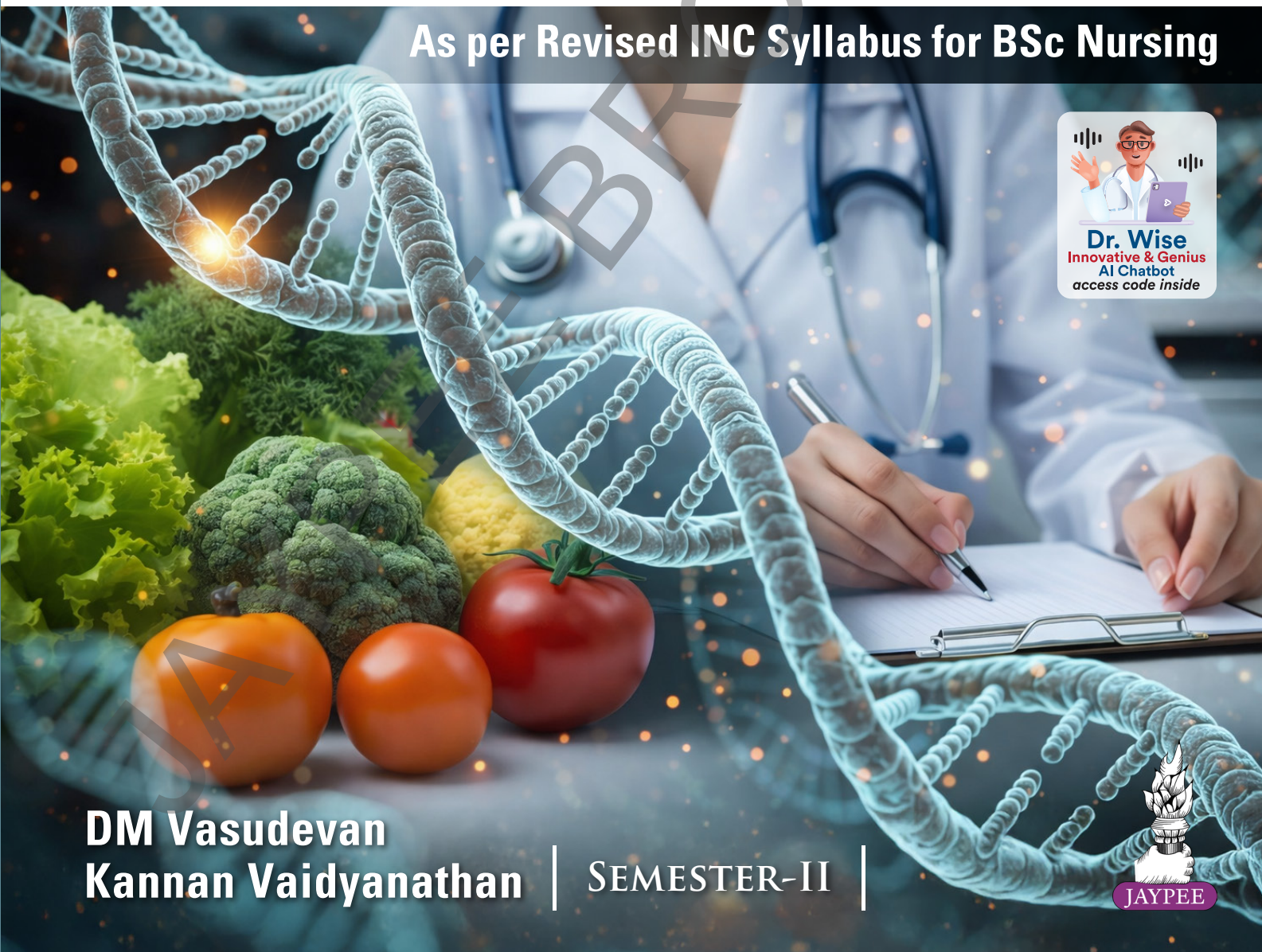
Applied Biochemistry, Nutrition & Dietetics

for Nursing Students

As per Revised INC Syllabus for BSc Nursing



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SEMESTER-II

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CHAPTER

3

Lipids

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Learning Objectives

The learner will be able to:

- Classify lipids into major classes
- Differentiate fatty acids based on their carbon number
- Explain the structure of different types of triglycerides
- Mention the structural features of phospholipids and glycolipids
- Briefly describe the important properties and functions of different types of lipids
- Indicate the metabolic origin and role of prostaglandins
- Highlight the functional importance of amphipathic lipids
- Describe the digestion and absorption of lipids
- Outline beta-oxidation of fatty acids
- Enumerate steps of de novo synthesis of fatty acids
- Briefly indicate synthesis of triglycerides
- Explain the metabolism of adipose tissue
- Trace the pathway of ketogenesis, ketolysis
- List consequences of ketosis
- Outline the importance of cholesterol in the body
- List plasma lipids and lipoproteins
- Explain the metabolic role of:
  - Chylomicrons
  - Very low density lipoproteins
  - Low density lipoproteins
  - High density lipoproteins
- Describe the genesis of atherosclerosis and coronary artery disease:
  - Enumerate the risk factors of coronary artery disease
  - Enumerate the biomarkers for coronary artery disease
  - Explain the principles of prevention of atherosclerosis

INTRODUCTION

Lipids may be defined as compounds that are relatively insoluble in water, but freely soluble in nonpolar organic solvents like benzene, chloroform, ether, hot alcohol, acetone, etc. Functions of lipids are shown in **Box 3.1** and the clinical relevance of lipids is shown in **Box 3.2**.

CLASSIFICATION OF LIPIDS

1. **Simple lipids:** They are esters of fatty acids with glycerol or other higher alcohols **(Box 3.3)**.
2. **Compound lipids:** They are fatty acids esterified with alcohol; but in addition, they contain other groups. Depending on these prosthetic groups, they are subclassified as: (a) Phospholipids, containing phosphoric acid and, (b) Non-phosphorylated lipids **(Box 3.3)**.
3. **Derived lipids:** They are compounds which are derived from lipids or precursors of lipids, e.g., fatty acids and steroids.

BOX 3.1 Functions of lipids.

- Storage form of energy (triglycerides)
- Structural components of biomembranes (phospholipids and cholesterol)
- Metabolic regulators (steroid hormones and prostaglandins)
- Act as surfactants, detergents and emulsifying agents (amphipathic lipids)
- Act as electric insulators in neurons
- Give shape and contour to the body
- Protect internal organs by providing a cushioning effect (pads of fat)
- Help in the absorption of fat soluble vitamins (A, D, E and K)
- Improve taste and palatability of food

Eicosanoids—They are 20C compounds (Greek, eikosi = twenty), derived from arachidonic acid.

- **Lipids complexed to other compounds.**

BOX 3.2 Clinical relevance of lipids.

- Excessive fat deposits cause obesity. Truncal obesity is a risk factor for heart attack.
- Abnormality in lipoprotein metabolism leads to atherosclerosis and cardiovascular diseases.
- In diabetes mellitus, the metabolisms of fatty acids and lipoproteins are deranged, leading to dyslipidemia and ketosis.

BOX 3.3 Classification of lipids.

I. **Simple lipids:**
   a. Triacylglycerol or triglycerides or neutral fat
   b. Waxes
II. **Compound lipids:**
   A. **Phospholipids, containing phosphoric acid:**
      – Nitrogen containing glycerophosphatides:
         - Lecithin (phosphatidylcholine)
         - Cephalin (phosphatidylethanolamine)
         - Phosphatidylserine
      – Non-nitrogen glycerophosphatides:
         - Phosphatidylinositol
         - Phosphatidylglycerol
         - Diphosphatidylglycerol (cardiolipin)
      – Plasmalogens, having long chain alcohol:
         - Choline plasmalogen
         - Ethanolamine plasmalogen
      – Phosphosphingosides, with sphingosine:
         - Sphingomyelin
   B. **Non-phosphorylated lipids:**
      – Glycosphingolipids (carbohydrate):
         - Cerebrosides (ceramide monohexosides)
         - Globosides (ceramide oligosaccharides)
         - Gangliosides (ceramide + oligosaccharides + neuraminic acid)
      – Sulfolipids or sulfatides:
         - Sulfated cerebrosides
         - Sulfated globosides
         - Sulfated gangliosides
III. **Derived lipids:** Fatty acids, steroids, prostaglandins, leukotrienes
IV. **Lipids complexed to other compounds:** Proteolipids and lipoproteins

FATTY ACIDS

Fatty acids are included in the group of derived lipids. It is the most common component of lipids in the body. They are generally found in ester linkage in different classes of lipids. In the human body, free fatty acids are formed only during metabolism. Fatty acids are **aliphatic carboxylic acids** and have the general structural formula, R–COOH, where COOH (carboxylic group) represents the functional group. Depending on the R group (the hydrocarbon chain), the fatty acids may vary. **Box 3.4** shows the classification of fatty acids.

BOX 3.4 Classification of fatty acids.

1. **Depending on total number of carbon atoms:**
   - **Even chain:** They have carbon atoms 2, 4, 6 and similar series. Most of the naturally occurring lipids contain even chain fatty acids.
   - **Odd chain:** They have carbon atoms 3, 5, 7, etc. Odd numbered fatty acids are seen in microbial cell walls. They are also present in milk.
2. **Depending on length of hydrocarbon chain:**
   - **Short chain** with 2 to 5 carbon atoms
   - **Medium chain** with 6 to 12 carbon atoms
   - **Long chain** with 14 and above, usually up to 22 carbon atoms
   - **Very long chain** fatty acids (more than 22 carbon).
3. **Depending on nature of hydrocarbon chain:**
   - **Saturated** fatty acids **(Table 3.1)**
   - **Unsaturated** fatty acids which may be subclassified into Monounsaturated (monoenoic) having single double bond or Polyunsaturated (polyenoic) with 2 or more double bonds.

Table 3.1 Characteristics of common fatty acids.

Common name of acid	*No of carbon atoms*	*Chemical nature*	*Occurrence*
A. Even chain, saturated fatty acids			
Acetic acid	2	Saturated; small chain	Vinegar
Butyric acid	4	do	Butter
Lauric	12	do	Coconut oil
Myristic	14	do	Coconut oil
Palmitic	16	Saturated; long chain	Body fat
Stearic	18	do	do
B. Odd-chain fatty acids			
Propionic	3	Saturated; Odd chain	Metabolism
C. Even chain, unsaturated fatty acids			
Palmitoleic	16	Monounsaturated (ω7)	Body fat
Oleic	18	do (ω9)	do
Erucic	22	do (ω9)	Mustard oil
Linoleic	18	2 double bonds (ω6)	Vegetable oils
Linolenic	18	3 double bonds (ω3)	do
Arachidonic	20	4 double bonds (ω6)	Vegetable oils

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Classification of Fatty Acid

Saturated Fatty Acids

- The two carbon acetic acid and 4 carbon butyric acid are important metabolic intermediates.
- C16 palmitic and C18 stearic acids are most abundant in body fat.
- The carbon atoms of fatty acids are numbered as C1, C2, etc., starting from the COOH group. Or, starting from the methyl end, the carbon atoms may be numbered as omega (ω)-1, 2, 3, etc.

