

MCFA, PUFA, Prostaglandins and Compound Lipids

? Digestion of Medium-Chain Fatty Acids (MCFAs)

Medium-chain fatty acids (MCFAs) are fatty acids containing **6–12 carbon atoms**. Their digestion is **simpler**, faster, and more efficient than long-chain fatty acids (LCFAs), and this gives them distinct metabolic features.

? Characteristics of Medium-Chain Fatty Acids

- Water-soluble compared to long-chain fatty acids
- Do not require bile salts for digestion
- Do not need micelle formation
- Absorbed **directly into portal circulation**
- Used rapidly for energy, less likely to be stored as fat

Common examples include **caproic (C6), caprylic (C8), capric (C10), lauric acid (C12)**.

? Process of Digestion

? 1. In the Stomach

- Minimal digestion occurs.
- Gastric lipase can act on milk fat (important in infants) but plays a minor role in adults.

? 2. In the Small Intestine

Unlike long-chain fatty acids:

Medium-chain fatty acids do NOT require:

- Bile salt emulsification
- Pancreatic lipase activation
- Micelle formation

Why?

Their smaller size makes them **naturally water-soluble**, allowing them to diffuse without complex processing.

? 3. Absorption into Enterocytes

- MCFAs cross the intestinal epithelial membrane **directly by simple diffusion**.
 - Unlike LCFAs, they are **not re-esterified into triglycerides** inside the enterocyte.
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? 4. Transport After Absorption

- MCFAs bind to **albumin** in the portal blood.
- Directly transported to the **liver via the portal vein**.

- Do **not** require formation of chylomicrons.
- Do **not** enter lymphatic circulation.

? Metabolic Fate in Liver

Once delivered to liver:

- Rapidly undergo **β -oxidation**
- Quickly generate **ATP**
- Used during fasting, exercise, or ketogenic diets
- Rarely stored as adipose fat
- Do not require carnitine for mitochondrial entry, unlike long-chain fatty acids

This is why MCT oil is used in:

- Malabsorption syndromes
- Ketogenic diets
- Premature infants
- Patients with pancreatic insufficiency

? Clinical Significance

- Useful in **fat malabsorption** (celiac disease, chronic pancreatitis).

- Useful in **cholecystectomy** patients because they do not need bile salts.
- Pregnant and breastfeeding women sometimes use MCT oil to increase energy availability.
- In mitochondrial disorders, MCFAs offer a rapid energy source.

? Monounsaturated Fatty Acids (MUFA)

Monounsaturated fatty acids contain **one double bond** in the hydrocarbon chain.

? Common MUFAs

- **Oleic acid (18:1, ?9)** — most abundant MUFA in human diet
- **Palmitoleic acid (16:1, ?9)**
- **Gadoleic acid (20:1)**

? Sources

- Olive oil
- Groundnut oil
- Avocado
- Nuts
- Almonds
- Sesame oil

? Structure and Properties

- One **cis** double bond creates a “kink,” lowering melting point.
- Liquid at room temperature, unlike saturated fat.
- More stable than polyunsaturated fatty acids ? less prone to oxidation.

? Functions of MUFAs

- Improve **insulin sensitivity**
- Lower **LDL cholesterol** without reducing HDL
- Provide membrane fluidity
- Serve as precursors for neutral lipids and phospholipids
- Reduce oxidative stress and inflammation
- Preferred cooking oils due to high oxidative stability

? Clinical Importance

- Diets rich in MUFAs (e.g., Mediterranean diet) reduce risk of:
 - Cardiovascular disease

- Atherosclerosis
- Metabolic syndrome
- Type 2 diabetes
- Oleic acid improves endothelial function and reduces systemic inflammation.

? β -Oxidation of Unsaturated Fatty Acids

Unsaturated fatty acids undergo β -oxidation **with additional steps**, because double bonds disrupt the regular β -oxidation spiral.

β -Oxidation normally requires a **trans- β^2 -enoyl CoA** intermediate, but natural double bonds are **cis** and may be at **odd or even positions**.

So, auxiliary enzymes are needed.

? Case 1: Oxidation of Monounsaturated Fatty Acids

Example: Oleic acid (18:1, β^9 , **cis**)

After several rounds of β -oxidation, the double bond eventually appears at position 3 (β^3 -cis).

? Problem

β -oxidation machinery cannot handle **cis- β^3** double bond.

? Solution: Enoyl-CoA Isomerase

The enzyme **Enoyl-CoA isomerase** converts:

cis- β^3 -enoyl CoA $\rightarrow$ trans- β^2 -enoyl CoA

This intermediate enters the normal β -oxidation cycle.

? Energy Yield

Monounsaturated fatty acids produce **slightly less ATP** than saturated fatty acids of the same length because one FADH₂-producing step is skipped (double bond bypasses the first dehydrogenation step).

? Case 2: Oxidation of Polyunsaturated Fatty Acids (PUFA)

(A preview for the next heading)

PUFAs require:

- **Enoyl-CoA isomerase**
- **2,4-Dienoyl-CoA reductase**
to handle conjugated double bonds.

I will expand fully when we reach PUFA.

? Combined Flow (?-Oxidation of Unsaturated Fatty Acids)

Unsaturated FA ? ?-oxidation begins normally ? Encounter cis double bond ? If cis-?³ ? Enoyl-CoA Isomerase ? trans-?² ? ?-oxidation continues ? (For PUFA) Conjugated double bond ? 2,4-Dienoyl-CoA reductase ? Enoyl-CoA Isomerase ? Normal ?-oxidation

? Clinical Significance

- Deficiency of Enoyl-CoA Isomerase leads to accumulation of unsaturated fatty acyl intermediates and impaired lipid oxidation.
- Disorders of PUFA oxidation can contribute to:

- Exercise intolerance
- Hypoketotic hypoglycemia
- Mitochondrial β -oxidation defects
- Fatty acid oxidation disorders require high-carbohydrate diets and avoidance of fasting.

