SHREE H. N. SHUKLA INSTITUTE OF PHARMACEUTICAL EDUCATION AND RESEARCH

B.PHARM
(SEMESTER –III)

SUBJECT NAME: BIOCHEMISTRY
CHAPTER 2: METABOLISM OF LIPIDS
SUBJECT CODE: BP303TP

Metabolism of Lipids

Lipids are indispensable to a cell structure and l-function. Due to their hydrophobic and nonpolar nature, lipids differ from rest of the body compounds and are unique in their action.

Triacylglycerols body fuel reserve

Lipids constitute about "15-20% of the body weight in humans. Triacylglycerols (formerly triglycerides) are the most abundant lipids comprising 85-90% of body lipids. Most of the triacylglycerols(TC; also called neutral fat or depot fat) are stored in the adipose tissue and serve as energy reserves of the body. This is in contrast to carbohydrates and proteins which cannot be stored to a significant extent for energy purposes. Fat also acts as an insulating material for maintaining the body temperature of animals.

Lipids are indispensable to or cell structure and l-function. Due to their hydrophobic and nonpolar nature, lipids differ from rest of the body compounds and are unique in their action.

Triacylglycerols are the most predominant storage form of energy. There are two main reasons for fat being the fuel reserve of the body

1. Triacylglycerols (TC) are highly concentrated forms of energy, yielding 9 Cal/g, in contrast to carbohydrates and proteins that produce only 4 Collage. This is because fatty acids found in TG are
in the reduced form.

2. The triacylglycerols are nonpolar and hydrophobic in nature, hence stored in pure form without any association with water(anhydrous form). On the other hand, glycogen and proteins are polar. One gram of glycogen combines with 2 g of water for storage.

TABLE 14.1 The plasma concentration of lipids (lipid profile) in humans

Lipid fraction	*Reference values (mg/dl)*
Total lipid	400-600
Total cholesterol	150–200
LDL-cholesterol	80–150
HDL-cholesterol	30–60
VLDL-cholesterol	20–40
Triglycerides	75–150
Phospholipids	150–200
Free fatty acids	5–15

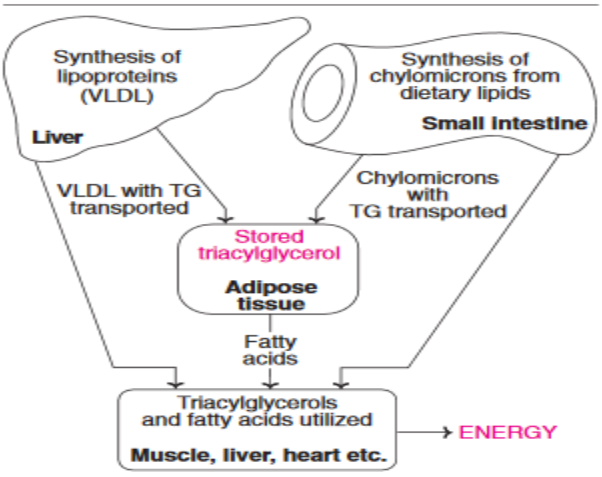


Fig. 14.1 : Overview of fat metabolism.

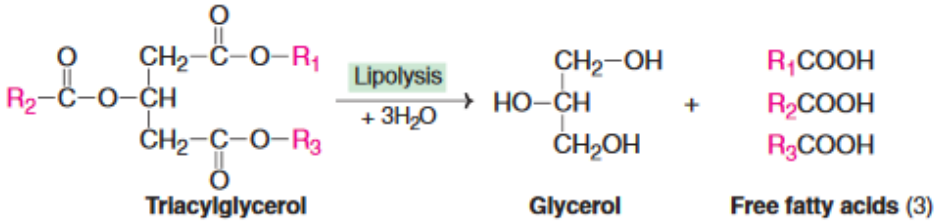


Fig. 14.2 : Complete hydrolysis (lipolysis) of triacylglycerol.

