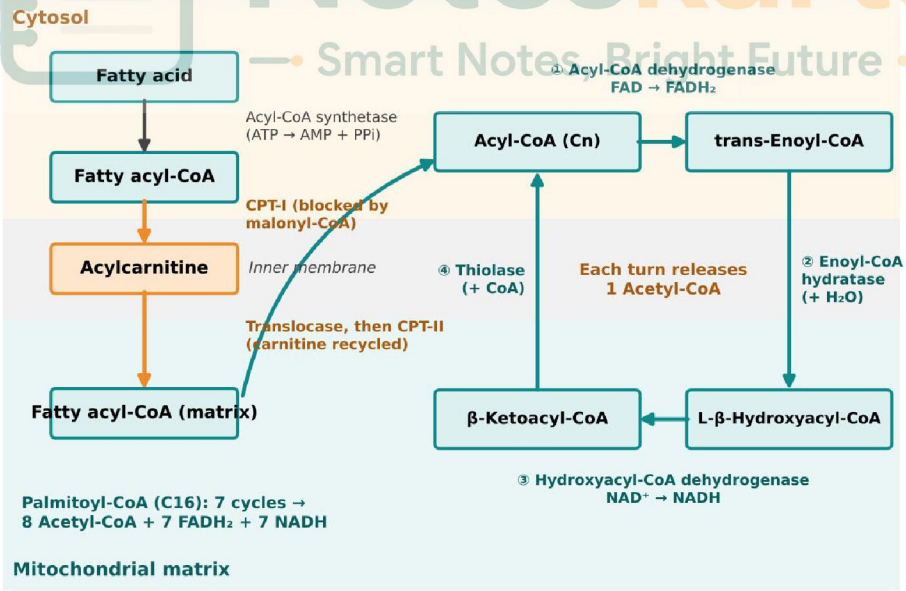

Figure 2: Carnitine shuttle and the β-oxidation cycle

Step	Enzyme	Reaction	Product
1 Oxidation	**Acyl-CoA dehydrogenase** (chain-length specific; FAD)	Forms a *trans* double bond between C-2 and C-3	trans-Δ²-Enoyl-CoA + **$FADH_2$**
2 Hydration	**Enoyl-CoA hydratase**	Adds water across the double bond	L-β-Hydroxyacyl-CoA
3 Oxidation	**β-Hydroxyacyl-CoA dehydrogenase** (NAD^+)	Oxidises the hydroxyl group to a keto group	β-Ketoacyl-CoA + **NADH**

Step	Enzyme	Reaction	Product
4 Thiolysis	**β-Ketoacyl-CoA thiolase**	Cleaves with CoA	**Acetyl-CoA** + acyl-CoA shorter by 2 C

Energetics: oxidation of palmitic acid (C16)

Item	Calculation	ATP (2.5 / 1.5)	ATP (older 3 / 2)
Number of cycles	n/2 – 1 = 7 cycles	—	—
7 $FADH_2$	7 × 1.5 (or × 2)	10.5	14
7 NADH	7 × 2.5 (or × 3)	17.5	21
8 acetyl-CoA in the TCA cycle	8 × 10 (or × 12)	80	96
Gross total		108	131
Activation (ATP → AMP = 2 high-energy bonds)	– 2	– 2	– 2
Net yield per palmitate		**106 ATP**	**129 ATP**

Fatty acid oxidation yields more energy per gram than glucose because fatty acids are highly reduced. For a fatty acid of n carbons, the number of acetyl-CoA is n/2 and the number of β-oxidation cycles is (n/2) – 1.

Worked example: stearic acid (C18)

Stearic acid has 18 carbons, so it gives 18/2 = **9 acetyl-CoA** through 18/2 – 1 = **8 cycles**. Energy: 8 $FADH_2$ × 1.5 = 12; 8 NADH × 2.5 = 20; 9 acetyl-CoA × 10 = 90. Total = 122; minus 2 for activation = **120 ATP** (older books: 146 ATP).

Regulation of β-oxidation

- **Supply of fatty acids:** controlled by hormone-sensitive lipase (glucagon and adrenaline raise it; insulin lowers it).
- **CPT-I** is blocked by **malonyl-CoA** in the fed state, and released in fasting, when malonyl-CoA falls.
- **Energy state:** a high NADH/NAD^+ and $FADH_2$ level slows the dehydrogenases (product inhibition); a high acetyl-CoA/CoA ratio inhibits thiolase.
- **Gene control:** PPAR-α (activated by fatty acids and fibrates) increases the enzymes of β-oxidation in fasting.

Mitochondrial versus peroxisomal β-oxidation

Feature	Mitochondrial	Peroxisomal
Substrates	Short-, medium- and long-chain fatty acids (up to C20)	Very-long-chain fatty acids (above C22), branched-chain acids
Carnitine needed	Yes (long chain)	No
First enzyme	Acyl-CoA dehydrogenase ($FADH_2$ goes to the chain, gives ATP)	Acyl-CoA oxidase (gives **H_2O_2**, no ATP; catalase destroys H_2O_2)
End result	Complete oxidation to acetyl-CoA	Chain shortened to medium length, then finished in mitochondria
Associated disease	MCAD, CPT deficiency	Zellweger syndrome, X-linked adrenoleukodystrophy

Oxidation of special fatty acids

Type	Pathway
Odd-chain fatty acids	β-Oxidation gives acetyl-CoA and one **propionyl-CoA** (3C). It is carboxylated (propionyl-CoA carboxylase, **biotin**) to methylmalonyl-CoA, then (methylmalonyl-CoA mutase, **vitamin B_{12}**) to **succinyl-CoA**, which enters the TCA cycle. In B_{12} deficiency, methylmalonic acid accumulates
Unsaturated fatty acids	Extra enzymes (**enoyl-CoA isomerase**; **2,4-dienoyl-CoA reductase**, NADPH) handle the *cis* double bonds. They give slightly less ATP than saturated acids because the FAD step is skipped