Unsaturated Fatty Acids

- Unsaturated fatty acids exhibit geometrical isomerism at the double bonds. Most naturally occurring unsaturated fatty acids have the **cis configuration**.
- The **polyunsaturated fatty acids** (PUFA) exist in cis configuration in naturally occurring lipids.
- **Essential Fatty Acids: Linoleic acid** (ω6, 18C, two double bonds) and **linolenic acid** (ω3, 18C, three double bonds) are the only fatty acids which cannot be synthesized in the body. They have to be provided in the food; hence they are essential fatty acids. Arachidonic acid (with 4 double bonds) can be formed in the body, if the dietary supply of linoleic acid is sufficient. The normal dietary allowance of PUFA is 2–3% of total calories. Deficiency causes acanthosis, hyperkeratosis and hypercholesterolemia. Clinical significance of PUFA is shown in **Box 3.5**.

Properties of Fatty Acids

Characteristics of common fatty acids (both saturated and unsaturated) are shown in **Table 3.1**.

BOX 3.5 Clinical significance of PUFA.

- Linoleic and linolenic acids are polyunsaturated fatty acids.
- They are called essential fatty acids because they cannot be synthesized by the body and have to be supplied in the diet.
- Unsaturated fatty acids are also designated:
  - ω3 (omega 3) family—linolenic acids
  - ω6 family—linoleic and arachidonic acids
  - ω9 family—oleic acid
- Arachidonic acid is the precursor of prostaglandins. Arachidonic acid can be synthesized in the body, if the essential fatty acids are supplied in the diet.
- The pentaenoic acid present in fish oils is of great nutritional importance (ω3 unsaturated fatty acid, e.g., EPA or eicosapentaenoic acid).
- Eicosanoids (eicosa = twenty) are derived from 20C arachidonic acid. They are polyenoic fatty acids. They are prostanoids (prostaglandins, prostacyclins, thromboxanes) and leukotrienes.

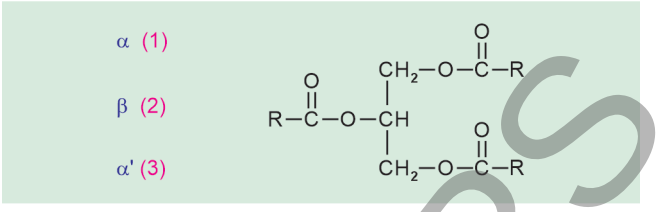


Fig. 3.1: Triacyl glycerol (TAG) (triglyceride).

Hydrogenation

Unsaturated fatty acids may be converted to the corresponding saturated fatty acids by hydrogenation of the double bond.

$$\text{Linolenic} \xrightarrow{(+)2H} \text{Linoleic} \xrightarrow{(+)2H} \text{Oleic} \xrightarrow{(+)2H} \text{Stearic}$$

Hydrogenation of oils can lead to solidification and saturation, e.g., Vanaspathi.

Salt Formation

Saturated and unsaturated fatty acids form salts with alkali.

$$CH_3\text{–}COOH + NaOH \rightarrow CH_3\text{–}COONa + H_2O$$

Sodium and potassium salts of long chain fatty acids are called **soaps**. Calcium and magnesium soaps are insoluble. Calcium soaps are used in grease.

Ester Formation

Both saturated and unsaturated fatty acids form esters with alcohols, especially with glycerol. Fatty acids can form mono-, di- or tri- esters with alcohol groups of glycerol. Triglycerides or triacylglycerols are also known as **neutral fat** **(Fig. 3.1)**.

Glycerol + fatty acid	→	Monoacylglycerol
Monoglyceride + fatty acid	→	Diacylglycerol
Diglyceride + fatty acid	→	Triglyceride or triacylglycerol

The composition of some of the common oils and fats are given in **Table 3.2**.

NEUTRAL FATS

Neutral fats are also called as triacylglycerols (TAG) or triglycerides (TG). These are esters of the trihydric alcohol, glycerol with fatty acids **(Fig. 3.1)**. The carbon atoms of glycerol are designated as α, β and α' or as 1, 2, 3 as shown in **Figure 3.1**, where R represents the side chain of fatty acids.

If all three hydroxyl groups of the glycerol are esterified to the same fatty acid, **simple** triacyl glycerol is formed. A **mixed** triglyceride is formed, when different fatty acids are esterified to the hydroxyl groups of glycerol. Naturally occurring fats and oils are mixtures of triglycerides. When a PUFA is present, it is commonly esterified to the 2nd or beta carbon atom.

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Table 3.2 Composition of oils and fats.

Name	Saturated fatty acids (%)	Mono-unsaturated fatty acids (%)	PUFA (%)
Coconut oil	86(*)	12	2
Groundnut oil	18	46	36
Gingelly oil (Til oil)	13	50	37
Palm oil	42	52	6
Cotton seed oil	26	19	55
Mustard oil (rapeseed)	34	48	18
Safflower oil (Kardi)	9	12	79
Sunflower oil	12	24	64
Butter	75	20	5
Ox (Tallow)	53	42	5
Pig (Lard)	42	46	12

(*) These saturated fatty acids are medium chain fatty acids.

Oils are liquids at 20°C; they are triglycerides which contain a higher proportion of unsaturated fatty acids or short chain triglycerides. Oils are generally of plant origin. **Fats are solids** at room temperature and contain mainly saturated long chain fatty acids. Fats are mainly of animal origin **(Table 3.2)**.

Triacylglycerides are the storage form of lipids in the **adipose tissue**. When stored as TAG, water molecules are repelled and the space requirement is minimal. Excess fat in the body leads to obesity.

Hydrolysis of Triglycerides

This occurs in the body during the digestion of dietary fat and mobilization of TAG from adipose tissue. Triglycerides in the body are hydrolyzed by enzymes, **lipases**. Triacyl glycerol is **sequentially hydrolyzed** to diacylglycerol and monoacylglycerol and finally glycerol plus 3 fatty acids. **(Fig. 3.2)**.

Saponification

When triglycerides are hydrolyzed by alkali, the process is known as saponification. The products are glycerol and soaps **(Fig. 3.3)**. The **saponification number** is defined

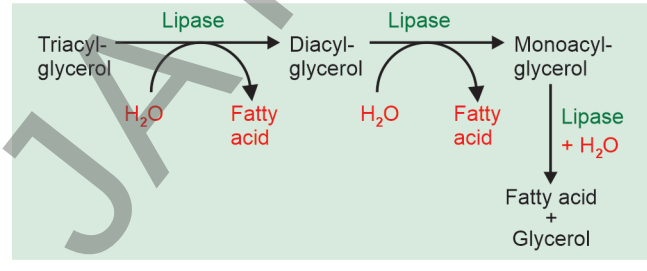


Fig. 3.2: Hydrolysis of triglycerides.

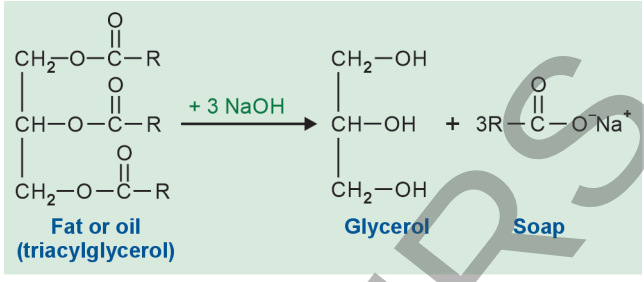


Fig. 3.3: Saponification.

as the number of milligrams of potassium hydroxide required to saponify one gram of fat. It is an indication of the molecular weight of the fat, and is inversely proportional to it. Human fat has a saponification number of 194–198, butter has 210–230 and coconut oil has 253–262.

Iodine Number

The iodine number of fat is defined as the number of grams of iodine taken up by 100 grams of fat. It is an index of the degree of unsaturation and is directly proportional to the content of unsaturated fatty acids. The higher the iodine number, the higher the degree of unsaturation, e.g., iodine number of butter is 28, and that of sunflower oil is 130.

Rancidity of Fat

Fats and oils tend to become rancid. The term rancidity refers to the appearance of an unpleasant smell and taste for fats and oils. **Hydrolytic rancidity** is due to partial hydrolysis of the triacylglycerol molecules due to traces of hydrolytic enzymes present in naturally occurring fats and oils. **Oxidative rancidity** is the result of partial oxidation of unsaturated fatty acids with resultant formation of epoxides and peroxides of small molecular weight fatty acids by peroxides and free radicals. The same process, if it occurs in vivo will affect the integrity of biomembranes, leading to cell death.

Many natural fats and oils may contain antioxidants (e.g., vitamin E), which prevent the occurrence of oxidative rancidity. PUFA are more easily oxidized; so vegetable oils with a high content of PUFA are usually preserved with the addition of antioxidants.

Repeated heating of oils would lead to the formation and polymerization of **cyclic hydrocarbons.** These will impart an unpleasant taste and color to the oil. Coconut oil having medium chain saturated fatty acids will withstand such polymerization.

PHOSPHOLIPIDS

They contain glycerol, fatty acids and in certain cases, a nitrogenous base.

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Phosphatidates

These are derivatives of phosphatidic acid which is the simplest phospholipid. **Phosphatidic acid** is made up of one glycerol to which two fatty acid residues are esterified to carbon atoms 1 and 2 **(Fig. 3.4)**. The 3rd hydroxyl group is esterified to phosphoric acid.

Phosphatidyl Choline or Lecithin

This is a nitrogen containing phospholipid. It contains the glycerol group. The alpha and beta positions are esterified with fatty acids. Usually, the fatty acid attached to the beta-carbon is a **PUFA** molecule. The phosphate group is esterified to the third carbon of glycerol, forming phosphatidic acid. The phosphate group is esterified to the quaternary nitrogen base, **Choline (Fig. 3.5)**.

Amphipathic Lipids

Phospholipids in general are amphipathic, particularly Lecithin. They have both hydrophobic and hydrophilic portion in their molecule **(Fig. 3.5)**. The biological importance of amphipathic lipid is described in **Box 3.6**. The glycerol along with the phosphoric acid and choline constitute the polar 'head' of a phospholipid molecule, whereas the hydrocarbon chains of the fatty acids represent the nonpolar 'tail' **(Fig. 3.6)**.

Micelle Formation

When phospholipids are distributed in water, their hydrophobic parts keep away from water, forming molecular aggregates called micelle **(Fig. 3.7)**. These are involved in the solubilization of lipids in aqueous media and help in the digestion and absorption of lipids.

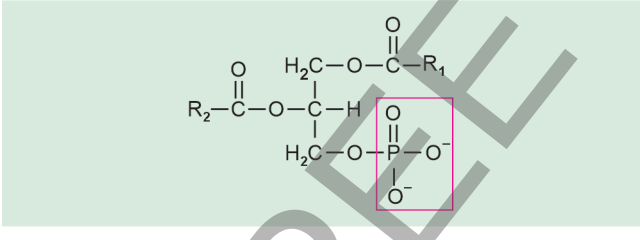


Fig. 3.4: L-phosphatidic acid.

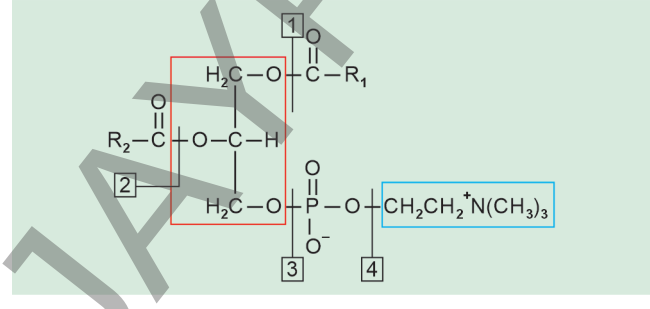


Fig. 3.5: Lecithin. R1 and R2 are fatty acids. The red rectangle depicts the glycerol group. The blue rectangle is choline which shows polar or hydrophilic property. 1, 2, 3, 4 are the sites of action of different phospholipases.