FATTY ACID OXIDATION

The fatty acids in the body are mostly oxidized by E-oxidation. E-Oxidation may be defined as the oxidation of fatty acids on theE-carbon atom. This results in the

sequential removal of a two carbon fragment, acetyl CoA.Fatty acid oxidation—stages and tissues

The b-oxidation of fatty acids involves three stages.
I.Activation of fatty acids occurring in the cytosol.
II.Transport of fatty acids into mitochondria
III.E-Oxidation proper in the mitochondrial matrix

Fatty acids are oxidized by most of the tissues in the body. However, the brain, erythrocytes and adrenal medulla cannot utilize fatty acids for energy requirement.

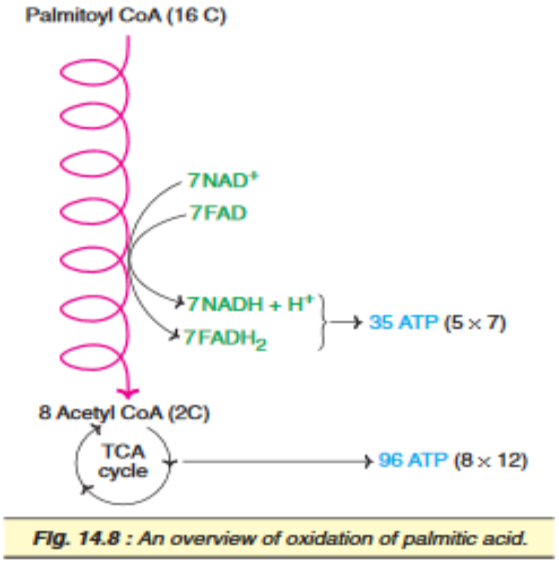


Fig. 14.8 : An overview of oxidation of palmitic acid.

I. Fatty acid activation

Fatty acids are activated to acyl CoA by **thiokinase** acyl CoA synthetases. The reaction occurs in two steps and requires **ATP,coenzyme A and Mg2+**.
Fatty acid reacts with ATP to form acyl adenylate which then combines with coenzyme A to produce acyl CoA(Fig.14.5).
In the activation, two high energy phosphates are utilized, since ATP is converted to pyrophosphate (PPi). The enzyme inorganic pyrophosphatase hydrolyses PPi to phosphate(Pi). The immediate elimination of PPi makes this reaction totally

irreversible.Three different thiokinase, to activate long chain (10-20 carbon), medium chain (4-12carbon) and short chain (< 4 carbon) fatty acids have been identified.

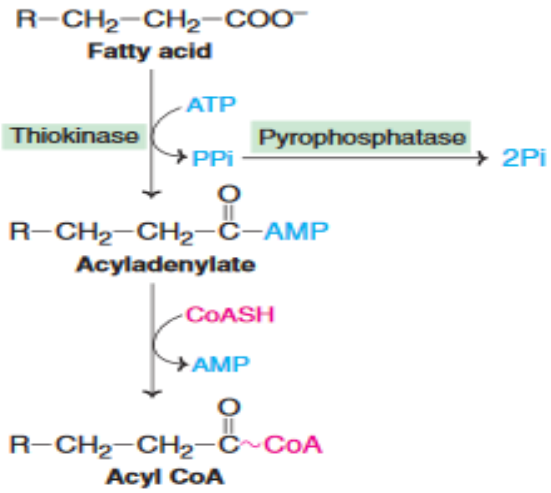


Fig. 14.5 : Activation of fatty acid to acyl CoA by the enzyme thiokinase.

II. Transport of acyl CoA into mitochondria

The inner mitochondrial membrane is impermeable to fatty acids. A specialized carnitine carrier system (carnitine shuttle)operates to transport activated fatty acids from cytosol to the mitochondria. This occurs in four steps (Fig.14.6).

1. Acyl group of acyl CoA is transferred to carnitine (E-hydroxy J-trimethyl aminobutyrate),catalysed by carnitine acyltransferase I (present on the outer surface of inner mitochondrial membrane).
2. The acyl-carnitine is transported across the membrane to the mitochondrial matrix by a specific carrier protein.
3. Carnitine acyltransferase II (found on the inner surface of inner mitochondrial membrane)converts acyl-carnitine to acetyl CoA.
4. The carnitine released returns to cytosol for reus

It should be noted that the coenzyme A used for activation is different from the one that finally combines with fatty acid in the mitochondria to form acyl CoA. Thus, the cell has two separate pools (cytosolic and mitochondrial) of coenzyme A.