? Polyunsaturated Fatty Acids (PUFA)

Polyunsaturated fatty acids contain two or more double bonds in their hydrocarbon chain.

These double bonds are almost always in the *cis* configuration, producing a kinked, flexible structure essential for membrane function.

? Common PUFAs

Omega-6 (n-6) family

- Linoleic acid (18:2, $\Delta^9,12$) — *Essential*
- Arachidonic acid (20:4, $\Delta^5,8,11,14$) — precursor of prostaglandins

Omega-3 (n-3) family

- α -Linolenic acid (18:3, $\Delta^9,12,15$) — *Essential*
- EPA (20:5)

- DHA (22:6)

Humans cannot synthesize linoleic and α -linolenic acids; hence they are essential.

? Functions of PUFAs

- Maintain membrane fluidity (especially neuronal membranes)
- Essential for brain and retinal development (DHA)
- Precursors for eicosanoids:
 - Prostaglandins
 - Thromboxanes
 - Leukotrienes
- Regulate inflammatory responses
- Decrease triglycerides
- Improve cardiovascular health
- Omega-3 reduces platelet aggregation

? Health Benefits

Omega-3

- Anti-inflammatory

- Anti-thrombotic
- Improves endothelial function
- Reduces risk of coronary artery disease

Omega-6

- Required for growth, skin integrity
- Excess omega-6 without omega-3 ? pro-inflammatory

Balanced omega-6 : omega-3 ratio (ideal ? 4:1) is important.

? Sources of PUFAs

Omega-6

- Sunflower oil
- Corn oil
- Soybean oil
- Nuts and seeds

Omega-3

- Fish oil (EPA, DHA)
- Flaxseed
- Chia seeds

- Walnuts
- Mustard oil

? Deficiency Features

- Scaly dermatitis
- Poor wound healing
- Reduced immunity
- Growth retardation
- Neurological defects in infants (DHA deficiency)

? Metabolism of PUFAs (Overview)

Essential fatty acids ? elongated & desaturated in the ER to produce long-chain PUFAs like:

- Arachidonic acid
- EPA
- DHA

These then serve as substrates for eicosanoid synthesis.

? Desaturation of Fatty Acids

Desaturation means introducing double bonds into a saturated fatty acid.

This occurs in the smooth endoplasmic reticulum.

? Key Features

- Requires O_2 , NADH, Cytochrome b5, and desaturase enzyme.
- Each reaction introduces one double bond.
- Humans have Δ^9 , Δ^6 , Δ^5 , and Δ^4 desaturases.

? Why Some Fatty Acids Are Essential?

Humans cannot introduce double bonds beyond carbon 9 from the carboxyl end.

So we cannot synthesize:

- Linoleic acid ($\Delta^9,12$)
- γ -Linolenic acid ($\Delta^9,12,15$)

These must be obtained from diet ? essential fatty acids.

? Desaturation Reaction (Simplified)

Saturated FA + O_2 + NADH ? Unsaturated FA + H_2O + NAD $^+$

Cytochrome b5 and Cytochrome-b5 reductase are required.

? Sequence of Desaturation + Elongation

Example: Synthesis of arachidonic acid (20:4)

Linoleic acid (18:2)

? (?6 desaturase)

Gamma-linolenic acid (18:3)

? (elongase)

Dihomo-gamma-linolenic acid (20:3)

? (?5 desaturase)

Arachidonic acid (20:4)

? Clinical Points

- ?6 desaturase activity declines in diabetes, aging, alcoholism ? low PUFA levels
- DHA deficiency affects cognitive development in infants
- PUFA deficiency leads to scaly dermatitis
- Excess omega-6 increases inflammatory mediators (prostaglandins, leukotrienes)

? Ultra-Short Revision

- PUFA = ?2 double bonds; essential ones: linoleic (?-6), ?-linolenic (?-3).
- Required for brain, retina, membrane fluidity.

- Omega-3 = anti-inflammatory, omega-6 = pro-inflammatory in excess.
- Humans lack $\Delta 12$ & $\Delta 15$ desaturases, making essential FA obligatory in diet.
- Desaturation occurs in ER, requires O_2 , NADH, cytochrome b5.

? Polyunsaturated Fatty Acids (PUFA)

Polyunsaturated fatty acids contain **two or more cis double bonds**. These bends caused by cis bonds make membranes flexible and biologically active.

? Essential PUFAs

Humans **cannot introduce double bonds beyond carbon 9**, so two fatty acids are essential:

- Linoleic acid (18:2, Δ -6)
- Δ -Linolenic acid (18:3, Δ -3)

All other long-chain PUFAs are made from these.

? Important PUFA Families

Omega-6 Series

- Linoleic acid $\rightarrow$ Arachidonic acid (20:4)
 - Arachidonic acid is the **main substrate** for prostaglandins, thromboxanes, and leukotrienes.
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Omega-3 Series

- **α-Linolenic acid** → EPA (20:5) → DHA (22:6)
 - DHA is crucial for **brain, retina, and fetal development**.
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→ Functions of PUFAs

- Maintain **membrane fluidity**, especially neurons
 - Essential for **brain growth and retinal function**
 - Form **eicosanoids** (prostaglandins, thromboxanes, leukotrienes)
 - Reduce **plasma triglycerides**
 - Omega-3 reduces inflammation and platelet aggregation
 - Required for **skin barrier and wound healing**
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→ Sources

- **Omega-6:** Sunflower oil, safflower oil, soybean, nuts
 - **Omega-3:** Fish oil, flaxseed, chia, walnuts, mustard oil
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? Deficiency

- Scaly dermatitis
 - Poor wound healing
 - Growth failure
 - Infertility
 - Reduced immunity
 - Poor visual development (DHA deficiency)
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? Clinical Notes

- Excess omega-6 without omega-3 ? pro-inflammatory state
 - Balanced ratio (~4:1) is important
 - PUFA deficiency resembles **essential fatty acid deficiency syndrome**
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? Desaturation of Fatty Acids

Desaturation is the process of **introducing double bonds** into saturated fatty acids. This occurs in the **smooth endoplasmic reticulum (SER)**.