BOX 3.6 Biological Importance of amphipathic lipids.

Amphipathic lipids are those which have a polar part (hydrophilic) and a non-polar part (hydrophobic). The most important ones are:

- **Phospholipids** containing glycerol like lecithin, cephalin, phosphatidyl inositol, cardiolipin.
- **Sphingomyelins** containing sphingosine as alcohol and different types of fatty acids.
- The plasma membrane is made up of bilayers of amphipathic lipids (Chapter 1) to confer the semipermeable nature of biomembranes. Lipophilic compounds can easily pass through.
- Amphipathic lipids also function as surfactants and detergents by reducing surface tension.
- Artificial membrane bound structures called liposomes have been prepared to serve as carriers of drugs, genes, antibodies, etc., into specific target cells.

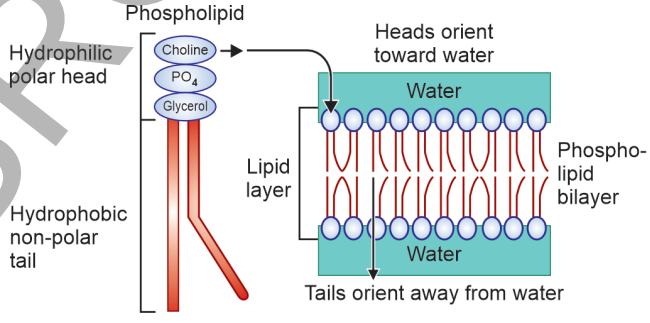


Fig. 3.6: Phospholipids form the bilayer.

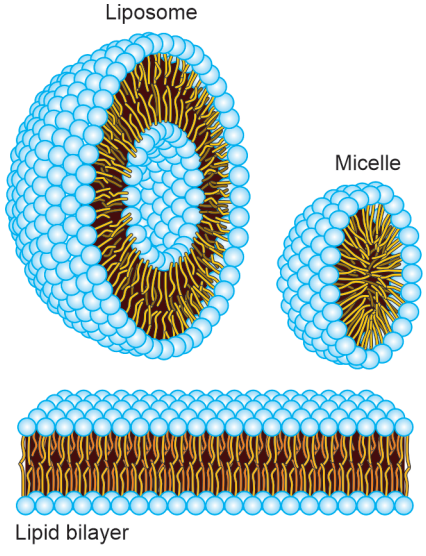


Fig. 3.7: Phospholipids form micelles and liposomes.

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Liposomes

Liposomes are spherical vesicles consisting of one or more phospholipid bilayers **(Fig. 3.7)**. A lipid bilayer will close on itself under appropriate conditions to form liposomes. They may be prepared by sonication of mixtures of phospholipids and cholesterol. The phospholipids arrange themselves to form a bilayer membrane which encloses some of the water in a phospholipid sphere. Drugs, proteins, enzymes, genes, etc. may be encapsulated by the liposomes which could act as carriers for these substances to target organs. Liposome-entrapped drugs exhibit superior pharmacological properties than those observed with conventional formulations. Liposomes have important applications in cancer chemotherapy, antimicrobial therapy, gene therapy, vaccines and diagnostic imaging. Oral iron preparations trapped in liposomes have been introduced to avoid gastric irritation (sucrosomal iron).

Lipoproteins

In these molecules, the lipid component comprises of triacylglycerol, phospholipids and cholesterol. The protein component has a high proportion of non-polar amino acid residues which can participate in the binding of lipids. They are found in membranes of mitochondria, endoplasmic reticulum and nuclei. Lipoproteins of plasma are described in detail later in this Chapter.

LIPID STORAGE DISEASES OR SPHINGOLIPIDOSES

They form a group of lysosomal storage diseases. The sphingolipids are normally catabolized by a series of bond-specific lysosomal hydrolases like alpha and beta glucosidases, galactosidase, neuraminidase, hexosaminidase and aryl sulfatase (for sulfate ester hydrolysis). The diseases result from the failure of the breakdown of a particular sphingolipid due to a deficiency of a single enzyme. The children afflicted by these diseases are severely retarded mentally and seldom survive for long. Diseases include **Niemann Pick's disease, Gaucher's disease and Tay-Sach's disease**. Mental retardation, neurological deficit and skeletal abnormalities are common presenting symptoms.

PROSTAGLANDINS

Prostaglandins (PGs) were originally isolated from prostate tissue and hence the name. But they are present in almost all tissues. They are the most potent biologically active substances; as low as one nanogram/ml of PG will cause smooth muscle contraction. The diverse physiological roles of prostaglandins confer on them the status of **local hormones**.

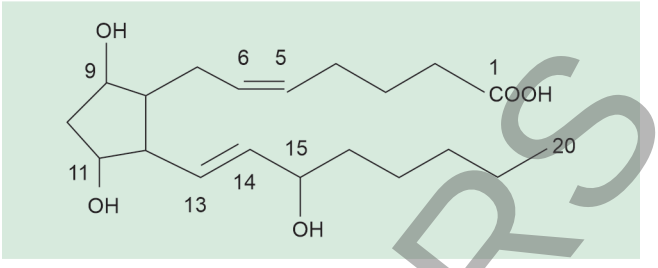


Fig. 3.8: Prostaglandin F2.

- **Chemical structure:** All prostaglandins are considered to be derived from the 20C cyclic saturated fatty acid, prostanoic acid. The five-carbon ring is saturated. All naturally occurring PGs have an alpha-oriented OH group at C15.
- **Classification of prostaglandins:** According to the attachment of different substituent groups to the ring, PGs are named with capital letters such as A, B, E and F. In the same series, depending on the number of double bonds on the side chains they are denoted by a subscript after the capital letter, e.g. PGE1, PGE2, PGE3, etc. Members of **series 2** have 2 double bonds at 13–14 (trans) and 5–6 (cis). The structure of PGF2 is shown in **Figure 3.8**.

Biosynthesis of Prostaglandins

Prostaglandins are derived from polyunsaturated fatty acids. All naturally occurring PGs belong to the 2 series. PGs are not stored as such; the precursor fatty acids are stored in the membrane as phospholipids. The arachidonic acid is released by the action of **phospholipase A2** on phospholipids. Synthesis is catalyzed by Prostaglandin synthase, containing two enzymes, **cyclo-oxygenase** and peroxidase.

Regulation of Synthesis

The **phospholipase** (PL) is activated by epinephrine. Steroids inhibit PL and prevent the release of arachidonic acid from membranes. **Cyclo-oxygenase** is activated by catecholamines and inhibited by non-steroid anti-inflammatory drugs (NSAIDs). **Aspirin** acetylates serine in the active site and irreversibly inhibits the cyclo-oxygenase Platelets cannot regenerate cyclo-oxygenase and so thromboxane is not formed in platelets. Hence there is decreased platelet aggregation. Therefore, aspirin is useful in the prevention of heart attacks.

Biological Actions

Effects on CVS: Prostacyclin or PGI2 is synthesized by the vascular endothelium. The major effect is vasodilatation. It also inhibits platelet aggregation and has a protective effect on the vessel wall against the deposition of platelets. **Thromboxane** (TXA2) is the

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main PG produced by platelets. The major effects are vasoconstriction and platelet aggregation. Prostacyclin and thromboxane are opposing in activity. Prostaglandins increase contractility and lower blood pressure. Hence it may be used in the treatment of hypertension.

- **Ovary and uterus:** PGF and PGE act on uterus and are used for medical termination of pregnancy, inducing labor and for arresting postpartum hemorrhage.
- **Respiratory tract:** PGF is a constrictor of bronchial smooth muscle; but PGE is a potent bronchodilator. PGE is used in aerosols for treating bronchospasm.
- **Effects on immunity:** PGE2 and PGD2 produce inflammation by increasing capillary permeability. Cortisol and aspirin are strong anti-inflammatory drugs, because they inhibit prostaglandin synthesis.
- **Effect on dental health:** Prostaglandins have been found to have a role in the pathogenesis of periodontal disease, tooth movement (orthodontics), dental cysts, periapical and pulpal pathologies.

DIGESTION OF LIPIDS

The major dietary lipids are triacylglycerol, cholesterol and phospholipids. The average normal Indian diet contains about 20–30 g of lipids per day.

Digestion in Stomach

Digestion in the stomach occurs with the help of lingual lipase and gastric lipase. Lingual lipase is more significant in newborn infants.

Digestion in Intestines

Emulsification is a pre-requisite for digestion of lipids. The lipids are dispersed into smaller droplets; surface tension is reduced; and the surface area of droplets is increased. The bile salts present in the bile (sodium glycocholate and sodium taurocholate) **lower surface tension.** They emulsify the fat droplets in the intestine. The emulsification increases the surface area of the particles for enhanced activity of enzymes. **Pancreatic lipase** with colipase will further hydrolyze the neutral fats. The bile (pH 7.7) entering the duodenum serves to neutralize the acid chyme from the stomach and provides a pH favorable for the action of pancreatic enzymes.

Digestion of Triglycerides

Digestion occurs with the help of pancreatic lipase, assisted by isomerase and colipase. Pancreatic lipase hydrolyzes triacylglycerol mainly to 2-monoacylglycerol (2-MAG) and free fatty acids, with smaller amounts of diacylglycerol (DAG) and 1-monoacylglycerol (1-MAG). Digestion of TAG is partial (incomplete).

ABSORPTION OF LIPIDS

Absorption of Long Chain Fatty Acids

Long chain fatty acids (chain length more than 14 carbons) are absorbed into the lymph and not directly to the blood **(Fig. 3.9)**. The absorption has the following four steps.

Mixed Micelle Formation

The products of digestion, namely 2-monoglycerides, long chain fatty acids, cholesterol, and phospholipids are incorporated into molecular aggregates to form a **mixed micelle**. The micelles are spherical particles with a hydrophilic exterior and hydrophobic interior core **(Fig. 3.7)**. Due to their detergent action, the **bile salts** help to form micellar aggregates. The micellar formation is essential for the absorption of fat soluble vitamins such as vitamins A, D and K. These micelles are absorbed in the microvillous surface of the **jejunal mucosa (Fig. 3.9)**.

Enterohepatic Circulation of Bile Salts

The bile salts are left behind which are mostly reabsorbed from the ileum and returned to the liver to be re-excreted (enterohepatic circulation). About 98% of dietary lipids are normally absorbed.

Re-esterification Inside the Mucosal Cell

Once inside the intestinal mucosal cell, the long chain fatty acids are re-esterified to form triglycerides **(Fig. 3.9)**. Two fatty acyl-CoA (activated fatty acids) react with monoacylglycerol (MAG) to form the triglyceride. The majority of molecules take up this MAG pathway.

Chylomicrons

The TAG, cholesterol ester and phospholipid molecules along with apoproteins B48, and apo-A are incorporated into chylomicrons. The chyle (milky fluid) from the

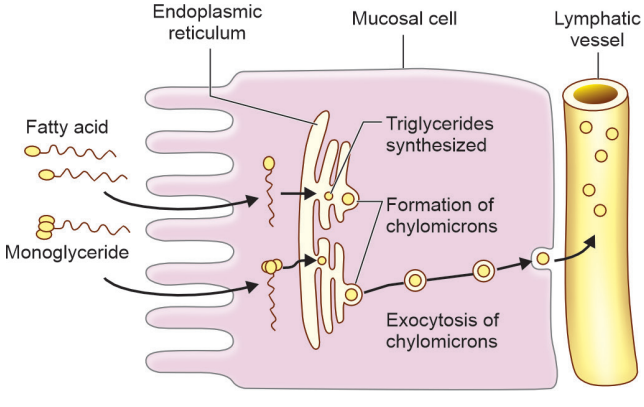


Fig. 3.9: Absorption of fatty acids. Long chain fatty acids are absorbed into the intestinal cell wall, where they are re-esterified to triglycerides, incorporated into the chylomicrons and enter into lymphatics. Bile salts are reabsorbed into the portal vein.