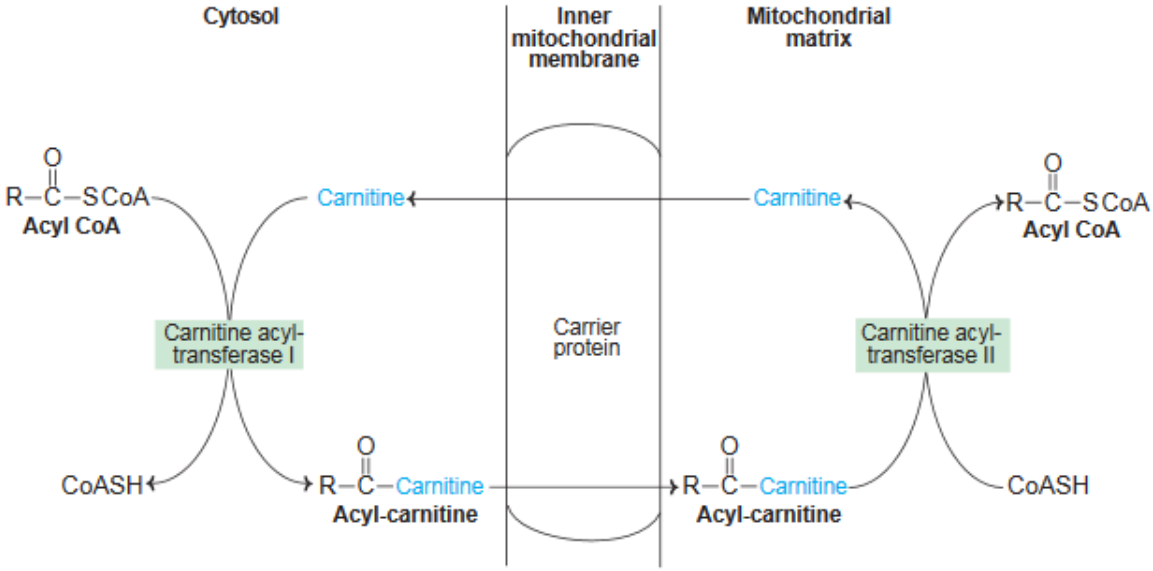


Fig. 14.6 : *Carnitine shuttle for transport of activated fatty acid (acyl CoA) into mitochondria.*

III. B-Oxidation proper

Each cycle of E-oxidation, liberating a two carbon unit-acetyl CoA, occurs in a sequence of four reactions (Fig.14.7).

1.Oxidation : Acyl CoA undergoes dehydrogenation by an FAD-dependent flavoenzyme, acyl CoA dehydrogenase. A Double bond is formed between D and E carbons(i.e., 2 and 3 carbons).

2.Hydration : Enoyl CoA hydratase brings about the hydration of the double bond to formE-hydroxyacyl CoA.

3.Oxidation :E-Hydroxyacyl CoA dehydro-genase catalyses the second oxidation and gene-rates NADH. The product formed is E-ketoacylCoA.

4.Cleavage : The final reaction inE-oxidation is the liberation of a 2 carbon

fragment, acetyl CoA from acetyl CoA. This occurs by a thiolytic cleavage catalysed by E-ketoacylCoA thiolase (or simply thiolase).The new acyl CoA, containing two carbon less than the original, reenters the E-oxidation cycle. The process continues till the fatty acid is completely oxidized.