Type	Pathway
Very-long-chain fatty acids (VLCFA, above C22)	First shortened in **peroxisomes** (the first step gives H_2O_2 instead of $FADH_2$) and finished in mitochondria. Defect: **X-linked adrenoleukodystrophy**, **Zellweger syndrome**
α-Oxidation	Removes one carbon at a time from the α-end of branched-chain fatty acids such as **phytanic acid** (from dairy and chlorophyll). Defect: **Refsum disease** (ataxia, retinitis pigmentosa, neuropathy)
ω-Oxidation	Minor pathway in the endoplasmic reticulum producing dicarboxylic acids; becomes important when β-oxidation is defective

CLINICAL CORRELATION

Primary carnitine deficiency / CPT-II deficiency: muscle weakness, cramps after exercise or fasting, myoglobinuria and non-ketotic hypoglycemia. **MCAD deficiency** (medium-chain acyl-CoA dehydrogenase) is the commonest inborn error of fatty acid oxidation: vomiting, hypoketotic hypoglycemia and coma after fasting; treated by avoiding fasting. **Jamaican vomiting sickness:** the unripe ackee fruit contains **hypoglycin**, which inhibits acyl-CoA dehydrogenase, giving severe hypoglycemia.

6. De Novo Synthesis of Fatty Acids

Fatty acid synthesis (lipogenesis) makes palmitic acid (C16) from acetyl-CoA when carbohydrate is plentiful. It occurs in the **cytosol** of **liver, adipose tissue, lactating mammary gland and kidney**. It is not simply the reverse of β-oxidation.

Steps

- **Supply of acetyl-CoA:** acetyl-CoA is made in mitochondria but cannot cross the membrane. It leaves as **citrate** (citrate synthase). In the cytosol, **ATP-citrate lyase** splits citrate to acetyl-CoA and oxaloacetate (uses ATP). Oxaloacetate returns as malate, which is converted by **malic enzyme** to pyruvate, giving **NADPH**.
- **Formation of malonyl-CoA (rate-limiting): acetyl-CoA carboxylase (ACC)** carboxylates acetyl-CoA to **malonyl-CoA**. It uses **biotin** and ATP.
- **Fatty acid synthase (FAS) complex:** a multi-enzyme dimer with seven activities and an **acyl carrier protein (ACP)** carrying phosphopantetheine (from pantothenic acid). The chain grows by **2 carbons** each cycle: malonyl group adds in (**condensation**, CO_2 is lost), then **reduction** (NADPH), **dehydration**, and a second **reduction** (NADPH).
- After **7 cycles**, **palmitoyl-ACP** is released as **palmitic acid** by thioesterase.

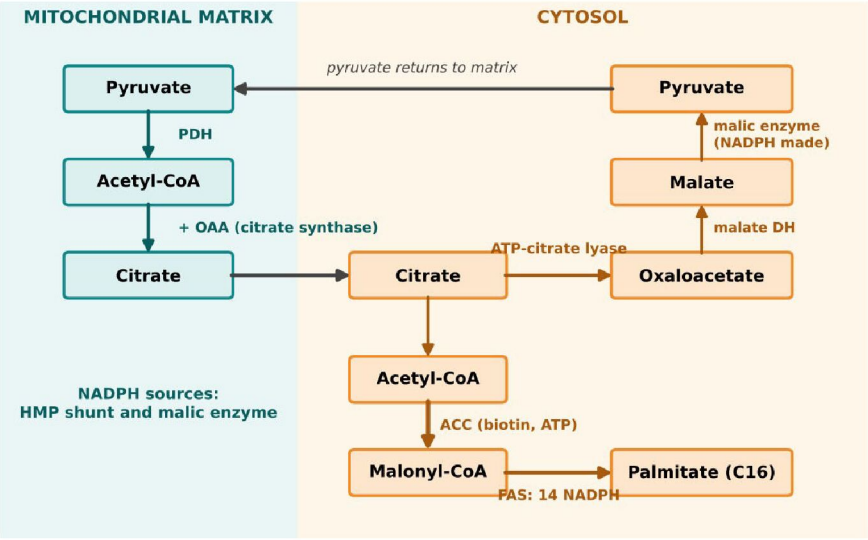

Figure 3: Citrate shuttle that supplies acetyl-CoA and NADPH for fatty acid synthesis

OVERALL REACTION FOR PALMITATE

8 Acetyl-CoA + 7 ATP + 14 NADPH + 14 H^+ → Palmitate + 8 CoA + 7 ADP + 7 Pi + 14 $NADP^+$ + 6 H_2O. **NADPH** comes from the **HMP shunt** and malic enzyme.

Regulation

Factor	Effect on lipogenesis
Insulin	**Stimulates**: activates ACC (dephosphorylation), induces ACC and FAS genes, increases glucose uptake and pyruvate dehydrogenase
Glucagon, adrenaline	**Inhibit**: phosphorylate (inactivate) ACC through cAMP-dependent protein kinase and AMPK
Citrate	Allosteric **activator** of ACC (signals plenty of acetyl-CoA)
Palmitoyl-CoA	Allosteric **inhibitor** of ACC (end-product feedback)
Diet	High-carbohydrate diet increases synthesis; fasting and high-fat diet decrease it

Elongation, desaturation and TAG synthesis

- **Elongation** (endoplasmic reticulum and mitochondria) adds 2-carbon units to palmitate to give stearate (C18) and longer acids.
- **Desaturation:** Δ^9-desaturase makes oleic acid from stearic acid. Humans lack enzymes to insert double bonds beyond carbon 9, so linoleic and linolenic acids are **essential**.
- **TAG synthesis:** glycerol-3-phosphate (from glucose, or from glycerol in the liver) is esterified with 2 acyl-CoA to give **phosphatidic acid**, which is dephosphorylated and acylated to **TAG**. Adipose tissue needs glucose for glycerol-3-phosphate, so fat storage depends on glucose and insulin.