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intestinal mucosal cells loaded with chylomicrons are transported through the lacteals into the thoracic duct and then emptied into lymph circulation (Fig. 3.9).

Absorption of Short Chain Fatty Acids

Short chain fatty acids (SCFA) (seen in milk, butter, and ghee) and **medium chain** fatty acids (MCFA) (in coconut oil and mother's milk) do not need re-esterification. They can directly enter into blood vessels, then to the portal vein, and finally to the liver where they are immediately utilized for energy. Their absorption is rapid. They are better absorbed than long chain fatty acids.

Abnormalities in Absorption of Lipids

- **Defective digestion:** In steatorrhea, daily excretion of fat in feces is more than 6 g per day. (Greek word, "stear", means fat). It is due to chronic diseases of the pancreas. In such cases, unsplit fat is seen in feces.
- **Defective absorption:** On the other hand, if the absorption alone is defective, most of the fat in feces may be split fat, i.e. fatty acids and monoglycerides. Defective absorption may be due to **obstruction of the bile duct.** This again may be due to gall stones, tumors of the head of the pancreas, enlarged lymph glands, etc. The result is a deficiency of bile salts. In such cases, triglycerides with short chain and medium chain fatty acids (SCFA and MCFA) are digested and absorbed properly, because they do not require micellization for absorption. Since human milk fat and coconut oil are made up of MCT, they are therapeutically useful in malabsorption syndromes.
- **Chyluria:** There is an abnormal connection between the urinary tract and the lymphatic drainage system of the intestine. Urine appears milky due to lipid droplets.

Fate of Absorbed Fat

- The absorbed (exogenous) triglycerides are transported in the blood as **chylomicrons**. They are taken up by adipose tissue and the liver.
- Liver synthesizes endogenous triglycerides. These are transported as **VLDL** (very low density lipoproteins) and are deposited in adipose tissue.
- Triglycerides in adipose tissue are lysed to produce **free fatty acids**. In the blood, they are transported, complexed with albumin.
- Free fatty acids are taken up by the cells, and are then oxidized to get energy.

BETA-OXIDATION OF FATTY ACIDS

The oxidation of the hydrocarbon chain occurs by sequential cleavage of two carbon atoms; or the splitting occurs at the beta carbon atom.

Preparative Steps for Beta-oxidation

Co-enzyme A (abbreviated as CoA) is a complex molecule containing beta-mercapto ethanolamine (MEA), beta-alanine, pantoic acid and ADP. The SH group present in MEA forms a thioester bond in acyl-CoA. To emphasize the function of this SH group, the CoA is sometimes written as CoA-SH. The transport of fatty acids into mitochondria constitutes the following four preparative steps.

Fatty acids are activated to their CoA derivative. ATP is hydrolyzed to AMP and PPi. The energy from the hydrolysis of PPi drives the reaction forward. Thus, **two high energy bonds** are utilized in this reaction. The enzyme is a **thiokinase** or fatty acyl-CoA **synthetase** (step 0, Fig. 3.10).



Do you KNOW?

Acetyl and acyl groups are different

- **Acetyl-CoA** is the combination of acetate or acetic acid (2 carbon unit) with coenzyme A.
- **Acyl-CoA** means acyl group (any fatty acid, C4 to C26 in length) combined with coenzyme A.

Fatty acids are activated in the cytoplasm; but the **beta-oxidation is in mitochondria.** So transport of fatty acids through the mitochondrial membrane is essential. The long chain fatty acyl-CoA cannot pass through the inner mitochondrial membrane. Therefore a transporter, carnitine is involved in the transfer of fatty acids. With the help of carnitine and translocase the fatty acyl molecules are transferred from cytoplasm to mitochondria.

Medium chain and short chain fatty acids do not require carnitine for transport across the inner mitochondrial membrane. So medium chain and short chain fatty acids are easily oxidized.

Beta-oxidation Steps

The next 4 reactions are sequentially repeated for complete oxidation of fatty acids. After one round of four metabolic steps, one acetyl-CoA unit is split off and acyl-CoA with 2 carbon atoms less is generated. This would undergo the same series of reactions again until the fatty acid is completely oxidized. Beta-oxidation steps are shown in Figure 3.10.

- **In step 1**, the fatty acyl-CoA is dehydrogenated with the FAD accepting the hydrogen atoms. **$FADH_2$** when oxidized in the electron transport chain will produce **1.5 ATP** molecules. **In step 3**, another dehydrogenation takes place using NAD^+ that gets reduced to **NADH**, which when oxidized in the electron transport chain will generate **2.5 ATPs**. **In step 4**, one molecule of acetyl-CoA is liberated, leaving behind a fatty acid with 2 carbon atoms less.

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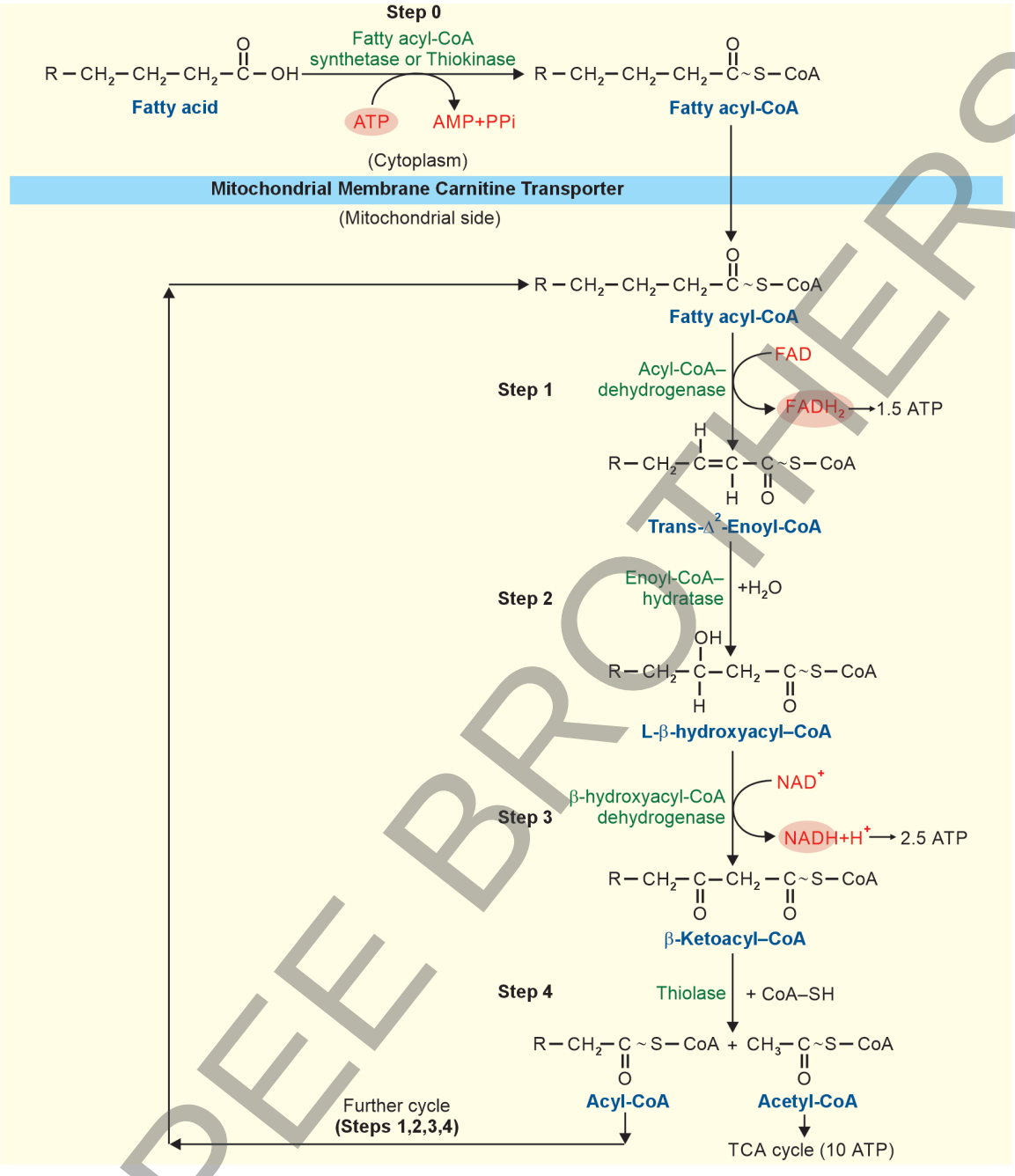


Fig. 3.10: Beta-oxidation of fatty acids. The first step is FAD dependent and the third step is NAD+ dependent.

- **Further cycles:** The newly formed fatty acyl-CoA will sequentially undergo further cycles of steps 1, 2, 3 and 4 of beta-oxidation until the fatty acid is completely converted to acetyl-CoA **(Fig. 3.10)**. Thus, palmitic acid (16 C) undergoes 7 cycles, which gives rise to 8 molecules of acetyl-CoA, 7 molecules of $FADH_2$ and 7 molecules of NADH.

Energetics of Beta-oxidation (ATP Yield)

Every molecule of acetyl-CoA when oxidized in the TCA cycle gives 10 molecules of ATP. Each molecule of $FADH_2$ produces 1.5 molecules and each NADH generates 2.5 molecules of ATP when oxidized in the electron transport chain. Hence the energy yield from one molecule of palmitate may be calculated as:

8 acetyl-CoA × 10	=	80	ATP
7 $FADH_2$ × 1.5	=	10.5	ATP
7 NADH × 2.5	=	17.5	ATP
Gross total	=	108	ATP
Net yield	**= 108 minus 2 = 106 ATP**		

(In the initial activation reaction, the equivalent of 2 high energy bonds are utilized). The efficiency of beta-oxidation is about 35%.

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DE NOVO SYNTHESIS OF FATTY ACIDS

The pathway is referred to as **Lynen's spiral**. It is not a reversal of oxidation. Important differences in the synthesis and breakdown of fatty acids are given in **Table 3.3**.

Fatty acids are synthesized mainly by a *de novo* synthetic pathway operating in the **cytoplasm**. So, it is referred to as the **extramitochondrial** or cytoplasmic fatty acid synthase system. The major fatty acid synthesized *de novo* is **palmitic acid**, the 16C saturated fatty acid. The process occurs in the liver, adipose tissue, kidney, brain, and mammary glands.

Transport of Acetyl-CoA to Cytoplasm

The starting material for *de novo* synthesis is acetyl-CoA. It is formed inside the mitochondria from pyruvate. The inner membrane is not freely permeable to acetyl-CoA. Hence the **acetyl-CoA units are delivered to the cytoplasm as citrate**.

Fatty Acid Synthase (FAS) Complex

This system exists as a **multi-enzyme complex**. The enzymes form a **dimer** with identical subunits. Each subunit of the complex is organized into 3 **domains** with 7 enzymes. The first domain is called the condensing unit; 2nd domain is the reduction unit and the 3rd domain is known as the releasing unit.

Step 1: The first step in fatty acid synthesis is the carboxylation of acetyl-CoA to form malonyl-CoA. The enzyme is acetyl-CoA carboxylase which is the **rate-limiting enzyme. Biotin**, a member of B complex vitamins, is necessary for this reaction (Step 1 in **Fig. 3.11**).

