MEDICAL EDUCATION RESOURCE

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.

? 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 **?-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.

? ?-Oxidation of Unsaturated Fatty Acids

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

?-Oxidation normally requires a **trans-?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, ?9, **cis**)

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

? Problem

?-oxidation machinery cannot handle **cis-?³** double bond.

? Solution: Enoyl-CoA Isomerase

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

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cis-?³-enoyl CoA ? trans-?²-enoyl CoA
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This intermediate enters the normal ?-oxidation cycle.

? Energy Yield

Monounsaturated fatty acids produce **slightly less ATP** than saturated fatty acids of the same length because one FADH?-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)

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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 ?-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, ?9,12) — *Essential***
- **Arachidonic acid (20:4, ?5,8,11,14) — precursor of prostaglandins**

Omega-3 (n-3) family

- **?-Linolenic acid (18:3, ?9,12,15) — *Essential***
- **EPA (20:5)**

- **DHA (22:6)**

Humans cannot synthesize linoleic and ?-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?, NADH, Cytochrome b5, and desaturase enzyme.**
- **Each reaction introduces one double bond.**
- **Humans have ?9, ?6, ?5, and ?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 (?9,12)**
- **?-Linolenic acid (?9,12,15)**

These must be obtained from diet ? essential fatty acids.

? Desaturation Reaction (Simplified)

Saturated FA + O? + NADH ? Unsaturated FA + H?O + 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 ?12 & ?15 desaturases, making essential FA obligatory in diet.**
- **Desaturation occurs in ER, requires O?, 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, ?-6)**
- **?-Linolenic acid (18:3, ?-3)**

All other long-chain PUFAs are made from these.

? Important PUFA Families

Omega-6 Series

- **Linoleic acid ? Arachidonic acid (20:4)**
- Arachidonic acid is the **main substrate** for prostaglandins, thromboxanes, and leukotrienes.

Omega-3 Series

- **?-Linolenic acid ? EPA (20:5) ? DHA (22:6)**
- DHA is crucial for **brain, retina, and fetal development**.

? 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**

? 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)

? 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**

? 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)

? ?6 desaturase

?-Linolenic acid (18:3)

? Elongase

Dihomo-?-linolenic acid (20:3)

? ?5 desaturase

Arachidonic acid (20:4)

? 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 introduc

? The Essential Fatty Acids

1. Linoleic Acid (18:2, ?-6)

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

2. ?-Linolenic Acid (18:3, ?-3)

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

? 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)

- 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

? Ultra-Short Revision Points

- EFAs = **linoleic (?-6)** & **?-linolenic (?-3)**.
- Arachidonic acid ? main precursor of **eicosanoids**.
- Eicosanoids act **locally** (autocrine/paracrine).
- COX pathway ? **PGs + TXA?**.
- LOX pathway ? **Leukotrienes**.
- **TXA? = platelet aggregation**; **PGI? = anti-aggregation**.
- **LTB? = neutrophil chemotaxis**; **LTC?/LTD? = bronchoconstriction**.
- NSAIDs block **COX**; montelukast blocks **LTD? 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., cerebrosides & 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

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? 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

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? 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 **?-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)

> **? 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.

Notes downloaded from **Medmentoredu** | Page 33

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: ?-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: GM? 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: ?-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**.

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2. What is the key component of lung surfactant?

Dipalmitoyl phosphatidylcholine (DPPC).

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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.

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4. What happens in phosphatidylcholine deficiency?

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

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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?

?-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?

?-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. Thiolysis
B. Carnitine shuttle activation
C. **Isomerization of cis-?³ to trans-?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. ?9 desaturase
B. **?12 and ?15 desaturases**
C. ?6 desaturase
D. ?5 desaturase

Answer: B

---

6. The precursor of arachidonic acid is:

A. Oleic acid
B. Palmitoleic acid
C. **Linoleic acid**
D. ?-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 ?-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 ?-oxidation ? excess TAG formation in liver.

---

17. Asthma well-controlled with Montelukast

A young woman responds dramatically to Montelukast.

Mechanism:

Montelukast blocks **LTD? 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 (?-6) and **?-linolenic acid (?-3)**.

---

5. Why are these fatty acids essential?

Humans lack **?12 and ?15 desaturase** enzymes.

---

6. What is the precursor of arachidonic acid?

Linoleic acid (?-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?

?-Glucocerebrosidase.

---

31. What is the histological hallmark of Gaucher cells?

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

---

32. What disease has GM? 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?

?-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-?³ double bond during unsaturated FA oxidation?

Enoyl-CoA isomerase.

---

45. Why do PUFA yield slightly less ATP?

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