β-Oxidation versus fatty acid synthesis

Feature	β-Oxidation	Fatty acid synthesis
Site	Mitochondrial matrix	Cytosol
Carrier of acyl groups	Coenzyme A	Acyl carrier protein (ACP)
Two-carbon unit	Removed as acetyl-CoA	Added from malonyl-CoA
Coenzymes	FAD and NAD^+ (oxidation)	NADPH (reduction)
Key regulatory enzyme	CPT-I (inhibited by malonyl-CoA)	Acetyl-CoA carboxylase (activated by insulin and citrate)
Hormonal control	Favoured by glucagon (fasting)	Favoured by insulin (fed state)
Stereochemistry	L-β-hydroxy intermediate	D-β-hydroxy intermediate

7. Ketone Bodies: Synthesis, Utilisation and Clinical Significance

Ketone bodies are **acetoacetate, β-hydroxybutyrate (BHB)** and **acetone**. They are water-soluble fuels made from acetyl-CoA in the **liver mitochondria** when fatty acid oxidation is high and carbohydrate supply is low. They carry energy from fat to the brain and other tissues. **β-Hydroxybutyrate** is quantitatively the main ketone body (it is not a true ketone because it has a hydroxyl group), and acetone is a minor by-product.

Ketogenesis (synthesis)

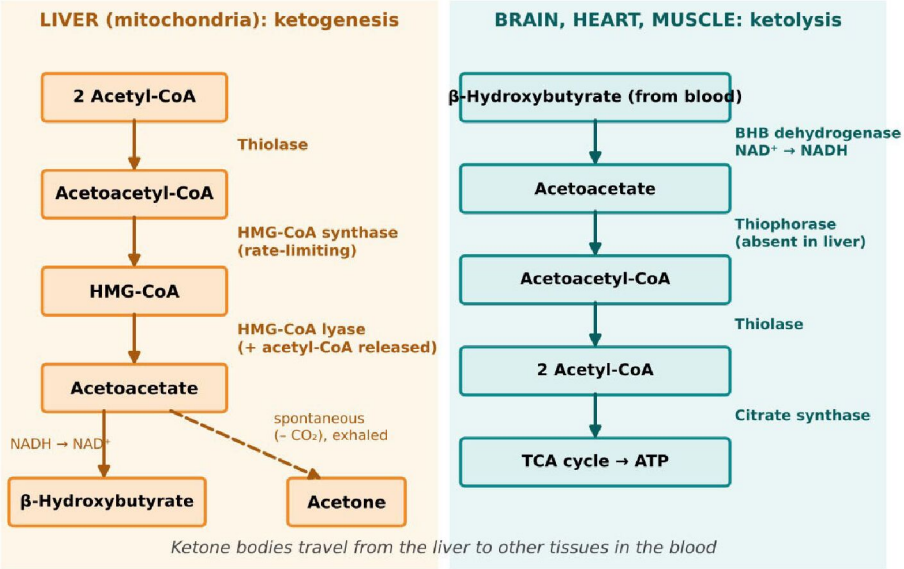

Figure 4: Synthesis and utilisation of ketone bodies

- Two acetyl-CoA join to form **acetoacetyl-CoA** (**thiolase**).
- A third acetyl-CoA is added to give **HMG-CoA** (**HMG-CoA synthase**, mitochondrial, the **rate-limiting step**).
- **HMG-CoA lyase** splits HMG-CoA to **acetoacetate** + acetyl-CoA.
- Acetoacetate is reduced to **β-hydroxybutyrate** by BHB dehydrogenase (NADH) or **decarboxylated to acetone** spontaneously. Acetone is exhaled (fruity breath).

Cytosolic HMG-CoA (used for cholesterol) is made by a different isoenzyme; do not confuse the two pools.

Utilisation (ketolysis)

- Ketone bodies are used by **brain, heart, skeletal muscle and kidney**. The **liver cannot use them** because it lacks **thiophorase** (succinyl-CoA–acetoacetate CoA transferase), and **red cells** cannot because they have no mitochondria.
- BHB is oxidised to acetoacetate ($NAD^+ \rightarrow NADH$). Acetoacetate + succinyl-CoA → **acetoacetyl-CoA** + succinate (thiophorase). Thiolase then gives **2 acetyl-CoA**, which enter the TCA cycle.
- Complete oxidation of one acetoacetate yields about **19–20 ATP**.

Regulation of ketogenesis

- **Low insulin / high glucagon:** lipolysis is high and more fatty acids reach the liver; malonyl-CoA falls, so **CPT-I is active** and fatty acids enter mitochondria.
- **Low oxaloacetate** (used for gluconeogenesis) means acetyl-CoA is not fully oxidised in the TCA cycle and goes to ketone bodies.
- In the fed state, insulin blocks lipolysis and raises malonyl-CoA, so ketogenesis is low.

The three ketone bodies

Ketone body	Formula type	Remarks
β-Hydroxybutyrate	Hydroxy acid (not a true ketone)	Most abundant (about 75–80% in ketosis); the form measured in blood; it is made when NADH is high
Acetoacetate	Keto acid	The primary ketone body; detected by Rothera's test and urine strips
Acetone	True ketone	Made by spontaneous decarboxylation; volatile; not used as fuel; gives the **fruity breath** odour

Clinical significance

Condition	Explanation
Physiological ketosis	Fasting, prolonged starvation, prolonged exercise, very low-carbohydrate (ketogenic) diet; the brain adapts to use ketones, which spares muscle protein. Blood ketones are mildly raised and pH stays normal

Condition	Explanation
Diabetic ketoacidosis (DKA)	Insulin lack: massive lipolysis and ketogenesis. Acetoacetate and BHB are strong acids, so the blood pH falls (**metabolic acidosis, high anion gap**); **Kussmaul breathing**, acetone odour, dehydration, vomiting and coma
Alcoholic ketoacidosis	Alcohol raises NADH, inhibits gluconeogenesis and causes starvation-like state with vomiting
Other causes	Hyperemesis of pregnancy, prolonged vomiting, glycogen storage disease type I, SGLT2 inhibitors (euglycemic DKA)

Starvation ketosis versus diabetic ketoacidosis

Feature	Starvation ketosis	Diabetic ketoacidosis
Insulin	Low but present (restrains lipolysis)	Absent or very low
Blood glucose	Low-normal	Very high (above 250 mg/dL)
Blood ketones	Mildly to moderately raised (up to about 7 mmol/L)	Very high (often above 10–20 mmol/L)
Blood pH	Normal (compensated)	Below 7.3, metabolic acidosis
Clinical state	Adaptive, brain uses ketones	Medical emergency

Therapeutic use

A strict **ketogenic diet** (high fat, very low carbohydrate) produces controlled ketosis and is used to treat **drug-resistant epilepsy in children** and some metabolic disorders (GLUT1 deficiency, PDH deficiency). It is not a safe long-term weight-loss method without supervision and is contraindicated in disorders of fatty acid oxidation.