Step 2: Units are added: The elongation of the fatty acid occurs by the addition of 2 carbon atoms at a time. But the 2-carbon units are added as 3-carbon, **malonyl units**. The acetyl transacylase catalyzes the transfer of the acetyl group (2 carbons) to the condensing enzyme (CE) (step 2A in **Fig. 3.11**). One molecule of acetyl-CoA (2 carbon) and one molecule of malonyl-CoA (3 carbon) bind to the multienzyme complex. Malonyl transacylase transfers the malonyl group to the enzyme (step 2B in **Fig. 3.11**).

Step 3: Condensation: The acetyl (2C) and malonyl (3C) units are condensed by the Condensing Enzyme, to form acetoacetyl ACP (4C) (step 3 in **Fig. 3.11**).

Step 4: Reduction: The acetoacetyl ACP is reduced by **NADPH** dependent reductase (step 4 in **Fig. 3.11**).

Step 5: Dehydration: It is then dehydrated by a dehydratase (DH) to form unsaturated acyl ACP (step 5 **Fig. 3.11**).

Step 6: Second reduction: It is again reduced by enoyl reductase (ER) utilizing another molecule of **NADPH** to form butyryl ACP (step 6 in **Fig. 3.11**).

Cycling of reactions: The butyryl group (4C) is now transferred to the condensing enzyme. Then condensation, reduction, dehydration and reduction (steps 3, 4, 5, 6) are repeated. The cycles are repeated a total of **seven times,** till the 16-Carbon, palmitic acid is formed.

Step 7: Release: The elongation of the fatty acid occurs by the addition of 2 carbon atoms at a time. But the 2-carbon units are added as 3-carbon, malonyl units. The thioesterase activity (TE) releases palmitate from the multienzyme complex (step 7, **Fig. 3.11**). The end point is palmitic acid (16C) in the liver and adipose tissue. But in the lactating mammary gland, the end products are capric (10C) and lauric (12C) acids. Mother's milk contains these medium chain fatty acids. Cow's milk contains odd numbered fatty acids.

Table 3.3 Difference in the two pathways of fatty acid metabolism.

	Beta-oxidation	*Fatty acid synthesis*
Site	Mitochondria	Cytoplasm
Intermediates	Present as CoA derivatives	Covalently linked to SH group of ACP
Enzymes	Present as independent proteins	Multi-enzyme complex
Sequential units	2 carbon units split off as acetyl-CoA	2 carbon units added, as 3 carbon malonyl-CoA
Coenzymes	NAD+ and FAD are reduced	NADPH is used as reducing power

Coenzymes of Fatty Acid Synthesis

The co-enzyme utilized for de novo synthesis is **NADPH.** The source of NADPH for fatty acid synthesis is mainly the **pentose phosphate pathway** (Chapter 2). Tissues having active lipogenesis (liver, adipose tissue, lactating mammary gland) have an active HMP shunt pathway also.

Regulation of Fatty Acid Synthesis

Acetyl-CoA carboxylase is the **key enzyme**; citrate activates this enzyme. The enzyme is inhibited by palmitoyl-CoA, the end product. Insulin enhances the uptake of glucose by adipocytes and increases the activity of pyruvate dehydrogenase, acetyl-CoA carboxylase. Insulin also causes inhibition of **hormone sensitive lipase**, and so lipolysis is decreased. **Glucagon** inhibits lipogenesis by inactivating the acetyl-CoA carboxylase.

OBESITY

The fat content of the adipose tissue can increase to unlimited amounts, depending on the amount of **excess**

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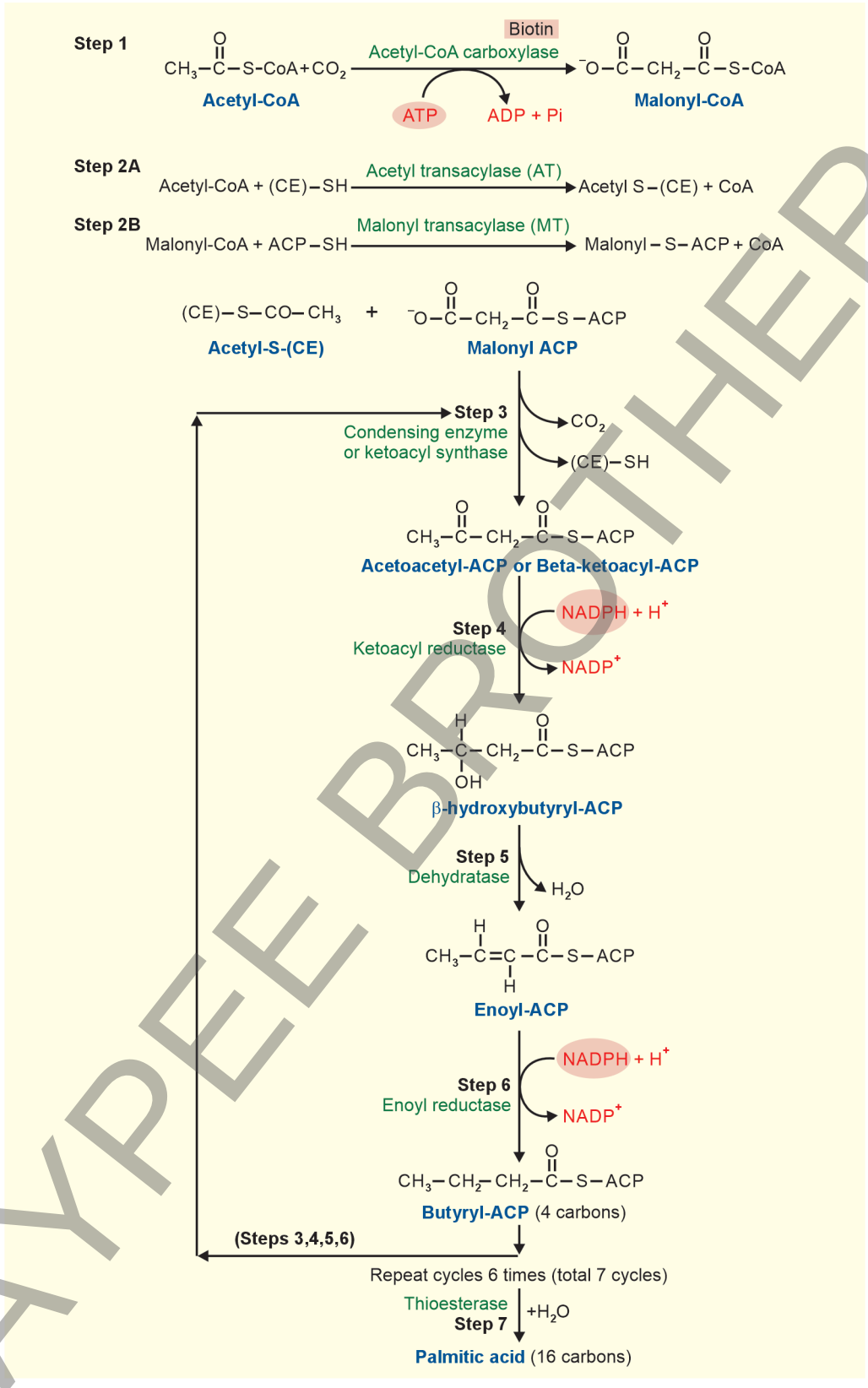


Fig. 3.11: De novo synthesis of fatty acid (Lynen cycle). Steps 4 and 6 utilize NADPH.

calories taken in. This leads to obesity. Body mass index is the indicator of a state of obesity/overweight. BMI is obtained by the formula Weight in Kg/Height in M^2. A value between 18.5 and 24 kg/M^2 is within normal limits.

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BMI up to 27.8 kg/M^2 is considered overweight and above that is called obesity (Indian specific parameters).

A high level of plasma insulin level is seen in obesity. But the **insulin receptors are decreased**; and there is peripheral resistance against insulin action. When fat droplets are overloaded, the nucleus of adipose tissue cell is degraded, the cell is destroyed, and TAG becomes extracellular. Such TAG cannot be metabolically reutilized in obese individuals.

Role of Liver in Fat Metabolism

- Secretion of bile salts.
- Synthesis of fatty acid, triacylglycerol and phospholipids.
- Oxidation of fatty acids.
- Production of lipoproteins.
- Production of ketone bodies.
- Synthesis and excretion of cholesterol.

Liver–adipose Tissue Axis

The liver produces fatty acid and TAG (triacylglycerol), which is transported as VLDL (very low density lipoprotein) in the blood. The fatty acids from VLDL are taken up by adipose tissue with the help of lipoprotein lipase, and stored as TAG. This neutral fat is hydrolyzed by hormone sensitive lipase into NEFA, which in the blood is carried by albumin. The NEFA is utilized by the peripheral tissues, excess of which can be taken up by liver cells.

METABOLISM OF KETONE BODIES

Acetyl-CoA formed from fatty acids can enter and get oxidized in the TCA cycle only when enough carbohydrates are available. During **starvation and diabetes mellitus**, the acetyl-CoA takes the alternate fate of the formation of ketone bodies.

Ketogenesis

Acetoacetate is the primary ketone body while beta-hydroxy butyrate and acetone are secondary ketone bodies. They are synthesized exclusively by the **liver mitochondria**.

Step 1. Two molecules of acetyl-CoA are condensed to form acetoacetyl-CoA.

Step 2. One more acetyl-CoA is added to form HMG-CoA (beta-hydroxy beta-methyl glutaryl-CoA). The enzyme is HMG-CoA synthase. Mitochondrial HMG-CoA is used for ketogenesis, while cytosolic fraction is used for cholesterol synthesis.

Step 3. Lysis: Then HMG-CoA is lysed to form acetoacetate.

Step 4. Reduction: Beta-hydroxy butyrate is formed by reduction of acetoacetate.

Step 5. Spontaneous decarboxylation: Acetone is formed by spontaneous (non-enzymatic) decarboxylation.

Ketolysis

The ketone bodies are formed in the liver; but they are utilized by **extrahepatic tissues**. The heart muscle and renal cortex prefer the ketone bodies to glucose as fuel. Tissues like skeletal muscle and brain can also utilize the ketone bodies as alternate sources of energy, if glucose is not available. Acetoacetate is activated to acetoacetyl-CoA by **thiophorase** enzyme. Then acetoacetyl-CoA is cleaved by thiolase to two acetyl-CoA molecules, which then enter the TCA cycle for energy production. A summary of ketone body metabolism is shown in **Figure 3.12**.

Ketosis

- Normally the rate of synthesis of ketone bodies by the liver is such that they can be easily metabolized by the extrahepatic tissues. Hence the blood level of ketone bodies is less than 1 mg/dL and only traces are excreted in urine (not detectable by usual tests).
- But when the rate of synthesis exceeds the ability of extrahepatic tissues to utilize them, there will be an accumulation of ketone bodies in the blood.
- This leads to **ketonemia**, excretion in urine (**ketonuria**) and the smell of **acetone** in breath. All these three together constitute the condition known as **ketosis**.

Causes for Ketosis

1. **Diabetes mellitus:** Untreated diabetes mellitus is the most common cause for ketosis. Even though glucose is in plenty, the **deficiency of insulin** causes accelerated lipolysis and more fatty acids are released into circulation.