? Desaturase Enzymes in Humans

Humans have the following desaturases:

- ?9 desaturase
- ?6 desaturase
- ?5 desaturase
- ?4 desaturase

Each enzyme introduces **one double bond**.

? Why Essential Fatty Acids Are Essential

Humans **lack ?12 and ?15 desaturases**, so we cannot make:

- Linoleic acid (?9,12)
- ?-Linolenic acid (?9,12,15)

These must be taken from diet ? **Essential Fatty Acids**.

? Requirements for Desaturation

Desaturation requires:

- **FAD ? FADH?**

- NADH → NAD?
- Cytochrome b?
- Cytochrome b? reductase
- Oxygen (O?)

One oxygen atom becomes part of water, the other inserted as the new double bond.

? Desaturation Reaction (Simplified)

Saturated acyl-CoA + NADH + O?

→ ? Desaturase

Unsaturated acyl-CoA + NAD? + H?O

? Example: Making Arachidonic Acid

From dietary linoleic acid:

Linoleic acid (18:2)

→ ? Δ⁶ desaturase

γ-Linolenic acid (18:3)

→ ? Elongase

Dihomo-γ-linolenic acid (20:3)

→ ? Δ⁵ desaturase

? Clinical Importance

- ?6 desaturase decreases with **age, diabetes, alcohol**
 - Leads to reduced EPA/DHA production
 - Infants, especially premature, need **dietary DHA**
 - Disorders of desaturation contribute to inflammatory and neurological problems
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? High-Yield Summary

- PUFA = ?2 cis double bonds; essential ones: linoleic (?-6), ?-linolenic (?-3)
- Omega-3 ? anti-inflammatory; Omega-6 ? pro-inflammatory if excess
- Humans **cannot desaturate beyond C9**, hence essential fatty acids
- Desaturation occurs in **SER**, requires NADH, Cytochrome b?, and O?

? Essential Fatty Acids (EFA)

Essential fatty acids are fatty acids that **cannot be synthesized by humans** because we lack ?12 and ?15 desaturase enzymes.

Therefore, double bonds cannot be introduced

? The Essential Fatty Acids

1. Linoleic Acid (18:2, ω -6)

- Precursor of **arachidonic acid (20:4)**
- Required for **prostaglandin synthesis**
- Maintains **skin integrity**

2. ω -Linolenic Acid (18:3, ω -3)

- Precursor of **EPA (20:5)** and **DHA (22:6)**
 - Important for **brain, retina, neural development**
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? Functions of EFAs

- Maintain **membrane fluidity**
 - Essential for **brain and retinal development** (DHA)
 - Required for **skin barrier**, preventing eczema
 - Precursors for **eicosanoids**
 - Reduce serum triglycerides (especially omega-3)
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- Influence inflammatory and immune responses

? Deficiency Features

- Dry, scaly dermatitis
- Poor wound healing
- Growth retardation
- Infertility
- Reduced immunity
- Neurological defects (DHA deficiency in infants)

? Eicosanoids

Eicosanoids are **short-lived, highly potent, hormone-like molecules** derived from **20-carbon PUFAs**—mainly **arachidonic acid (20:4)**.

They include:

- **Prostaglandins (PGs)**
- **Thromboxanes (TXs)**
- **Leukotrienes (LTs)**
- **Lipoxins**

They act as **local mediators** (autocrine/paracrine).

? Sources of Eicosanoids

- **Arachidonic acid (omega-6)**
 - **EPA (omega-3)** ? produces “less inflammatory” eicosanoids
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? Pathways

1. Cyclooxygenase (COX) Pathway ? Prostaglandins + Thromboxanes

Enzymes: **COX-1** and **COX-2**

2. Lipoxygenase (LOX) Pathway ? Leukotrienes + Lipoxins

Enzyme: **5-Lipoxygenase**

? Prostaglandins

Prostaglandins (PGs) are produced from the **COX pathway**.

? Precursor

Arachidonic acid ? **PGG?** ? **PGH?** ? various PGs (PGE?, PGF??, PGI?, etc.)

? Types & Functions

1. PGE? – “Inflammatory Prostaglandin”

- Fever (acts on hypothalamus)
- Pain sensitivity
- Vasodilation
- Uterine contractions
- Protects gastric mucosa

2. PGI? (Prostacyclin) – “Platelet Protector”

- Formed by **vascular endothelium**
- Vasodilation
- Inhibits platelet aggregation
- Opposes TXA?

3. TXA? (Thromboxane A?) – “Platelet Activator”

- Formed by **platelets**
- Vasoconstriction
- Promotes platelet aggregation
- Opposes PGI?

4. PGF??

- Uterine contraction
- Used clinically to induce labor or abortion
- Vasoconstriction in some tissues

? Clinical Points (Prostaglandins)

- **NSAIDs (aspirin, ibuprofen)** inhibit COX ?? PG synthesis
- **Low-dose aspirin** inhibits platelet TXA? ? anti-thrombotic
- COX-2 inhibitors (celecoxib) spare gastric mucosa (COX-1 preserved)

? Leukotrienes

Leukotrienes are formed via the **5-lipoxygenase (LOX) pathway**.

? Precursor

Arachidonic acid ? 5-HPETE ? **LTA?**

LTA? gives rise to two pathways:

1. **LTB?**
2. **LTC? ? LTD? ? LTE?**

? Functions

1. LTB? – Neutrophil Activator

- Chemotaxis
- Neutrophil adhesion
- Superoxide production
- Strong inflammatory mediator

2. LTC?, LTD?, LTE? – Bronchoconstrictors (Slow Reacting Substances of Anaphylaxis)

- Potent **bronchoconstriction**
- Increase vascular permeability
- Mucus hypersecretion
- Major role in **asthma and allergic reactions**

? Clinical Relevance (Leukotrienes)

- **Montelukast / Zafirlukast** ? Block **LTD? receptor** ? used in asthma
 - **Zileuton** ? inhibits **5-LOX** ? decreases all leukotrienes
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? Ultra-Short Revision Points

- EFAs = **linoleic (18:2)** & **α-linolenic (18:3)**.
- Arachidonic acid is main precursor of **eicosanoids**.
- Eicosanoids act **locally** (autocrine/paracrine).
- COX pathway → **PGs + TXA₂**.
- LOX pathway → **Leukotrienes**.
- **TXA₂** = platelet aggregation; **PGI₂** = anti-aggregation.
- **LTB₄** = neutrophil chemotaxis; **LTC₄/LTD₄** = bronchoconstriction.
- NSAIDs block **COX**; montelukast blocks **LTD₄ receptor**.