Laboratory detection

- **Ketonemia:** blood ketones above 0.6 mmol/L are abnormal; above about 3 mmol/L with acidosis suggests DKA.
- **Ketonuria:** appears when ketone production exceeds the kidney's reabsorption.
- **Rothera's test** (sodium nitroprusside + ammonia → purple ring) and dipsticks detect acetoacetate and acetone but **not BHB**. In severe DKA, most of the ketone is BHB, so the test may underestimate ketosis; blood BHB measurement is better.

Integration of lipid metabolism: fed versus fasting state

Process	Fed state (insulin high)	Fasting (glucagon high)
Adipose tissue	TAG synthesis and storage; **LPL** ↑; HSL inhibited	**Lipolysis** ↑ **(HSL active)**; release of FFA and glycerol
Liver	**Fatty acid synthesis** ↑; VLDL secretion; ACC active; CPT-I blocked	**β-Oxidation** ↑; **ketogenesis** ↑; fatty acid synthesis ↓
Muscle and heart	Use glucose	Oxidise fatty acids and ketone bodies
Brain	Glucose only	Glucose, then ketone bodies in prolonged fasting
Blood lipids	Chylomicrons and VLDL (TAG) high	Free fatty acids on albumin and ketone bodies high

PART C: CHOLESTEROL AND LIPID PROFILE

8. Biological Significance of Cholesterol

Cholesterol is a 27-carbon steroid alcohol with the **cyclopentanoperhydrophenanthrene** ring, a hydroxyl group at C-3, a double bond between C-5 and C-6, and an 8-carbon side chain at C-17. It is found only in **animal tissues** (not in plants). The body contains about **140 g**; most is in cell membranes, brain and nervous tissue, adrenal glands and liver. About **1 g/day** is made in the body (mainly liver, also intestine, adrenal cortex, testis and skin) and about **0.3 g/day** comes from the diet (egg yolk, meat, organ meats, butter).

Biological functions

Function	Details
Membrane structure	Regulates **membrane fluidity** and permeability; part of lipid rafts
Bile acids	Converted in the liver to **cholic acid and chenodeoxycholic acid** (primary bile acids) for fat digestion. This is the **main route of cholesterol removal** (about 0.5 g/day)
Steroid hormones	Precursor of **cortisol, aldosterone, sex hormones** (testosterone, oestrogen, progesterone)
Vitamin D	7-Dehydrocholesterol in the skin is converted by UV light to cholecalciferol (vitamin D_3)
Lipoproteins	Carried in lipoproteins as free cholesterol and cholesteryl esters
Myelin and nerve tissue	Essential for the myelin sheath and brain function

Biosynthesis of cholesterol

All 27 carbons come from **acetyl-CoA**. Synthesis occurs in the **cytosol and endoplasmic reticulum**, needs ATP and **NADPH**, and has four stages.

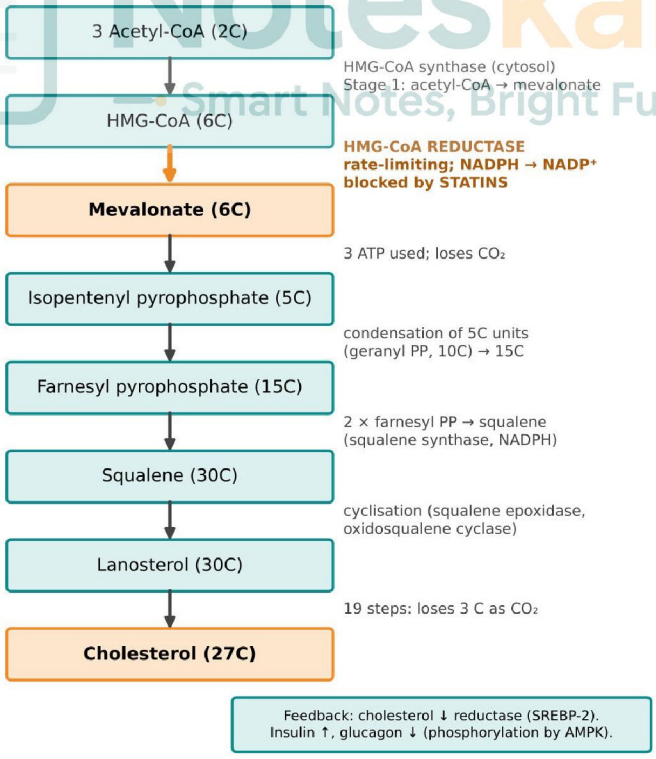

Figure 5: Biosynthesis of cholesterol and the site of statin action

- **Stage 1: formation of mevalonate.** Three acetyl-CoA make HMG-CoA (thiolase and cytosolic HMG-CoA synthase). **HMG-CoA reductase** (in the ER, uses 2 NADPH) reduces HMG-CoA to **mevalonate**. This is the **rate-limiting, committed step**.
- **Stage 2: isoprenoid units.** Mevalonate is phosphorylated (3 ATP) and decarboxylated to **isopentenyl pyrophosphate (5C)**.

- **Stage 3: squalene.** Six isoprenoid units condense to **squalene (30C)** through geranyl and farnesyl pyrophosphate (squalene synthase).
- **Stage 4: cyclisation.** Squalene is converted to **lanosterol** and then, by about 19 reactions that remove 3 carbons as CO_2, to **cholesterol (27C)**.

Side products: the isoprenoid intermediates also give coenzyme Q (ubiquinone), dolichol, and prenylated proteins. **Statins lower CoQ_{10},** which may contribute to statin muscle pain.