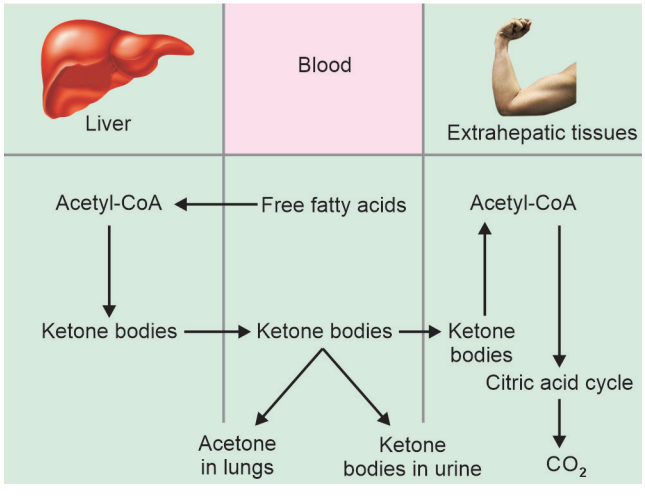


Fig. 3.12: Formation, utilization and excretion of ketone bodies.

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2. **Starvation:** In starvation, the dietary supply of glucose is decreased. The increased rate of lipolysis is to provide an alternate source of fuel. The excess acetyl CoA is converted to ketone bodies. The high **glucagon** favors ketogenesis. The brain derives 75% of energy from ketone bodies under conditions of fasting.
3. **Hyperemesis in early pregnancy**

Regulation of Ketogenesis

During starvation and diabetes mellitus, the blood level of **glucagon** is increased. Glucagon inhibits glycolysis, activates gluconeogenesis, activates lipolysis, and stimulates ketogenesis. **Insulin** has the opposite effect; it favors glycolysis, inhibits gluconeogenesis, depresses lipolysis, and decreases ketogenesis.

Consequences of Ketosis

- **Metabolic acidosis:** Acetoacetate and beta-hydroxy butyrate are acids. When they accumulate, metabolic acidosis results (Chapter 7).
- **Buffers:** The plasma bicarbonate is used up for buffering of these acids.
- **Kussmaul's respiration:** Patients will have typical acidotic breathing due to compensatory hyperventilation.
- **Smell of acetone** in patient's breath.
- **Coma:** Ketoacidosis leads to coma. Hypokalemia, dehydration and acidosis are the contributing factors to the lethal effect of ketosis.

Diagnosis of Ketosis

The presence of ketosis can be established by the detection of ketone bodies in urine by **Rothera's test.** Supportive evidence may be derived from an estimation of serum electrolytes, acid-base parameters, glucose and urea estimation.

Rothera's test: Saturate 5 mL of urine with solid ammonium sulfate. Add a few drops of freshly prepared sodium nitroprusside followed by 2 mL of liquor ammonia along the sides of the test tube. The development of a purple ring indicates the presence of ketone bodies in urine. Strip tests based on the same principle are also available.

Management of Ketoacidosis

- Treatment is to give insulin and glucose. When glucose and insulin are given intravenously, potassium is trapped within the cells. Hence nurses should always monitor the electrolytes.
- Administration of bicarbonate, and maintenance of electrolyte and fluid balance are very important aspects.

CHOLESTEROL

Cholesterol is soluble in chloroform and other fat solvents. Cholesterol is widely distributed in animal tissues; but not seen in the vegetable kingdom. Cholesterol has 27 carbon atoms; and has a cyclopentanophenanthrene ring. The clinical significance of cholesterol is described in **Box 3.7**

The major sites of synthesis of cholesterol are the liver, adrenal cortex, testis, ovaries and intestine. The liver is responsible for 80% of the endogenous cholesterol synthesis. All nucleated cells can synthesize cholesterol. Cholesterol synthesis starts from acetyl-CoA, and it needs NADPH. Beta hydroxy beta methyl glutaryl CoA (HMG-CoA)-reductase is the key enzyme. Insulin increase the activity of this enzyme, while glucagon and cortisol will reduce the activity. Lovastatin and other "statin" group of drugs (Atorvostatin, Simvastatin, etc.) are competitive inhibitors of HMG-CoA reductase. So, they are used in clinical practice to reduce cholesterol levels in the blood.

Cholesterol is the parent compound for the following important compounds:

- Bile acids (24C) produced in the liver
- Steroid hormones of adrenal cortex; glucocorticoids and mineralocorticoids (21C)
- Male sex hormones, testosterone (19C) from adrenal cortex and testis
- Female sex hormones, progesterone (21C) and estrogens (18C) from adrenal cortex and ovary
- Vitamin D_3 is produced in the skin from a cholesterol derivative.

Bile Salts

Bile acids are synthesized in the liver from cholesterol. Three carbon atoms are removed from cholesterol to

BOX 3.7 Significance and functions of cholesterol.

- **Heart diseases:** The level of cholesterol in the blood is related to the development of **atherosclerosis**. Abnormality of cholesterol metabolism may lead to cardiovascular accidents and heart attacks, as described in this chapter.
- **Cell membranes:** Cholesterol is a component of membranes and has a modulating effect on the fluid state of the membrane.
- **Nerve conduction:** Cholesterol is a poor conductor of electricity, and is used to insulate nerve fibers.
- **Bile acids and bile salts:** The 24 carbon bile acids are derived from cholesterol. These are described in this chapter. Bile salts are important for fat absorption.
- **Steroid hormones:** Glucocorticoids (21 carbon), androgens (19 carbon) and estrogens (18 carbon) are synthesized from cholesterol.
- **Vitamin D** is synthesized from cholesterol.

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become **24 carbon** atoms. They are then conjugated with either **glycine or taurine** to form bile acids. The major conjugated bile acid is glycocholic acid. The conjugated bile acids are excreted through the bile. In the bile, they exist as bile salts (sodium or potassium salts of conjugated bile acids).

Of the total bile salts reaching the intestine (15–30 g/day) only a very small fraction, about 300–500 mg/day is excreted through feces. The rest is reabsorbed from the ileum, reaches the liver and re-excreted through bile. This is referred to as the enterohepatic circulation. When bile acid binding resin (cholestyramine) is given, the re-absorption of bile acids is inhibited. Hence more cholesterol gets converted to bile acids and cholesterol is decreased.

Cholesterol Pool

The LDL (low-density lipoprotein) transports cholesterol from the liver to the peripheral tissues and HDL (high-density lipoprotein) transports cholesterol from tissues to the liver. Cells of extrahepatic tissues take up cholesterol from LDL. The free cholesterol released within the cell has the following fates:

- Incorporated into cell membranes.
- Metabolized to steroid hormones, especially in the adrenal cortex and gonads.
- Esterified with saturated fatty acids and stored in the cell. The enzyme **ACAT** (acyl cholesterol acyl transferase) helps in this reaction.
- Esterified with polyunsaturated fatty acids (PUFA) by the action of **LCAT** (lecithin cholesterol acyl-transferase) and incorporated into HDL, transported and finally excreted through the liver.

Liver and Cholesterol

- Liver synthesizes cholesterol.
- Liver removes cholesterol from lipoprotein remnants.
- Liver is the only organ that can excrete cholesterol through bile.
- Liver converts cholesterol to bile acids.

Plasma Lipids

Total plasma lipid is 400–600 mg/dL. Normal values of lipid fractions are shown in **Table 3.4**. Roughly speaking, one-third is cholesterol; one-third is triglyceride and one-third is phospholipid.

Carriage of Cholesterol in Blood

Cholesterol, being a lipid, is insoluble in water. But blood is a watery medium. So, the transport of lipids in blood needs special transporters or carriers. Therefore, different lipids such as cholesterol, triacylglycerol and phospholipids are complexed with proteins to form **lipoproteins.** The protein part of lipoprotein is called **apolipoprotein**. The lipoproteins are usually abbreviated as Lp. Free fatty acids are transported bound to albumin.

Table 3.4 Plasma lipid profile, reference values (normal values).

Analyte	*Normal value*
Total plasma lipids	400–600 mg/dL
Total cholesterol	**150–200 mg/dL**
HDL cholesterol, male	30–60 mg/dL
HDL cholesterol, female	35–75 mg/dL
LDL cholesterol, 30–39 yrs	80–130 mg/dL
Triglycerides, male	50–150 mg/dL
Triglycerides, female	40–150 mg/dL
Phospholipids	150–200 mg/dL
Free fatty acids (FFA) (NEFA)	10–20 mg/dL

CLASSIFICATION OF LIPOPROTEINS

Depending on the density (by ultracentrifuge) or on the electrophoretic mobility, the lipoproteins in plasma are classified into the following varieties:

- Chylomicrons
- Very low density lipoproteins (VLDL) or pre-beta lipoproteins
- Intermediate density lipoproteins (IDL) or broad-beta lipoproteins
- Low density lipoproteins (LDL) or beta-lipoproteins
- High density lipoproteins (HDL) or alpha-lipoproteins
- Free fatty acids (FFA) or non-esterified fatty acids (NEFA) are complexed with albumin. FFA is not generally considered as a lipoprotein, because it is loosely bound to the protein.

General Characteristics of Lipoproteins

Their salient characteristics and compositions of lipoproteins are given in **Table 3.5**. The lipoprotein molecules have a polar periphery made of proteins, polar heads of phospholipids and cholesterol. The inner core consists of the hydrophobic TAGs and tails of phospholipids. The apoproteins also increase the solubility of lipids.

Different Classes of Lipoproteins

Chylomicrons

They are the transport form of dietary triglycerides **from intestines to the adipose tissue** for storage; and to muscle or heart for their energy needs. Chylomicrons are formed in the **intestinal mucosal** cells, and secreted into the lacteals of the lymphatic system. They are **rich**

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in triglycerides .When the chylomicrons are synthesized by the intestinal mucosa, they contain **apo-B-48**. The half-life of chylomicrons in the blood is about 1 hour. The enzyme **lipoprotein lipase** (LpL) is located in the adipose tissue, muscles and heart; but not in the liver. Muscle or adipose tissue cells take up the liberated fatty acids **(Fig. 3.13)**. **Insulin** increases LpL activity.

Liver takes chylomicron remnants: As the TAG content is progressively decreased, the chylomicrons shrink in size. These remnants containing apo B-48 and apo E are taken up by hepatic cells by receptor-mediated endocytosis. Apo E binds the hepatic receptors **(Fig. 3.13)**.

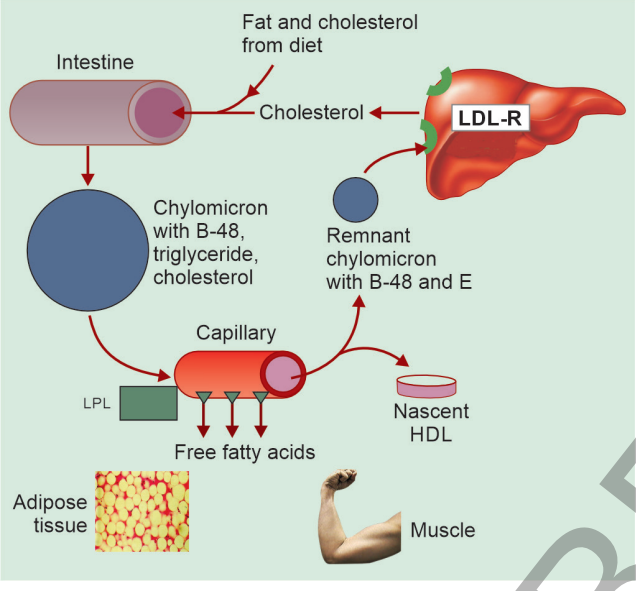


Fig. 3.13: Metabolism of chylomicrons.
(LDL-R: LDL-receptor; LPL: lipoprotein lipase)

Very Low Density Lipoproteins (VLDL)

VLDL carries triglycerides **(endogenous triglycerides)** from the liver to peripheral tissues for energy needs. They are synthesized in the liver from glycerol and fatty acids and incorporated into VLDL. **Apo-B-100** is the major lipoprotein present in VLDL. Lipoprotein lipase (LpL) liberates fatty acids that are taken up by adipose tissue and muscle. The remnant is now designated as IDL (intermediate density lipoprotein) and contains less TAG. The IDL further loses triglyceride, so as to be converted to LDL (low density lipoprotein). This conversion of VLDL to IDL and then to LDL is referred to as the **lipoprotein cascade pathway (Fig. 3.14)**.