? Very Long Chain Fatty Acids (VLCFA)

Very long chain fatty acids are fatty acids with **more than 22 carbon atoms**.

Examples include:

- **Lignoceric acid (24:0)**
- **Cerotic acid (26:0)**

They have crucial roles in **nervous system structure** and **membrane integrity**.

? Where Are VLCFAs Found?

- Myelin sheath of neurons

- Retina
- Testes
- Skin barrier lipids
- Sphingolipids (e.g., cerebroside & sphingomyelin)

? Metabolism of VLCFAs

? Synthesis

- Occurs in **endoplasmic reticulum** via elongation of long-chain fatty acids
- Uses **elongase enzymes** and **malonyl-CoA** for adding 2-carbon units

? Oxidation

- VLCFAs **cannot enter mitochondria**
- They undergo **?-oxidation in peroxisomes**, not mitochondria

Process:

1. VLCFA transported into peroxisome
2. Shortened through peroxisomal ?-oxidation
3. Once shortened to C16–C20 ? shifted to mitochondria for further oxidation

? Clinical Points (VLCFA Disorders)

? 1. X-Linked Adrenoleukodystrophy (X-ALD)

- Defect in **peroxisomal membrane transporter (ABCD1 gene)**
- VLCFAs accumulate in:
 - Brain white matter
 - Adrenal cortex
- Leads to:
 - Progressive neurological deterioration
 - Adrenal insufficiency

? 2. Zellweger Syndrome

- Peroxisome biogenesis disorder
- VLCFA accumulate because peroxisomes cannot function
- Severe hypotonia, seizures, craniofacial abnormalities

? 3. Refsum Disease

- Disorder of **α-oxidation** (phytanic acid metabolism)
- Not VLCFA directly, but associated with similar peroxisomal pathways

? Why VLCFAs Require Peroxisomes?

- Their chains are too long to be handled by mitochondrial carnitine shuttle
- Peroxisomes start the process, then mitochondria finish the oxidation

? Key Points to Remember

- VLCFA = **>22 carbons**
- Oxidized in **peroxisomes**, not mitochondria
- Defects ? severe neurological diseases due to myelin damage
- Abnormal accumulation is a hallmark of X-ALD and Zellweger syndrome

? Synthesis of Compound Lipids

Compound lipids are lipids that contain **fatty acids + alcohol + an additional group** (phosphate, carbohydrate, etc.).

They include:

- **Phospholipids**
- **Glycolipids** (cerebrosides, gangliosides)
- **Sphingolipids**
- **Plasmalogens**

? 1. Synthesis of Phospholipids

Phospholipids contain:

- **Glycerol backbone**
 - **Two fatty acids**
 - **Phosphate group + head group** (choline, ethanolamine, serine, inositol)
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? Synthesis Pathway (Glycerophospholipids)

? Step 1: Formation of Phosphatidic Acid

Glycerol-3-phosphate + 2 Fatty acyl-CoA

? Acyltransferases

Phosphatidic acid (PA)

? Step 2: Conversion to CDP-Activated Intermediates

Two possible routes:

Route A:

PA + CTP ? CDP-diacylglycerol

Used to form:

- Phosphatidylinositol

- Cardiolipin
- Phosphatidylglycerol

Route B:

Choline/Ethanolamine + ATP → CDP-choline / CDP-ethanolamine

Combined with DAG to form:

- **Phosphatidylcholine (lecithin)**
- **Phosphatidylethanolamine**

? 2. Synthesis of Sphingolipids

Sphingolipids use **sphingosine** instead of glycerol.

? Step 1: Formation of Sphingosine

Serine + Palmitoyl-CoA

?

Sphinganine → Sphingosine

? Step 2: Formation of Ceramide

Sphingosine + Fatty acyl-CoA → Ceramide

? Step 3: Formation of Complex Sphingolipids

- Ceramide + Phosphocholine ? Sphingomyelin
- Ceramide + Sugar ? Cerebroside
- Ceramide + Oligosaccharide ? Ganglioside

? 3. Synthesis of Glycolipids

? Cerebrosides

Ceramide + UDP-sugar ? Cerebroside

- Glucocerebroside
- Galactocerebroside

? Gangliosides

Ceramide + multiple sugars + sialic acid (NANA) ? Ganglioside

Highly important in **neuronal membranes**.

? 4. Synthesis of Plasmalogens

These contain a **vinyl-ether linkage** at position 1 of glycerol.

Precursor: **Dihydroxyacetone phosphate (DHAP)**

Plasmalogens act as:

- Antioxidants

- Membrane components in nerve & muscle

? Clinical Relevance of Compound Lipid Synthesis

- **Gaucher disease:** glucocerebrosidase deficiency
- **Tay–Sachs disease:** hexosaminidase A deficiency ? GM? accumulation
- **Niemann–Pick:** sphingomyelinase deficiency
- **Multiple sclerosis:** loss of myelin sphingolipids

? Ultra-High-Yield Summary

- VLCFA (>22C) ? oxidized **only in peroxisomes**.
- Peroxisome disorders ? accumulation and neurological disease.
- Compound lipids include phospholipids, glycolipids, sphingolipids, plasmalogens.
- Ceramide is the **central precursor** for sphingolipids.
- Phospholipids synthesized via **CDP-choline**, **CDP-ethanolamine**, and **CDP-DAG** pathways.