Regulation of cholesterol synthesis

Factor	Effect on HMG-CoA reductase
Cholesterol (end-product)	**Feedback inhibition:** high cholesterol blocks activation of **SREBP-2** (sterol regulatory element binding protein) so fewer reductase molecules are made; also speeds up enzyme degradation
Insulin and thyroid hormone	Increase activity (dephosphorylation, more gene expression)
Glucagon, cortisol	Decrease activity (phosphorylation by AMPK inactivates it)
Statins (atorvastatin, rosuvastatin, simvastatin)	Competitive inhibitors of HMG-CoA reductase; they lower liver cholesterol, so liver cells make **more LDL receptors** and remove more LDL from blood
Fasting	Reduces synthesis

Fate of cholesterol

- **Bile acid synthesis: 7α-hydroxylase** (rate-limiting, inhibited by bile acids) makes cholic and chenodeoxycholic acids, which are **conjugated with glycine or taurine** to give bile salts. About 95% are reabsorbed in the ileum and return to the liver (**enterohepatic circulation**). **Bile acid sequestrants** (cholestyramine) interrupt this and lower cholesterol.
- **Excretion** as neutral sterols (coprostanol and cholestanol) in the faeces.
- **Esterification:** ACAT in cells and LCAT in plasma make cholesteryl esters for storage and transport.
- Conversion to steroid hormones and vitamin D.

Bile acids and bile salts

Feature	Details
Primary bile acids	**Cholic acid** (3 hydroxyl groups) and **chenodeoxycholic acid** (2), made in the liver from cholesterol
Secondary bile acids	**Deoxycholic acid** and **lithocholic acid**, formed by gut bacteria by 7α-dehydroxylation
Conjugation	With **glycine** (glycocholate) or **taurine** (taurocholate); this makes them more water-soluble and stronger detergents (bile salts)
Functions	Emulsify fats, activate pancreatic lipase, form micelles for absorption of fats and fat-soluble vitamins, and excrete cholesterol
Enterohepatic circulation	About 95% reabsorbed in the terminal ileum and returned to the liver; the bile acid pool of about 3 g recycles 6–10 times a day
Clinical	Ileal disease or resection causes bile acid loss, steatorrhoea and gallstones; cholestyramine binds bile acids

GALLSTONES

Cholesterol is insoluble. When bile has too much cholesterol relative to bile salts and phospholipids, cholesterol crystallises, forming **cholesterol gallstones** (the commonest type). Risk factors are obesity, female sex, age, rapid weight loss and pregnancy. **Chenodeoxycholic acid and ursodeoxycholic acid** can dissolve small stones.

9. Lipid Profile and its Clinical Significance

The **lipid profile** is a group of blood tests that estimates the risk of **cardiovascular disease** and monitors treatment of dyslipidaemia. The sample is taken after **9–12 hours of fasting** (water is allowed). Total cholesterol and HDL can be measured non-fasting, but triglycerides and the calculated LDL need a fasting sample.

Components and reference values (adult, mg/dL)

Test	Desirable / normal	Borderline	High / abnormal
Total cholesterol	Below 200	200–239	240 or more
LDL cholesterol	Below 100 (optimal)	130–159 (borderline high); 100–129 (near optimal)	160–189 high; 190 or more very high
HDL cholesterol	60 or more (protective)	—	**Below 40 (men), below 50 (women)** = low, a risk factor
Triglycerides	Below 150	150–199	200–499 high; 500 or more very high (pancreatitis risk)
VLDL cholesterol	5–40 (= TG / 5)	—	Above 40
Non-HDL cholesterol (TC – HDL)	Below 130	130–159	160 or more

FRIEDEWALD EQUATION

LDL-C = Total cholesterol – HDL-C – (Triglycerides / 5) (mg/dL). It is valid only when triglycerides are **below 400 mg/dL** and the sample is fasting; above this, LDL is measured directly.

Other useful measurements

Parameter	Significance
TC / HDL ratio	Below 5 is desirable (ideal below 3.5); higher ratio means higher risk
LDL / HDL ratio	Below 3 desirable
Apo B-100 and apo A-I	Apo B reflects the number of atherogenic particles; apo A-I reflects HDL particles
Lp(a)	Above 30 mg/dL (about 50 nmol/L or more) is an independent risk factor
High-sensitivity CRP	Marker of inflammation; above 3 mg/L suggests higher risk
Appearance of serum on standing	Chylomicrons form a creamy top layer (type I, V); raised VLDL gives uniform turbidity

Worked examples of interpretation

Patient	Results (mg/dL)	Interpretation
A	TC 280, TG 120, HDL 45, LDL (Friedewald) = 280 – 45 – 24 = **211**	High LDL (type IIa pattern); suspect familial hypercholesterolemia; also check TSH (hypothyroidism)
B	TC 210, TG 340, HDL 32, LDL = 210 – 32 – 68 = **110**	High TG, low HDL (atherogenic dyslipidaemia); look for diabetes, obesity, alcohol; treat with lifestyle, fibrate or statin as needed
C	TC 190, TG 110, HDL 62, LDL = 190 – 62 – 22 = **106**	Normal profile; HDL is protective

Clinical significance and interpretation

- **Raised LDL-C** is the main treatable cause of atherosclerosis; it guides statin therapy.
- **Low HDL-C** and **high TG** are common in diabetes, obesity and metabolic syndrome (atherogenic dyslipidaemia, often with small dense LDL).
- **Very high TG** (above 500 mg/dL) risks **acute pancreatitis**.
- **Secondary causes** must be excluded before labelling a primary disorder: diabetes mellitus, hypothyroidism, nephrotic syndrome, cholestasis, alcohol, drugs.
- The lipid profile is repeated 4–12 weeks after starting lipid-lowering treatment and then yearly.

REMEMBER

Cholesterol is carried as LDL (bad), HDL (good) and VLDL; triglycerides are carried mostly in chylomicrons and VLDL. Recent guidelines focus on **LDL-C goals lower in patients at higher risk**; the target depends on the patient's risk category.

PART D: DISORDERS OF LIPID METABOLISM

10. Hyperlipidaemias and Hypercholesterolemia

Dyslipidaemia is an abnormal level of one or more plasma lipids or lipoproteins. **Hyperlipoproteinemia** (hyperlipidaemia) is an increase in lipoproteins and may be **primary (genetic)** or **secondary** to another disease or drug.