Low Density Lipoproteins (LDL)

The LDL molecules are cholesterol rich lipoprotein molecules containing only **apo B-100**. Most of the LDL particles are derived from VLDL **(Fig. 3.14)**. LDL receptors are present in liver cells. When the apo B-100 binds to the receptor, the receptor-LDL complex is internalized by endocytosis. The cholesterol thus taken up by the liver cells, and then either deposited, or used for synthesis of bile acids.

Function of LDL: The LDL transports cholesterol **from the liver to the peripheral tissues**. LDL concentration

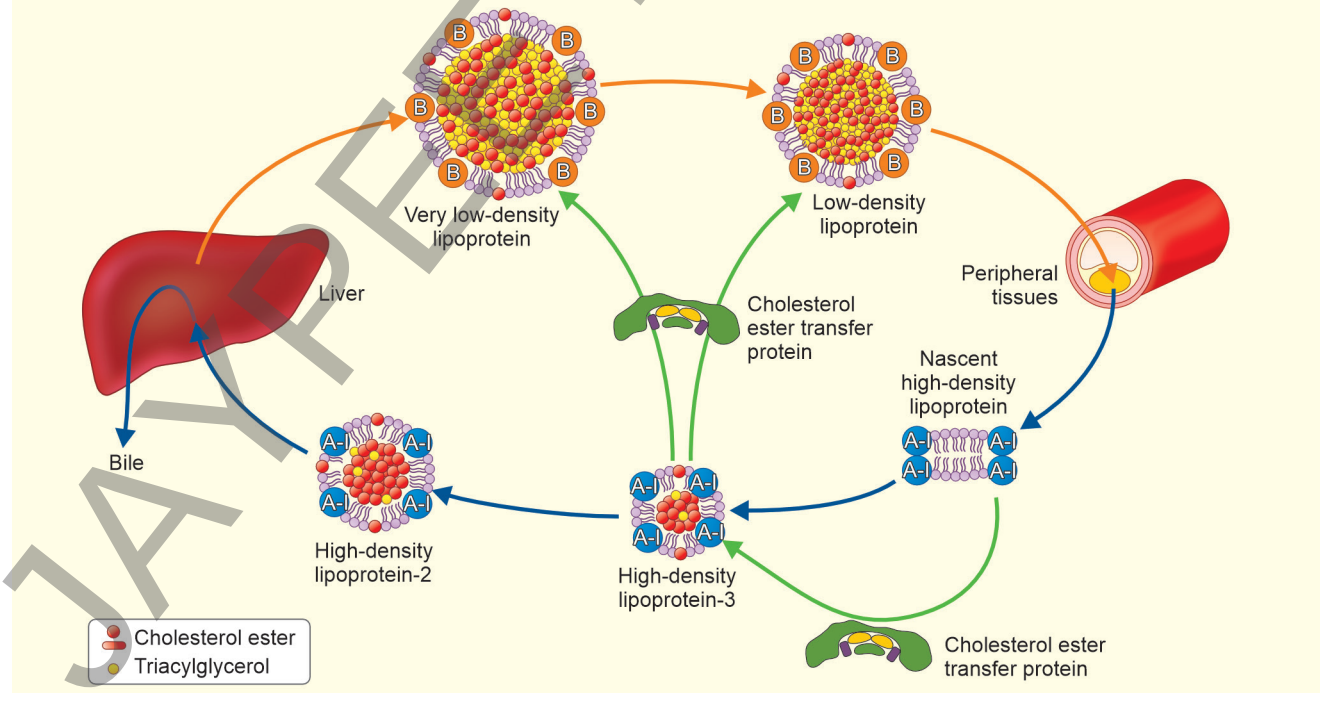


Fig. 3.14: Overview of lipoprotein metabolism.

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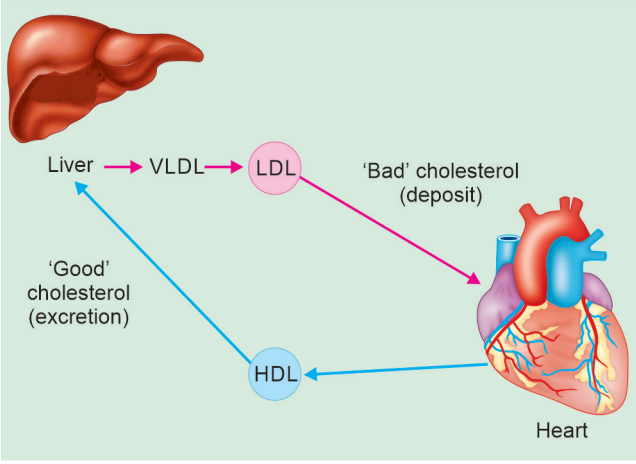


Fig. 3.15: Forward and reverse transport of cholesterol.

in blood has a positive correlation with the incidence of **cardiovascular diseases**. About 75% of the plasma cholesterol is incorporated into the LDL particles.

LDL and clinical application: LDL infiltrates through arterial walls, and is taken up by macrophages or scavenger cells. This is the starting event of **atherosclerosis** leading to myocardial infarction (see coronary artery diseases section in this chapter). Since LDL-cholesterol is thus deposited in tissues, the LDL (low density lipoprotein) variety is called "**bad cholesterol**" in common parlance **(Fig. 3.15)**.

High Density Lipoprotein (HDL)

Metabolism of HDL: The intestinal cells synthesize components of HDL and release them into the blood. The free cholesterol derived from peripheral tissue cells is taken up by the HDL. The **LCAT** (lecithin cholesterol acyltransferase) present in the plasma helps in this reaction. Polyunsaturated fatty acids bind to HDL to form esterified cholesterol. Mature HDL spheres are taken up by the liver cells by **apo A-I** mediated receptor mechanism.

Function of HDL: HDL is the main transport form of cholesterol from peripheral tissue to the liver, which is later excreted through bile. This is called reverse cholesterol transport by HDL. The only excretory route of cholesterol from the body is through the bile. Excretion of cholesterol needs prior esterification with PUFA. Thus *PUFA will help in lowering cholesterol in the body,* and so PUFA is anti-atherogenic.

Clinical significance of HDL: The level of HDL in serum is inversely related to the incidence of myocardial infarction. As it is "anti-atherogenic" or "protective" in nature, HDL is known as "good cholesterol" in common parlance **(Fig. 3.15)**. HDL level below 35 mg/dL increases the risk, while a level above 60 mg/dL protects the person from coronary artery diseases.

Free Fatty Acid (FFA)

It is also known as non-esterified fatty acids (**NEFA**). **(Table 3.5)**. It is complexed with **albumin** in plasma. The FFA is derived from the lipolysis of triglyceride stored in adipose tissue by **hormone sensitive lipase**. Free fatty acids contain long chain saturated or unsaturated fatty acids. The free fatty acids are either oxidized to supply energy or incorporated into tissue lipids by esterification. The half-life of free fatty acids in plasma is very short.

Hyperlipidemia

The primary familial hypercholesterolemia is due to the **LDL receptor** defect. The elevation of lipids in plasma leads to the deposition of cholesterol on the arterial walls, leading to **atherosclerosis,** which leads to

Table 3.5 Characteristics of different classes of lipoproteins

	Chylomicron	*VLDL*	*LDL*	*HDL*	*FFA (*)*
Density (g/mL)	<0.95	0.95–1.006	1.019–1.063	1.063–1.121	1.28–1.3
Diameter (nm)	500	70	25	15	---
Electrophoretic mobility	origin	pre-beta	beta	alpha	albumin
Protein %	2	5	20	50	99
TAG%	90	60	10	5	0
Cholesterol %	10	20	50	25	0
FFA %	0	0	0	0	1
Apoproteins	A, B-48, C-II, E	B-100, C-II, E	B-100	A-I, E	Albumin
Transport function	TAG from gut to muscle and adipose	TAG from liver to muscle	Cholesterol from liver to peripheral tissues	Cholesterol from peripheral tissues to liver	FFA from adipose tissue to muscle and liver

(*) Free fatty acids are not generally included in the lipoproteins. They are seen in circulation, weakly bound to albumin.

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ischemic heart disease and cerebrovascular accidents. The deposition of lipids in subcutaneous tissue leads to **xanthomas**. Deposits of lipids in the cornea lead to **corneal arcus**; indicating hypercholesterolemia. Patients seldom survive the second decade of life due to ischemic heart disease.

ATHEROSCLEROSIS

Coronary artery obstruction and myocardial infarction are the number one killers in the world. In India, 20–30% of deaths are due to coronary artery disease (CAD).

Atherosclerosis and LDL

LDL-cholesterol, especially **oxidized** LDL particles are deposited in the subintimal regions of arteries. The aorta, coronary arteries and cerebral vessels are predominantly affected by this process. Plasma LDL is mainly catabolized via the apo-B LDL-receptor pathway. But some LDL particles are degraded by non-specific uptake of macrophages. Free radical induced **oxidative damage** of LDL will accelerate this process. Later, the macrophages become overloaded with cholesterol, and these are then called **"foam cells"**. These form the hallmark of atherosclerotic plaques **(Fig. 3.16)**.

Progression of atherosclerosis: During the early stages of atherosclerosis, the condition is reversible if plasma lipid levels, especially LDL-cholesterol levels are lowered. But when lipid is accumulated, the lesion progresses unchecked and the arterial changes become irreversible. The formation of an atherosclerotic **plaque** leads to the narrowing of the vessel wall when proliferative changes occur. This fibrous proliferation is due to the liberation of various **growth factors** by macrophages and platelets.

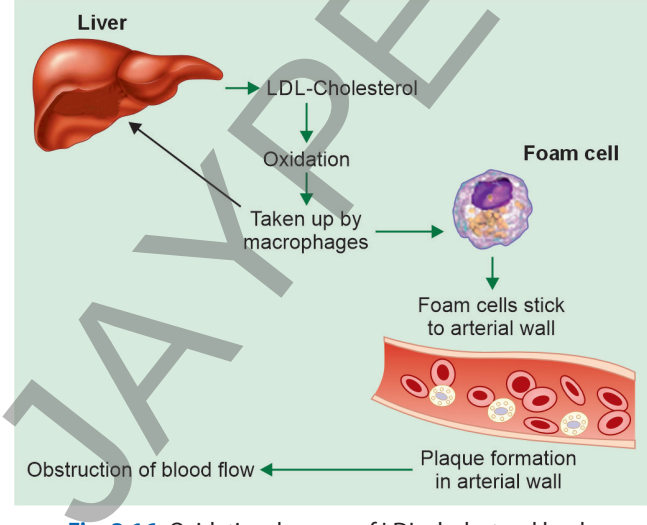


Fig. 3.16: Oxidative damage of LDL-cholesterol leads to plaque formation.

Coronary Artery Disease (CAD)

The blood flow through the narrow lumen is more turbulent and there is a tendency for clot formation. Thus a clot is formed which occludes one of the major vessels. **Thrombosis** (coronary, cerebral or peripheral vascular) leads to ischemia of the tissue supplied, due to hindrance to oxygen supply. Finally, **infarction** (death of tissue) occurs **(Fig. 3.17)**.