? Phosphatidylcholine (Lecithin)

Phosphatidylcholine (PC) is the **most abundant phospholipid** in cell membranes and plasma lipoproteins.

It plays major roles in membrane structure,

? Structure

- Glycerol backbone
- Two fatty acids (usually saturated at C1, unsaturated at C2)
- Phosphate
- **Choline** head group

? Synthesis of Phosphatidylcholine

1. CDP–Choline Pathway (Kennedy Pathway) — Major in most tissues

Choline + ATP → Phosphocholine

Phosphocholine + CTP → CDP–choline

CDP–choline + DAG → Phosphatidylcholine

2. PEMT Pathway (Liver only)

Phosphatidylethanolamine → methylated three times using **SAM** → PC

This pathway is important when dietary choline is low.

? Functions of Phosphatidylcholine

1. Structural role

- Major phospholipid of **cell membranes**
- Maintains membrane fluidity

2. Lung Surfactant

- Dipalmitoyl phosphatidylcholine (DPPC) is the **key surfactant component**
- Prevents alveolar collapse
- Low levels ? neonatal respiratory distress syndrome (RDS)

3. Lipoprotein Metabolism

- Essential for **VLDL formation and secretion**
- Prevents fatty liver (choline deficiency ? hepatic steatosis)

4. Bile Component

- Solubilizes cholesterol in bile
- Prevents gallstone formation

? Clinical Notes

- Choline deficiency ? fatty liver
- Premature infants have low DPPC ? high risk of RDS
- Lecithin:Sphingomyelin ratio in amniotic fluid predicts fetal lung maturity
(L/S ratio **> 2** = mature lungs)

? Sphingomyelin

Sphingomyelin is the **major sphingophospholipid**, abundant in **myelin sheath**.

? Structure

- **Sphingosine** backbone
- Fatty acid (amide linkage) ? **Ceramide**
- **Phosphocholine** head group

Sphingomyelin = Ceramide + Phosphocholine

? Synthesis of Sphingomyelin

Serine + Palmitoyl-CoA ? Sphinganine

Sphinganine + Fatty acyl-CoA ? Ceramide

Ceramide + CDP–choline ? Sphingomyelin

Occurs in the **Golgi apparatus**.

? Functions of Sphingomyelin

- Major component of **myelin** (nerve insulation)

- Important in **signal transduction**
- Component of lipid rafts
- Regulates cell–cell interactions
- Maintains plasma membrane stability

? Clinical Note: Niemann–Pick Disease (Type A & B)

Deficiency: Sphingomyelinase

Accumulation: Sphingomyelin

Features:

- Hepatosplenomegaly
- Cherry-red spot on macula
- Neurodegeneration (Type A)
- “Foam cells” in bone marrow

? Lipid Storage Diseases (Sphingolipidoses)

Lipid storage diseases result from defects in lysosomal enzymes ? accumulation of specific sphingolipids.

? 1. Gaucher Disease

Deficiency: β -Glucocerebrosidase

Accumulation: Glucocerebroside

Features:

- Hepatosplenomegaly
- Bone crises
- Pancytopenia
- “**Gaucher cells**” — crumpled tissue paper macrophages
- Most common lysosomal storage disorder

? 2. Niemann–Pick Disease (Type A/B)

Deficiency: Sphingomyelinase

Accumulation: Sphingomyelin

Features:

- Cherry-red spot
- Neurodegeneration
- Hepatosplenomegaly
- Foam cells

? 3. Tay–Sachs Disease

Deficiency: Hexosaminidase A

Accumulation: GM2 ganglioside

Features:

- Cherry-red spot
- No hepatosplenomegaly
- Severe neurodegeneration
- Startle reflex exaggerated

? 4. Krabbe Disease

Deficiency: Galactocerebrosidase

Accumulation: Galactocerebroside, psychosine

Features:

- Peripheral neuropathy
- Optic atrophy
- Developmental delay
- **Globoid cells**

? 5. Metachromatic Leukodystrophy

Deficiency: Arylsulfatase A

Accumulation: Sulfatides

Features:

- Ataxia
- Demyelination

- Peripheral neuropathy
- Cognitive decline
- “Metachromasia” on staining

? 6. Fabry Disease

Inheritance: X-linked

Deficiency: α -Galactosidase A

Accumulation: Ceramide trihexoside

Features:

- Angiokeratomas
- Peripheral neuropathy
- Hypohidrosis
- Renal and cardiac involvement

? 7. Farber Disease

Deficiency: Ceramidase

Accumulation: Ceramide

Features:

- Hoarseness
- Joint deformity
- Subcutaneous nodules

? 8. Pompe Disease (*not a sphingolipidosis, but a glycogen storage disorder often grouped in lysosomal diseases*)

Deficiency: Acid maltase

Effect: Glycogen accumulation in lysosomes

Features: Cardiomyopathy, hypotonia

? Ultra-High-Yield Summary

- Phosphatidylcholine = major membrane lipid + surfactant + VLDL assembly
- Sphingomyelin = major myelin phospholipid; defect ? Niemann–Pick
- Lipid storage diseases ? enzyme defect ? specific lipid accumulation
 - Gaucher ? glucocerebroside
 - Tay–Sachs ? GM?
 - Krabbe ? galactocerebroside
 - Metachromatic ? sulfatides
 - Fabry ? ceramide trihexoside
 - Niemann–Pick ? sphingomyelin

? FAQs — Phosphatidylcholine, Sphingomyelin & Lipid Storage Diseases

1. What is phosphatidylcholine?

It is the **most abundant phospholipid** in cell membranes and lipoproteins; also known as **lecithin**.

2. What is the key component of lung surfactant?

Dipalmitoyl phosphatidylcholine (DPPC).

3. What is the L/S ratio and why is it important?

Lecithin : Sphingomyelin ratio in amniotic fluid.

L/S > 2 indicates fetal lung maturity.

4. What happens in phosphatidylcholine deficiency?

Liver cannot export VLDL ? **fatty liver** (hepatic steatosis).

5. How is phosphatidylcholine synthesized in most tissues?

Via the **CDP-choline (Kennedy) pathway**.