Fredrickson (WHO) classification

Type	Lipoprotein raised	Lipid raised	Defect and features
I	Chylomicrons	TG	**LPL or apo C-II deficiency.** Eruptive xanthomas, lipaemia retinalis, abdominal pain, **pancreatitis**, hepatosplenomegaly. Not atherogenic. Plasma is creamy on standing
IIa	LDL	Cholesterol	**Familial hypercholesterolemia** (LDL receptor defect). Tendon xanthomas, xanthelasma, corneal arcus, premature coronary disease
IIb	LDL + VLDL	Cholesterol + TG	Familial combined hyperlipidaemia; very common; coronary disease
III	IDL (remnants)	Cholesterol + TG	**Dysbetalipoproteinemia**: apo E2/E2 genotype; **palmar xanthomas**, tuberoeruptive xanthomas; atherosclerosis
IV	VLDL	TG	Common; obesity, diabetes, alcohol; increased risk of coronary disease and pancreatitis at very high levels
V	VLDL + chylomicrons	TG (very high)	Obesity, diabetes, alcohol; pancreatitis; eruptive xanthomas

Familial hypercholesterolemia (FH)

- Autosomal dominant disorder of **LDL receptor** (also apo B-100 or **PCSK9** gain-of-function mutations), so LDL is not cleared and **plasma LDL rises**.
- **Heterozygous** FH (about 1 in 250): LDL 190–400 mg/dL; coronary disease in the 30s–50s. **Homozygous** FH (rare): LDL above 500 mg/dL; xanthomas in childhood and heart attack in childhood or teens.
- Brown and Goldstein received the **Nobel Prize in 1985** for the LDL receptor discovery.

Secondary causes

Cause	Lipid change
Diabetes mellitus (poor control)	↑ TG (VLDL), ↓ HDL (↓ LPL activity)
Hypothyroidism	↑ LDL cholesterol (↓ LDL receptors)
Nephrotic syndrome	↑ LDL and VLDL (liver makes more lipoprotein with albumin)
Obstructive liver disease	↑ Cholesterol (lipoprotein X)
Alcohol	↑ TG, ↑ HDL
Drugs	Thiazides, β-blockers, corticosteroids, oral contraceptives, retinoids, protease inhibitors

Hypolipoproteinemias

Disorder	Defect	Features
Abetalipoproteinemia	Microsomal triglyceride transfer protein (MTP)	No chylomicrons, VLDL or LDL; fat malabsorption, acanthocytes, retinitis pigmentosa, ataxia; vitamin E deficiency
Tangier disease	ABCA1 transporter	Very low HDL; orange-yellow tonsils; cholesterol accumulates in macrophages
LCAT deficiency	Lecithin–cholesterol acyltransferase	Low HDL, corneal opacity, anaemia, renal disease

Lipid-lowering drugs and their biochemical basis

Class	Examples	Mechanism
Statins	Atorvastatin, rosuvastatin, simvastatin	Inhibit HMG-CoA reductase; lower LDL by 30–55%; side effects: myopathy, raised liver enzymes
Cholesterol absorption inhibitor	Ezetimibe	Blocks NPC1L1 transporter in the intestine
Fibrates	Fenofibrate, gemfibrozil	PPAR-α agonists; increase LPL; lower TG by 30–50%, raise HDL
Niacin (nicotinic acid)	Niacin	Inhibits hormone-sensitive lipase in adipose tissue; lowers VLDL and LDL, raises HDL; flushing
Bile acid sequestrants	Cholestyramine, colesevelam	Bind bile acids in the gut, so the liver uses more cholesterol
PCSK9 inhibitors	Evolocumab, alirocumab	Antibodies that prevent LDL receptor degradation; large LDL reduction
Omega-3 fatty acids	Icosapent ethyl, fish oil	Lower triglycerides
Bempedoic acid	Bempedoic acid	Inhibits ATP-citrate lyase (earlier step in cholesterol synthesis)

11. Lipid Storage Diseases

Lipid storage diseases (lipidoses) are inherited disorders in which a **lysosomal enzyme** needed to break down a complex lipid is missing. The undegraded lipid builds up in lysosomes of cells (brain, liver, spleen, bone marrow). Most are **autosomal recessive**; **Fabry disease is X-linked**. Many involve **sphingolipids** and are therefore also called sphingolipidoses.

Disease	Enzyme deficiency	Lipid accumulated	Key features
Gaucher disease	Glucocerebrosidase (β-glucosidase)	Glucocerebroside	Commonest lysosomal storage disease. **Hepatosplenomegaly**, anaemia, thrombocytopenia, bone pain and fractures; 'crumpled tissue paper' Gaucher cells
Niemann–Pick disease (A and B)	Sphingomyelinase	Sphingomyelin	Hepatosplenomegaly, neurodegeneration (type A), **cherry-red spot**, foam cells
Tay–Sachs disease	Hexosaminidase A	GM_2 ganglioside	Progressive neurodegeneration from 6 months, **cherry-red spot**, hyperacusis; **no hepatosplenomegaly**; common in Ashkenazi Jews; death by 2–5 years
Fabry disease (X-linked)	α-Galactosidase A	Globotriaosylceramide (ceramide trihexoside)	Burning pain in hands and feet, **angiokeratomas**, corneal opacity, kidney and heart failure
Krabbe disease	Galactocerebrosidase	Galactocerebroside	Demyelination, globoid cells, irritability, early death
Metachromatic leukodystrophy	Arylsulfatase A	Sulfatide	Demyelination, ataxia, mental deterioration
GM_1 gangliosidosis	β-Galactosidase	GM_1 ganglioside	Neurodegeneration, coarse features, hepatosplenomegaly
Farber disease	Acid ceramidase	Ceramide	Painful joints, nodules, hoarse voice
Wolman disease / CESD	Lysosomal acid lipase	Cholesteryl esters, TAG	Hepatosplenomegaly, adrenal calcification, diarrhoea; fatal in infancy (Wolman)
Niemann–Pick type C	NPC1 (cholesterol transport)	Cholesterol, glycolipids	Neurological decline, vertical gaze palsy, liver disease

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DIAGNOSIS AND TREATMENT

Diagnosis is by **enzyme assay** in leukocytes or fibroblasts and gene testing; prenatal diagnosis is possible by amniocentesis. Treatment is mainly supportive. **Enzyme replacement therapy** (imiglucerase for Gaucher disease; agalsidase for Fabry disease) and **substrate reduction therapy** (miglustat, eliglustat) are available for some. There is no effective cure for Tay–Sachs disease.