Serum Cholesterol is Increased in

- **Coronary artery disease and atherosclerosis**
- **Familial hyper lipoproteinemia**
- **Diabetes mellitus:** Acetyl CoA pool is increased and more molecules are Channeled to cholesterol.
- **Obstructive jaundice:** The excretion of cholesterol through bile is blocked.
- **Hypothyroidism:** The receptors for HDL on liver cells are decreased, and so excretion is not effective.
- **Nephrotic syndrome:** Albumin is lost through urine, and globulins are increased as a compensatory mechanism. So, apolipoproteins are increased, and then cholesterol is correspondingly increased.

Risk Factors of Atherosclerosis

- **Serum cholesterol level:** Risk factors are enumerated in **Box 3.8**. In normal persons, cholesterol level varies from 150 to 200 mg/dL. It should be preferably **below 180 mg/dL.** Values around 220 mg/dL will have moderate risk and values above 240 mg/dL will need active treatment. Females have a lower level of cholesterol which affords protection against atherosclerosis.
- **LDL-cholesterol level:** Blood level **under 130 mg/dL** is desirable. Levels between 130 and 159 are borderline; while above 160 mg/dl carry definite risk. Hence LDL is **"bad"** cholesterol.

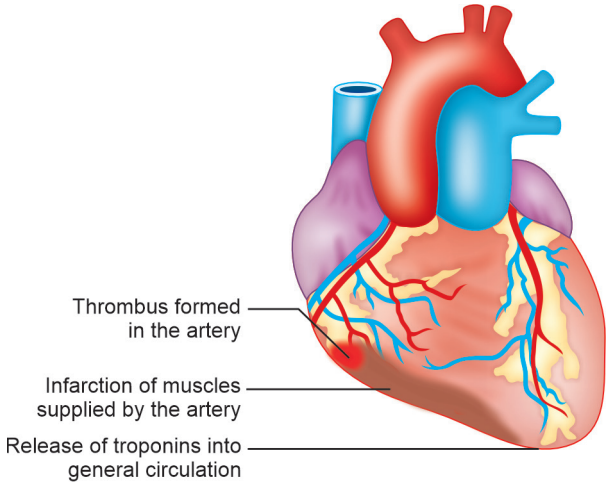


Fig. 3.17: Myocardial infarction.

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BOX 3.8 Risk factors for cardiovascular disease.

Class 1: Modifiable risk factors, interventions have been proven to lower CAD risk.
- Cigarette smoking
- High total cholesterol
- High LDL cholesterol
- Low HDL cholesterol
- Left ventricular hypertrophy (LVH)

Class 2: Modifiable risk factors, interventions are likely to lower CAD risk.
- Lipoprotein (a) or Lp(a)
- Diabetes mellitus
- Hypertension
- Physical inactivity
- Obesity
- High serum triglyceride
- Increased high-sensitivity-CRP (hs-CRP)
- Stress

- **HDL-cholesterol level:** HDL level **above 60 mg/dL** protects against heart disease. Hence HDL is **"good"** cholesterol. A level below 40 mg/dL increases the risk of CAD.
- **Apoprotein levels and ratios:** Apo A-I is a measure of HDL-cholesterol (good) and apo B measures LDL-cholesterol (bad). The ratio of **Apo B : A-I** is the most reliable index. The ratio of 0.4 is very good; the ratio of 1.4 has the highest risk of cardiovascular accidents.
- **Cigarette:** Nicotine in cigarettes will cause lipolysis and thereby increase the acetyl-CoA and cholesterol synthesis. Nicotine also causes transient constriction of coronary and carotid arteries.
- **Hypertension:** Systolic blood pressure of more than 160 further increases the risk of CAD.
- **Diabetes mellitus:** In the absence of insulin, hormone sensitive lipase is activated, more free fatty acids are formed, and these are catabolized to produce acetyl-CoA. These cannot be readily utilized, and it is channeled to cholesterol synthesis.
- **Serum triglyceride:** Normal level is 50–150 mg/dL. A blood level of **more than 150 mg/dL** is injurious to health.
- **Obesity and Sedentary life style:** People with "apple type" obesity with a protruded belly are more prone to get myocardial infarction.
- **C-reactive protein (CRP)** is an acute phase protein and its level will rise in response to inflammation. CRP level is increased in a wide range of acute and chronic inflammatory conditions such as bacterial, viral, or fungal infections; rheumatic and other inflammatory diseases; malignancy; and tissue injury and necrosis. CRP is widely used in clinical laboratories to assess the severity of the infection, and to see whether the patient is responding to the antibiotics.
- **High sensitivity CRP (hs-CRP)**, otherwise called ultrasensitive CRP, is the same molecule of CRP described above. However, the hs-CRP measures very low levels of CRP. Atherosclerosis has an inflammatory component, which causes the production of CRP in small quantities. This CRP binds selectively to LDL, and activates complement, resulting in plaque formation. CRP directly participates in the atherothrombotic process. The hs-CRP level is an independent risk factor for atherosclerotic disease.

Prevention of Atherosclerosis

Almost 90% of CAD is predictable, preventable and treatable. Lifestyle changes are required. The aim is to reduce total cholesterol below 180 mg/dL; to decrease LDL-cholesterol below 130 mg/dL and to keep HDL-cholesterol above 35 mg/dL. The following measures are useful:

- **Vegetable oils and PUFA:** Vegetable oils (e.g. sunflower oil) and fish oils contain polyunsaturated fatty acids (PUFA). They are required for the esterification and final excretion of cholesterol. So PUFA is helpful to reduce cholesterol levels in the blood. **Omega-3 fatty acids** from fish oils reduce LDL and decrease the risk of CAD. However, excess PUFA is also harmful. The accepted standard is that about 20% of total calories may be obtained from fat, out of which about one-third from saturated, another one-third from mono-unsaturated and the rest one-third from polyunsaturated fatty acids. The recommended daily allowance will be about **20–25 g of oils** and about 2–3 g of PUFA per day for a normal adult.
- **Green leafy vegetables:** Due to their **high fiber content,** leafy vegetables will increase the motility of bowels and reduce the reabsorption of bile salts. Vegetables also contain plant sterols (**sitosterol**) which decrease the absorption of cholesterol. About 400 g/day of fruit and vegetables are desired.
- **Avoid sucrose and cigarette:** Sucrose will raise plasma triglycerides. Sucrose should be avoided.
- **Exercise:** Regular moderate exercise will lower LDL (bad cholesterol) and raise HDL (good cholesterol) levels in the blood. It will also reduce obesity.
- **Hypolipidemic drugs:** When all other measures fail, HMGCoA reductase inhibitors ("statins") such as Atorvastatin and Simvastatin could be tried. They are effective in reducing the cholesterol level and decreasing the incidence of CAD.

CARDIAC BIOMARKERS

A biomarker is defined as one naturally occurring molecule by which a particular disease can be identified. Another definition is that a biomarker is a substance used

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BOX 3.9 Classification of cardiac markers.

A. Cardiac markers of myocardial infarction (MI)
- Cardiac troponins (cTnT and cTnI)
- High sensitivity troponin (hs-cTnT and hs-cTnI)
- Creatine kinase isoenzyme (CK-MB)

B. Markers for risk prediction
- Total cholesterol level in serum
- LDL cholesterol and Apo B-100 level
- HDL cholesterol and Apo A-I level
- Lp(a) level
- Serum triglycerides
- Plasma hs-CRP

as a diagnostic indicator of a particular disease. Cardiac markers may be classified as those for assessing acute cardiac injury or those used to identify long term risks.

These cardiac markers include:
- Markers used to detect acute myocardial infarction are cardiac troponins (cTnI and cTnT) and creatine kinase isoenzyme (CK-MB). Other markers are listed in **Box 3.9**).
- The risk factors (risk predictors) mainly include cholesterol, lipoproteins and hs-CRP in plasma **(Box 3.9)**.

Cardiac Troponins (cTnT and cTnI)

Troponins are specific markers for myocardial infarction. Measurement of cardiac troponin has become the main test for early detection of an ischemic episode and in monitoring the patient. The troponin complex consists of 3 components; troponin C (calcium binding subunit), troponin I (actomyosin ATPase inhibitory subunit), and troponin T (tropomyosin binding subunit). Troponin I is released into the blood within 4 hours after the onset of symptoms of myocardial ischemia; peaks at 14–24 hours and remains elevated for 7–10 days post-infarction. Serum level of Troponin T (cTnT or TnT) increases within 6 hrs of myocardial infarction, peaks at 72 hours and then remains elevated up to 10–14 days. Nowadays, high-sensitivity cTnT (hs-cTnT) and high-sensitivity cTnI (hs-cTnI) tests have been developed. It enables the determination of very low cTnT concentrations, and therefore are very useful for very early detection of myocardial infarction.

Creatine Kinase (CK)

CK value in serum is increased in myocardial infarction. The CK level starts to rise **within 4 hours** of myocardial infarction. Therefore CK estimation is very useful to detect early cases, where ECG changes may be ambiguous. However, CK has now been replaced by more specific troponins.

Isoenzymes of CK

CK is a dimer; the subunits are called B (brain) and M (muscle). Therefore, there are three different isoenzymes: CK-MM, CK-BB and CK-MB. Skeletal muscle expresses CK-MM; the myocardium (heart muscle), expresses CK-MB; while CK-BB is predominantly expressed in the brain. Hence the estimation of CK-MB isoenzyme is important for the diagnosis of myocardial infarction.

RECAP

Clinical Relevance of Lipids

- **Obesity and cardiovascular diseases:** Excessive fat accumulation leads to obesity and related health risks, including cardiovascular diseases.
- **Atherosclerosis:** Abnormal lipid metabolism can cause plaque formation in arteries, leading to atherosclerosis.
- **Diabetes mellitus**: Disruptions in lipid metabolism in diabetes can lead to complications like ketosis.

Classification of Lipids

- **Simple lipids:** Ester forms of fatty acids and glycerol or other alcohols.
- **Compound lipids:** Compound lipids are Phospholipids, Sphingolipids, Sulfolipids, etc. Compound lipids containing alcohol sphingosine and one or more carbohydrate residues are called glycolipids.
- **Derived lipids:** Include fatty acids, steroids, and others derived from or precursors of other lipid classes. Cholesterol is an animal sterol which is a derived lipid. It is the precursor of all steroids in the body.

Fatty Acids

- Fatty acids are classified based on (i) Number of carbon atoms, (ii) Length of the hydrocarbon chain, and (iii) Nature of the hydrocarbon chain.
- Depending on the number of carbon atoms, fatty acids may be even chain or odd chain, which are further subdivided into short chain (2–6C), medium chain (8–14C) and long chain (16–20C).
- Fatty acids may be saturated (no double bonds), monounsaturated (one double bond) or polyunsaturated (2 or more double bonds).
- Polyunsaturated fatty acids (PUFA) may be essential or nonessential. Essential fatty acids are those, which cannot be synthesized in the human body and have to be supplemented in the diet. For example, Linoleic acid, and alpha-Linolenic acid.
- Arachidonic acid is the precursor of prostaglandins.
- Triacylglycerol or neutral fat is the storage form of energy in adipose tissue.

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Applied Biochemistry, Nutrition & Dietetics for Nursing Students

This book is designed to guide students and practitioners through both foundational principles and advanced dietary management. Dietetics is a discipline that plays an essential role in both disease prevention and patient recovery. It ensures that individuals receive the optimal balance of macronutrients and micronutrients necessary for growth, energy production, and immune function—key elements in sustaining long-term health and well-being. The predominant aim of this book is to effectively bridge the gap between classroom learning and clinical nutrition practice.



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