6. Which tissue can synthesize PC without dietary choline?

Liver, via methylation of phosphatidylethanolamine (PEMT pathway).

7. What is sphingomyelin?

A phospholipid containing **ceramide + phosphocholine**, abundant in **myelin sheaths**.

8. What is the key precursor for both sphingomyelin and glycolipids?

Ceramide.

9. Which enzyme deficiency causes Niemann–Pick disease?

Sphingomyelinase.

10. What accumulates in Niemann–Pick disease?

Sphingomyelin.

11. What are the typical findings in Niemann–Pick disease?

Hepatosplenomegaly, neurodegeneration, cherry-red spot, foam cells.

12. What accumulates in Gaucher disease?

Glucocerebroside.

13. What is the enzyme deficient in Gaucher disease?

β-Glucocerebrosidase.

14. What is the histological hallmark of Gaucher disease?

Gaucher cells — macrophages with “crumpled tissue paper” cytoplasm.

15. Which storage disease presents with a cherry-red spot but NO hepatosplenomegaly?

Tay–Sachs disease.

16. What accumulates in Tay–Sachs disease?

GM? ganglioside.

17. What enzyme is deficient in Tay–Sachs?

Hexosaminidase A.

18. What accumulates in Krabbe disease?

Galactocerebroside and psychosine.

19. What is the deficient enzyme in Krabbe disease?

Galactocerebrosidase.

20. What accumulates in Metachromatic leukodystrophy?

Sulfatides.

21. Which enzyme is deficient in Metachromatic leukodystrophy?

Arylsulfatase A.

22. What accumulates in Fabry disease?

Ceramide trihexoside.

23. What is the inheritance pattern of Fabry disease?

X-linked recessive.

24. What is the enzyme deficient in Fabry disease?

α-Galactosidase A.

25. What is the typical presentation of Fabry disease?

Angiokeratomas, peripheral neuropathy, hypohidrosis, renal/cardiac involvement.

26. What accumulates in Farber disease?

Ceramide.

27. What enzyme is deficient in Farber disease?

Ceramidase.

28. Which storage diseases show a cherry-red spot?

- Tay–Sachs
 - Niemann–Pick
-

29. Which disease presents with “globoid cells”?

Krabbe disease.

30. What is the most common lysosomal storage disorder?

Gaucher disease.

? MCQs — Whole Chapter (Complete Coverage)

1. Medium-chain fatty acids are absorbed directly into:

- A. Lymphatics
 - B. Portal circulation
 - C. Chylomicrons
-

D. HDL

Answer: B

Explanation: MCFAs bypass micelles/chylomicrons ? directly enter portal blood bound to albumin.

2. Digestion of MCFAs requires which of the following?

- A. Bile salts
- B. Pancreatic lipase
- C. Micelles
- D. **None of the above**

Answer: D

Explanation: MCFAs are water-soluble; no bile, no lipase required.

3. The first step required for oxidation of monounsaturated fatty acids is:

- A. Thiolytic
- B. Carnitine shuttle activation
- C. **Isomerization of cis- Δ^3 to trans- Δ^2**
- D. Reduction of 2,4-dienoyl CoA

Answer: C

4. The additional enzyme required for PUFA oxidation is:

- A. Enoyl CoA hydratase
- B. Thiolase
- C. **2,4-Dienoyl CoA reductase**
- D. Acyl CoA dehydrogenase

Answer: C

5. Essential fatty acids are essential because humans lack:

- A. Δ^9 desaturase
- B. Δ^{12} and Δ^{15} desaturases
- C. Δ^6 desaturase
- D. Δ^5 desaturase

Answer: B

6. The precursor of arachidonic acid is:

- A. Oleic acid
- B. Palmitoleic acid
- C. **Linoleic acid**
- D. γ -Linolenic acid

Answer: C

7. DHA and EPA belong to which fatty acid family?

- A. Omega-6
- B. Trans fats
- C. Saturated fats
- D. **Omega-3**

Answer: D

8. Prostaglandins are synthesized from:

- A. Stearic acid
- B. Palmitic acid

C. **Arachidonic acid**

D. DHA

Answer: C

9. The enzyme inhibited by NSAIDs (like aspirin) is:

A. Lipoxygenase

B. Phospholipase A?

C. **Cyclooxygenase (COX)**

D. Peroxidase

Answer: C

10. LTB? is known for which action?

A. Bronchodilation

B. Platelet aggregation

C. **Neutrophil chemotaxis**

D. Vasoconstriction

Answer: C

11. The “Slow Reacting Substances of Anaphylaxis” (SRS-A) include:

A. PGI?

B. TXA?

C. LTB?

D. **LTC?, LTD?, LTE?**

Answer: D

12. Very long-chain fatty acids (VLCFA) are oxidized in:

- A. Cytosol
- B. Mitochondria
- C. **Peroxisomes**
- D. Ribosomes

Answer: C

13. Defect in peroxisomal VLCFA transporter causes:

- A. Tay–Sachs disease
- B. Niemann–Pick B
- C. Gaucher disease
- D. **X-linked adrenoleukodystrophy**

Answer: D

14. Plasmalogens differ from phospholipids because they contain:

- A. Trans fatty acids
- B. No phosphate
- C. **A vinyl-ether linkage**
- D. Sphingosine

Answer: C

15. The central precursor for sphingolipid synthesis is:

- A. Phosphatidic acid
- B. Glycerol-3-phosphate
- C. **Ceramide**

D. Cholesterol

Answer: C

16. The major surfactant phospholipid in lungs is:

- A. Phosphatidylinositol
- B. Sphingomyelin
- C. **Dipalmitoyl phosphatidylcholine (DPPC)**
- D. Phosphatidylserine

Answer: C

17. Low L/S ratio in amniotic fluid indicates:

- A. Kidney immaturity
- B. Excess bile salts
- C. **Risk of neonatal respiratory distress syndrome**
- D. Hypercholesterolemia