12. Atherosclerosis

Atherosclerosis is a chronic inflammatory disease of large and medium arteries in which **lipid-rich plaques (atheromas)** build up in the intima, narrowing the lumen and weakening the wall. It is the main cause of **coronary artery disease (CAD), stroke and peripheral vascular disease**, and of most deaths worldwide.

Risk factors

Non-modifiable	Modifiable
	High LDL, low HDL, high TG
Age (men over 45, women over 55)	Hypertension
Male sex (and postmenopausal women)	**Smoking**
Family history of premature CAD	Diabetes mellitus and obesity
Genetic disorders (familial hypercholesterolemia, high Lp(a))	Physical inactivity, unhealthy diet
	Hyperhomocysteinemia, raised CRP, chronic kidney disease

Pathogenesis (response-to-injury and lipid hypothesis)

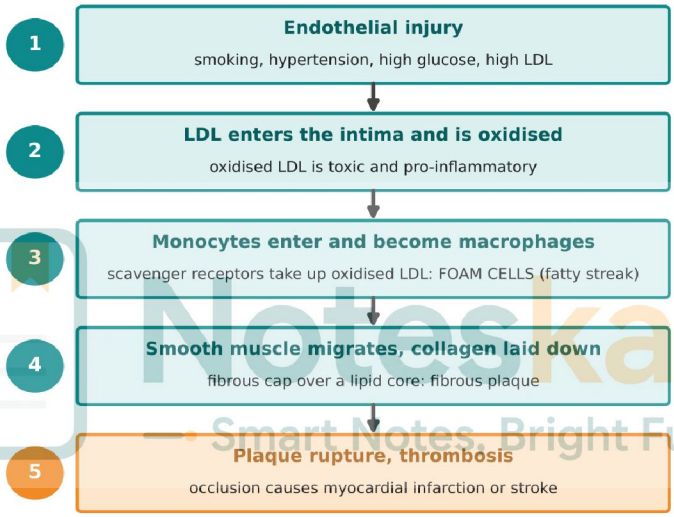

Figure 6: Steps in the development of an atherosclerotic plaque

- **Endothelial injury or dysfunction** (smoking, hypertension, hyperglycemia, high LDL, shear stress) increases permeability and adhesion molecules.
- **LDL enters the intima** and undergoes **oxidation** by free radicals, giving **oxidised LDL (oxLDL)**, which is cytotoxic and pro-inflammatory. Small dense LDL is oxidised more easily.
- **Monocytes** adhere, enter and become **macrophages**. They take up oxLDL through **scavenger receptors (CD36, SR-A)**, which are not downregulated by cholesterol, so macrophages become **foam cells**. A collection of foam cells is the **fatty streak**, the earliest lesion.
- Macrophages and platelets release growth factors and cytokines. **Smooth muscle cells migrate** from the media, divide and lay down collagen, forming a **fibrous cap** over a necrotic lipid core: the **fibrous plaque**.
- A thin cap can **rupture**, exposing the core to blood, which triggers **platelet aggregation and thrombosis**. This causes acute **myocardial infarction, unstable angina or stroke**.

Stages of the atherosclerotic lesion

Stage	Description	Clinical effect
Fatty streak	Foam cells in the intima; flat, yellow streak	None; may appear in childhood and can regress
Fibrous plaque	Lipid core with a collagen cap, smooth muscle cells	Narrows lumen; angina on effort when stenosis is above about 70%
Complicated plaque	Calcification, ulceration, haemorrhage, thrombosis	Acute coronary syndrome, stroke, embolism

Protective and harmful factors

- **HDL** removes cholesterol from foam cells (reverse cholesterol transport) and has antioxidant (paraoxonase) and anti-inflammatory effects.
- **Antioxidants** and the **Mediterranean diet** may lower risk. **Trans fats** and saturated fats raise risk.
- **Lp(a)** and **homocysteine** promote thrombosis and vascular injury.

Cardiac biomarkers in myocardial infarction

Marker	Rises after	Peaks	Returns to normal	Remarks
Troponin I / T	3–4 h	12–24 h	7–14 days	Most sensitive and specific; high-sensitivity assays are standard
CK-MB	3–6 h	12–24 h	48–72 h	Useful for detecting re-infarction
Myoglobin	1–3 h	6–9 h	24 h	Early but non-specific
LDH-1	12–24 h	48–72 h	10–14 days	Late marker, rarely used now ('flipped' LDH-1 greater than LDH-2)

Complications and prevention

Artery	Disease
Coronary	Angina, myocardial infarction, sudden death
Cerebral	Transient ischemic attack, ischemic stroke
Peripheral	Intermittent claudication, gangrene
Aorta, renal arteries	Aneurysm, renovascular hypertension

- **Lifestyle:** stop smoking, healthy diet (less saturated and trans fat, more fibre, fruit, vegetables and omega-3), exercise, weight control.
- **Drugs:** statins, antihypertensives, aspirin or other antiplatelets (when indicated), strict control of diabetes.

13. Fatty Liver Disease

Fatty liver (hepatic steatosis) is the accumulation of **triacylglycerol in hepatocytes** to above **5% of liver weight**. The liver normally takes up fatty acids, makes TAG and exports it as VLDL; fatty liver results when **input exceeds output**.

Mechanisms and causes

Mechanism	Examples
↑ Free fatty acid delivery to the liver	Obesity, insulin resistance and type 2 diabetes, fasting or starvation, high-fat diet
↑ De novo lipogenesis	High carbohydrate and fructose intake, hyperinsulinemia
↓ Fatty acid oxidation	**Alcohol** (high NADH inhibits β-oxidation), drugs (amiodarone, valproate, tetracycline), mitochondrial dysfunction
↓ VLDL synthesis and export	Deficiency of **choline**, protein malnutrition (kwashiorkor), **carbon tetrachloride**, orotic acid, abetalipoproteinemia, lack of lipotropic factors

Lipotropic factors prevent fat accumulation in the liver by helping phospholipid synthesis or VLDL export. They are **choline, methionine, betaine, inositol, vitamin B_{12}, folic acid and essential fatty acids**. Phosphatidylcholine is needed to make the VLDL shell.