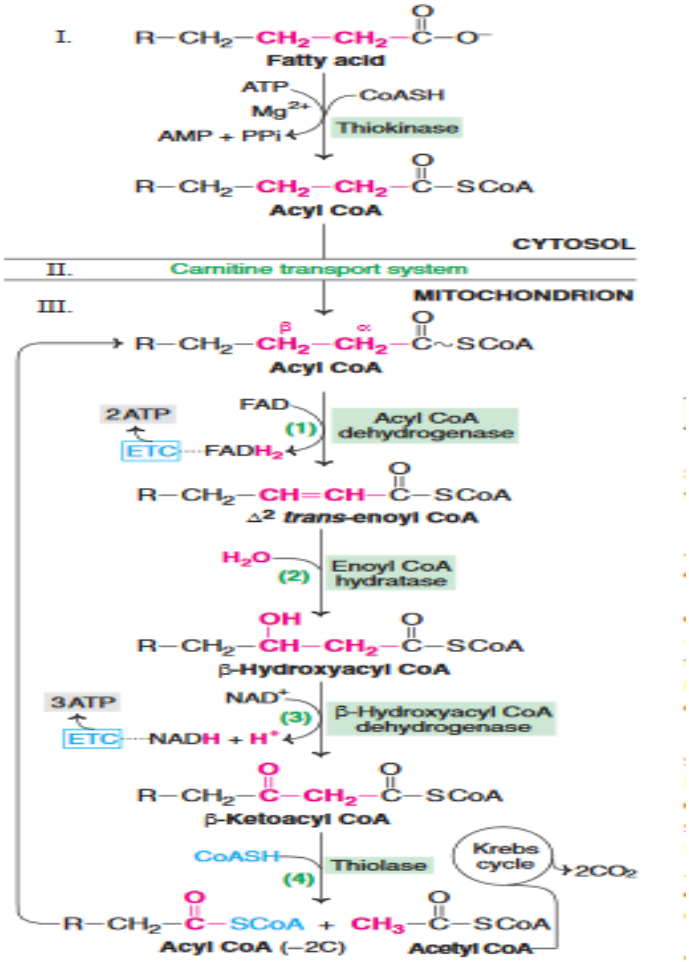


Fig. 14.7 : β-Oxidation of fatty acids : Palmitoyl CoA (16 carbon) undergoes seven cycles to yield 8 acetyl CoA [I–Activation; II–Transport; III–β Oxidation proper— (1) Oxidation, (2) Hydration, (3) Oxidation and (4) Cleavage].

The overall reaction for each cycle of B -oxidation

Cn Acyl CoA + FAD + NAD+ + H2O +CoASH >>>>A C(n–2) Acyl CoA + Acetyl CoA +FADH2 + NADH + H+.

The scheme of fatty acid oxidation discussed above corresponds to saturated (no double bond)and even carbon fatty acids. This occurs most predominantly in biological systems.

Oxidation of palmitoyl CoA

The summary of B-oxidation of palmitoyl CoA is shown below.
Palmitoyl CoA + 7 CoASH + 7 FAD + 7 NAD^+ + 7H2O >>>>> 8 Acetyl CoA + 7 FADH2 +7 NADH + $7H^+$
Palmitoyl CoA undergoes 7 cycles of -oxidation to yield 8 acetyl CoA. Acetyl CoA can enter the citric acid cycle and get completely oxidized to CO2 and H2O.

TABLE 14.2 Energetics of palmitic acid oxidation

Mechanism	*ATP yield*
I. **β-Oxidation 7 cycles**	
7 $FADH_2$ [oxidized by electron transport chain (ETC), each $FADH_2$ gives 2 ATP]	14(10.5)
7 NADH (oxidized by ETC, each NADH liberates 3 ATP)	21(17.5)
II. **From 8 acetyl CoA**	
Oxidized by citric acid cycle, each acetyl CoA provides 12 ATP	96(80)
Total energy from one mole of palmitoyl CoA	131(108)
Energy utilized for activation (formation of palmitoyl CoA)	–2
Net yield for one molecule of palmitate	129(106)

Note : Values in brackets in red colour represent ATP synthesized as per P:O ratios of 2.5 for NADH and 1.5 for $FADH_2$.

KETONE BODIES

The compounds namely **acetone, aceto-acetate and E-hydroxybutyrate** (or 3-hydroxy-butyrate) are known as ketone bodies (Fig.14.10).Only the first two are true ketones while E-hydroxybutyrate does not possess a keto (CO)group. Ketone bodies are water-soluble and energy yielding. Acetone, however, is an exception, since it cannot be metabolized.