Answer: C

18. Sphingomyelin accumulates in which disease?

- A. Tay–Sachs
- B. Metachromatic leukodystrophy
- C. **Niemann–Pick (A & B)**
- D. Gaucher

Answer: C

19. “Crumpled tissue paper” macrophages are seen in:

- A. Niemann–Pick
- B. **Gaucher disease**
- C. Krabbe
- D. Fabry

Answer: B

20. Cherry-red macula WITHOUT hepatosplenomegaly is seen in:

- A. Niemann–Pick
- B. Krabbe
- C. **Tay–Sachs disease**
- D. Metachromatic leukodystrophy

Answer: C

21. Accumulation of GM? ganglioside suggests:

- A. Gaucher
- B. Metachromatic leukodystrophy
- C. **Tay–Sachs**
- D. Krabbe

Answer: C

22. Deficiency of arylsulfatase A causes:

- A. Niemann–Pick
- B. Tay–Sachs
- C. Krabbe

D. Metachromatic leukodystrophy

Answer: D

23. X-linked sphingolipidosis is:

- A. Tay–Sachs
- B. Gaucher
- C. **Fabry disease**
- D. Krabbe

Answer: C

24. Ceramide trihexoside accumulation occurs in:

- A. Krabbe
- B. Tay–Sachs
- C. Gaucher
- D. **Fabry disease**

Answer: D

25. The enzyme that releases arachidonic acid from membrane phospholipids is:

- A. COX-2
- B. 5-LOX
- C. **Phospholipase A?**
- D. Acyl CoA oxidase

Answer: C

26. Which fatty acid is needed for normal vision and retinal function?

- A. Linoleic
- B. Oleic
- C. **DHA**
- D. Stearic

Answer: C

27. PC synthesis via PEMT pathway needs:

- A. NADPH
- B. Serine
- C. **S-adenosyl methionine (SAM)**
- D. Carnitine

Answer: C

28. Which lipid is MOST important in myelin membranes?

- A. Cholesterol
- B. Lecithin
- C. **Sphingomyelin**
- D. Plasmalogen

Answer: C

29. Peroxisomal α -oxidation is required for metabolism of:

- A. DHA
- B. **Phytanic acid**
- C. Linoleic acid

D. Palmitate

Answer: B

(Defect ? Refsum disease)

30. Arachidonic acid belongs to which series?

- A. Omega-3
- B. **Omega-6**
- C. Omega-9
- D. Trans fatty acids

Answer: B

? Clinical Case–Based Questions (Whole Chapter)

1. A child with chronic diarrhea improves on MCT oil

A 4-year-old child with severe pancreatic insufficiency has steatorrhea. When started on **medium-chain triglyceride formula**, stools improve immediately.

Most likely explanation:

MCFA **do not need bile salts or pancreatic lipase** and are absorbed **directly into portal blood**, bypassing chylomicrons.

2. Premature baby with respiratory distress

A preterm infant (32 weeks) develops rapid breathing, chest retractions, and cyanosis shortly after birth.

Amniotic fluid L/S ratio was **1.2**.

Diagnosis:

Neonatal **Respiratory Distress Syndrome** (RDS)

Mechanism:

Low **dipalmitoyl phosphatidylcholine (DPPC)** ? reduced surfactant ? alveolar collapse.

3. Severe asthma attack triggered by aspirin

A young woman with asthma develops bronchospasm after taking aspirin.

Mechanism:

Aspirin inhibits **COX**, diverting arachidonic acid to **LOX pathway** ? excess **LTC?**, **LTD?**, **LTE?** ? bronchoconstriction.

4. Patient with chronic eczema improves with omega-3 supplementation

A 29-year-old woman with atopic dermatitis improves on fish oil supplements.

Reason:

Omega-3 PUFA (EPA, DHA) produce **less inflammatory eicosanoids** and improve skin barrier.

5. Patient with recurrent fever & joint pain; high LTB? levels

A 35-year-old male with chronic inflammatory pain has elevated LTB?.

Mechanism:

LTB? acts as a **strong neutrophil chemoattractant** ? sustained inflammation.

6. Child with poor vision and learning difficulty

A 3-year-old child has delayed brain development and poor visual acuity. Diet lacks fish, nuts, and seeds.

Most likely deficiency:

DHA (omega-3 PUFA)

Why?

DHA is critical for **retinal development** and **neuronal myelination**.

7. A teenager with progressive neurological decline & adrenal failure

He develops behavioral changes, vision loss, and hyperpigmented skin. VLCFA elevated in plasma.

Diagnosis:

X-linked adrenoleukodystrophy (X-ALD)

Mechanism:

Defective **peroxisomal transporter (ABCD1)** ? VLCFA accumulation in brain white matter and adrenal cortex.

8. Newborn with craniofacial anomalies, hypotonia, seizures

VLCFA markedly elevated; peroxisomes absent in biopsy.

Diagnosis:

Zellweger syndrome

9. A man with hepatosplenomegaly & bone pain

Bone marrow shows macrophages filled with "crumpled tissue paper".

Diagnosis:

Gaucher disease

Defect:

?-Glucocerebrosidase deficiency ? glucocerebroside accumulation.

10. Cherry-red spot + NO hepatosplenomegaly

A baby presents with neurodegeneration and exaggerated startle reflex. No liver enlargement.

Diagnosis:

Tay–Sachs disease

Defect:

Hexosaminidase A deficiency ? GM? accumulation.

11. Cherry-red spot + hepatosplenomegaly

A baby shows neuroregression, cherry-red macula, and hepatosplenomegaly.

Diagnosis:

Niemann–Pick disease (Type A)

Defect:

Sphingomyelinase deficiency ? sphingomyelin buildup.

12. Teenager with ataxia and demyelination

Peripheral neuropathy, MRI shows loss of white matter. Sulfatides accumulate.

Diagnosis:

Metachromatic leukodystrophy

Defect:

Arylsulfatase A deficiency.

13. Child with globoid cells on biopsy

A boy has seizures, optic atrophy, and developmental regression.