Types

Alcohol-related liver disease

- Ethanol is oxidised by **alcohol dehydrogenase** to acetaldehyde, then by aldehyde dehydrogenase to acetate, generating a large amount of **NADH**.

- High NADH **inhibits β-oxidation and the TCA cycle** and favours fatty acid and TAG synthesis (and lactate and ketone formation). Acetaldehyde damages proteins and causes inflammation.
- Progression: **fatty liver → alcoholic hepatitis → fibrosis → cirrhosis**. **AST is higher than ALT (ratio above 2)** and GGT is raised.

Metabolic dysfunction-associated steatotic liver disease (MASLD)

- Formerly called non-alcoholic fatty liver disease (NAFLD), it is the commonest chronic liver disease, linked to **obesity, type 2 diabetes, dyslipidaemia and metabolic syndrome**.
- It ranges from simple steatosis to **steatohepatitis (MASH, formerly NASH)** with inflammation and ballooned hepatocytes, then **fibrosis, cirrhosis and hepatocellular carcinoma**.
- Insulin resistance increases lipolysis, so more fatty acids reach the liver, while high insulin increases lipogenesis in the liver. Lipotoxicity, oxidative stress and inflammatory cytokines cause injury.

Liver enzyme patterns

Pattern	Interpretation
ALT greater than AST, mild rise (below 4× normal)	Typical of MASLD
AST : ALT ratio above 2, with raised GGT	Alcohol-related liver disease
Marked rise (above 10× normal)	Acute hepatitis (viral, drug, ischemic), not fatty liver

Diagnosis and management

- Often silent. **ALT and AST** may be mildly raised; **ultrasound** shows a bright liver; **FibroScan** (elastography) and scores such as **FIB-4** assess fibrosis; **liver biopsy** is the gold standard.
- **Treatment:** weight loss of 7–10% of body weight, a healthy diet, regular exercise, complete avoidance of alcohol (alcoholic type), control of diabetes and lipids, and screening for fibrosis. **Resmetirom** (a thyroid hormone receptor-β agonist) was approved in the US in 2024 for MASH with fibrosis.

14. Obesity

Obesity is an excess accumulation of body fat that harms health. It develops when **energy intake exceeds energy expenditure** over a long period; the excess is stored as TAG in adipose tissue.

Assessment

Measure	Category
BMI = weight (kg) / height² (m²), WHO	Underweight below 18.5; normal 18.5–24.9; overweight 25–29.9; **obese 30 or more** (class I 30–34.9, class II 35–39.9, class III 40 or more)
BMI for Asian Indians	Overweight 23–24.9; **obese 25 or more** (lower cut-offs because of more visceral fat at the same BMI)
Waist circumference	Central obesity, Indian consensus: **men 90 cm or more, women 80 cm or more**
Waist–hip ratio	Above 0.9 (men) and above 0.85 (women) indicates central obesity

Energy balance

- **Total energy expenditure** = basal metabolic rate (BMR, about 60–70%) + thermic effect of food (about 10%) + physical activity (20–30%).
- Energy stored as fat: 1 kg of body fat holds about **7700 kcal**, so a daily deficit of 500 kcal gives a loss of about 0.5 kg per week.
- **Metabolic syndrome:** central obesity with any two of raised triglycerides, low HDL, raised blood pressure and raised fasting glucose (see Unit II).

Causes

- **Lifestyle:** excess calories (high fat, sugar, processed food) and a sedentary life.
- **Genetic:** polygenic influence; rare single-gene forms (leptin or leptin-receptor deficiency, **MC4R mutation**, Prader–Willi syndrome).
- **Endocrine:** hypothyroidism, Cushing syndrome, polycystic ovary syndrome. **Drugs:** corticosteroids, insulin, sulphonylureas, antipsychotics, antidepressants and antiepileptics.

Biochemical basis: regulation of appetite and fat as an endocrine organ

Signal	Source	Action
Leptin	Adipocytes (ob gene)	Level rises with fat mass; acts on the **hypothalamus** to reduce appetite and raise energy use. In common obesity there is **leptin resistance**
Adiponectin	Adipocytes	Improves insulin sensitivity and fat oxidation; **low in obesity**
Resistin, TNF-α, IL-6	Adipose tissue and macrophages	Promote **insulin resistance** and inflammation
Ghrelin	Stomach	Hunger hormone; rises before meals
Insulin, CCK, PYY, GLP-1	Pancreas, gut	Satiety signals
NPY/AgRP and POMC/CART neurons	Hypothalamic arcuate nucleus	NPY/AgRP **increase** appetite; POMC (α-MSH acting on MC4R) **decreases** appetite

White adipose tissue stores energy and secretes adipokines; **brown adipose tissue** burns fat to make heat through **thermogenin (UCP1)**, an uncoupler of oxidative phosphorylation. **Visceral (central) fat** is more harmful than subcutaneous fat because it releases free fatty acids directly to the liver and is more inflammatory.

Complications

System	Complications
Metabolic	Insulin resistance, **type 2 diabetes**, dyslipidaemia, **metabolic syndrome**, gout
Cardiovascular	Hypertension, atherosclerosis and coronary disease, stroke, heart failure
Liver and gallbladder	**Fatty liver (MASLD)**, cholesterol gallstones
Other	Sleep apnoea, osteoarthritis, certain cancers (breast, colon, endometrium), infertility, depression

Management

- **Lifestyle:** calorie-controlled diet, at least 150 minutes of exercise per week, behaviour therapy; loss of even 5–10% of body weight improves metabolic health.
- **Drugs: orlistat** (inhibits pancreatic lipase), GLP-1 receptor agonists (**liraglutide, semaglutide**) and the dual GIP/GLP-1 agonist **tirzepatide**, naltrexone–bupropion. Older appetite suppressants such as sibutramine were withdrawn for cardiovascular risk.
- **Bariatric surgery** (sleeve gastrectomy, gastric bypass) for BMI of 40 or more, or 35 or more with complications; Asian guidelines accept lower cut-offs (BMI 32.5 or more, or 27.5 or more with complications).

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NOTE FOR STUDENTS

These notes are prepared for study and revision. Normal values and drug doses vary between laboratories and textbooks; always follow your prescribed textbook and the reference range of your laboratory.