Diagnosis:

Krabbe disease

Defect:

Galactocerebrosidase deficiency.

14. Male with angiokeratomas & burning neuropathy

A 15-year-old boy has painful extremities, reduced sweating, and reddish skin lesions on trunk.

Diagnosis:

Fabry disease (X-linked)

Defect:

?-Galactosidase A deficiency ? ceramide trihexoside accumulation.

15. Infant with hoarse cry + joint deformity

Ceramide accumulation is seen in biopsy.

Diagnosis:

Farber disease

Defect:

Ceramidase deficiency.

16. Fatty liver in a chronic alcoholic

A man with chronic alcoholism develops fatty liver despite normal diet.

Mechanism:

Alcohol ? **NADH**, inhibiting β -oxidation ? excess TAG formation in liver.

17. Asthma well-controlled with Montelukast

A young woman responds dramatically to Montelukast.

Mechanism:

Montelukast blocks **LTD₄ receptor**, preventing leukotriene-mediated bronchoconstriction.

18. Patient with abnormal bleeding & platelet dysfunction

Low prostacyclin and thromboxane levels.

Most likely enzyme inhibited:

Cyclooxygenase (COX) by aspirin ? ? TXA? & PGI? synthesis.

19. Adult with fat malabsorption; long-chain fats worsen symptoms

Patient improves when diet includes medium-chain triglycerides.

Reason:

MCFA bypass:

- bile
 - micelles
 - chylomicrons
 - ? directly absorbed to portal vein.
-

20. Child with scaly dermatitis and growth delay

Diet low in vegetable oils, fish, nuts.

Deficiency:

Essential fatty acids (linoleic & ?-linolenic)

Mechanism:

Defective skin barrier & eicosanoid production.

? Viva Voce — Whole Chapter

1. What is the special feature of medium-chain fatty acids?

They **do not require bile salts or micelles** and are absorbed **directly into portal circulation**.

2. Why do MCFAs not need chylomicrons?

They are **water-soluble** and travel bound to **albumin**.

3. What is the key difference between MUFA and PUFA?

MUFA have **one double bond**, PUFA have **two or more**.

4. Name the two essential fatty acids.

Linoleic acid (ω-6) and **α-linolenic acid (ω-3)**.

5. Why are these fatty acids essential?

Humans lack **ω12 and ω15 desaturase** enzymes.

6. What is the precursor of arachidonic acid?

Linoleic acid (ω-6).

7. What are the major omega-3 derivatives?

EPA and DHA.

8. Which fatty acid is crucial for retinal and brain development?

DHA.

9. What enzyme releases arachidonic acid from membranes?

Phospholipase A?.

10. Which pathways convert arachidonic acid to eicosanoids?

COX pathway and LOX pathway.

11. What does COX produce?

Prostaglandins and Thromboxanes.

12. What does 5-Lipoxygenase (LOX) produce?

Leukotrienes (LTB?, LTC?, LTD?, LTE?).

13. What is the action of LTB??

Strong neutrophil chemotaxis.

14. Which leukotrienes cause bronchoconstriction?

LTC?, LTD?, LTE?.

15. What drug blocks leukotriene receptors?

Montelukast.

16. What enzyme is inhibited by aspirin?

COX-1 and COX-2.

17. What is PGI?? Where is it produced?

Prostacyclin, produced by **endothelium**.

It **inhibits platelet aggregation**.

18. What is TXA?? Where is it produced?

Thromboxane A?, produced by **platelets**.

It **promotes aggregation**.

19. What are very long-chain fatty acids (VLCFA)?

Fatty acids with **>22 carbons**.

20. Where are VLCFAs oxidized?

In **peroxisomes**.

21. Which disease involves VLCFA accumulation?

X-linked adrenoleukodystrophy (ALD).

22. Name the major lung surfactant component.

Dipalmitoyl phosphatidylcholine (DPPC).

23. What is the L/S ratio?

Lecithin : Sphingomyelin ratio.
>2 indicates fetal lung maturity.

24. What happens in phosphatidylcholine deficiency?

Impaired VLDL secretion ? **fatty liver**.

25. What is the precursor of sphingomyelin?

Ceramide.

26. Which enzyme converts ceramide + phosphocholine ? sphingomyelin?

Sphingomyelin synthase.

27. Name the storage disease with sphingomyelin accumulation.

Niemann–Pick disease (sphingomyelinase deficiency).

28. What is the classic sign of Niemann–Pick disease?

Cherry-red spot + hepatosplenomegaly.

29. What lipid accumulates in Gaucher disease?

Glucocerebroside.

30. What enzyme is deficient in Gaucher disease?

β-Glucocerebrosidase.

31. What is the histological hallmark of Gaucher cells?

Macrophages with **crumpled tissue-paper cytoplasm**.

32. What disease has GM2 ganglioside accumulation?

Tay–Sachs disease.

33. What is the enzyme deficiency in Tay–Sachs?

Hexosaminidase A.

34. What is unique about Tay–Sachs compared to Niemann–Pick?

Cherry-red spot **without hepatosplenomegaly.**

35. Which disease has “globoid cells”?

Krabbe disease (galactocerebrosidase deficiency).

36. What accumulates in Metachromatic leukodystrophy?

Sulfatides.

37. What enzyme is deficient in Metachromatic leukodystrophy?

Arylsulfatase A.

38. Which storage disease is X-linked?

Fabry disease.

39. What accumulates in Fabry disease?

Ceramide trihexoside.

40. What enzyme is deficient in Fabry disease?

α -Galactosidase A.

41. What disease involves ceramide accumulation?

Farber disease (ceramidase deficiency).

42. Why are PUFA important for skin health?

They maintain **skin barrier** and reduce inflammation.

43. Which fatty acid metabolism step is bypassed in MCFA oxidation?

Carnitine shuttle (not required).

44. What enzyme rearranges cis- Δ^3 double bond during unsaturated FA oxidation?

Enoyl-CoA isomerase.

45. Why do PUFA yield slightly less ATP?

Because **FADH₂-generating steps are skipped** due to double bonds.