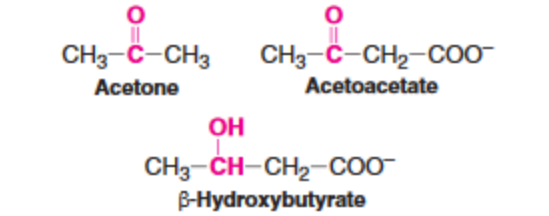
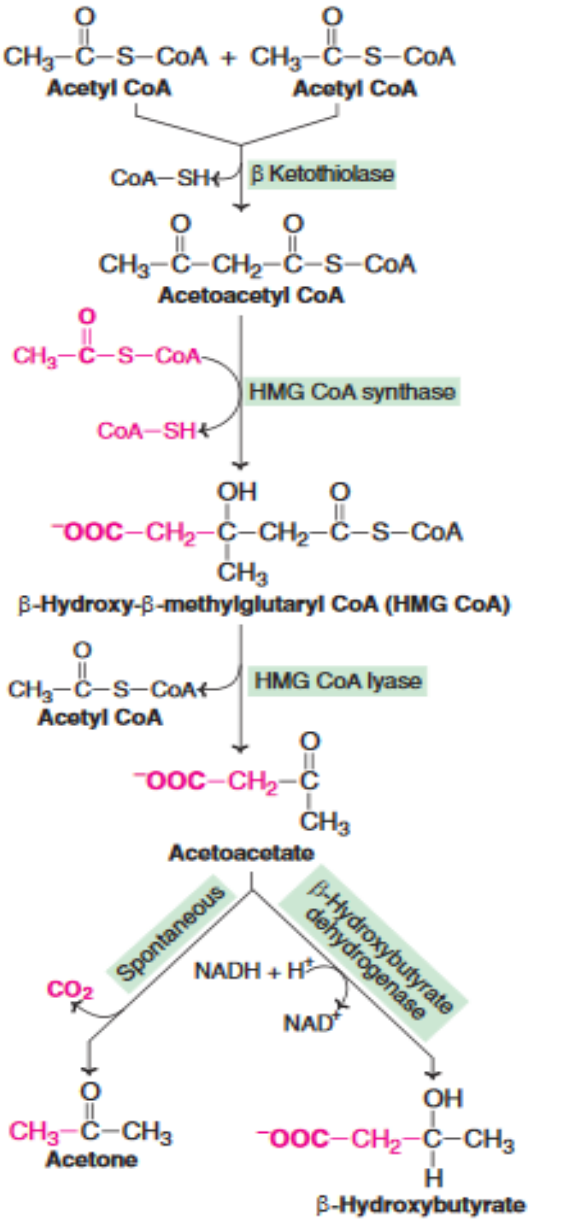


Fig. 14.10 : Structures of ketone bodies.

Ketogenesis

The synthesis of ketone bodies occurs in the liver. The enzymes for ketone body synthesis are located in the mitochondrial matrix. Acetyl CoA,formed by oxidation of fatty acids, pyruvate or some amino acids, is the precursor for ketone bodies. Ketogenesis occurs through the following reactions (Fig.14.11).

1. Two moles of acetyl CoA condense to form acetoacetyl CoA. This reaction is catalysed by thiolase, an enzyme involved in the final step of E-oxidation. Hence, acetoacetate synthesis is appropriately regarded as the reversal of thiolase reaction of fatty acid oxidation.
2. Acetoacetyl CoA combines with another molecule of acetyl CoA to produce E-hydroxyE-methyl glutaryl CoA (HMG CoA). HMG CoAsynthase, catalysing this reaction, regulates the synthesis of ketone bodies.
3. HMG CoA lyase cleaves HMG CoA to produce acetoacetate and acetyl CoA.
4. Acetoacetate can undergo spontaneous decarboxylation to form acetone.
5. Acetoacetate can be reduced by adehydrogenease to E-hydroxybutyrate.The carbon skeleton of some amino acids(ketogenic) is degraded to acetoacetate or acetylCoA and, therefore, to ketone bodies, e.g.leucine, lysine, phenylalanine etc.



14.11 : *Synthesis of ketone bodies (ketogenesis).*

Utilization of ketone bodiesThe ketone bodies, being water-soluble, are easily transported from the liver to various tissues. The two ketone bodies—acetoacetate and E-hydroxybutyrate serve as important sources of energy for the peripheral tissues such as skeletal muscle, cardiac muscle, renal cortex etc. The tissues which lack mitochondria (e.g.erythrocytes) however, cannot utilize ketone bodies. The

production of ketone bodies and their utilization become more significant when glucose is in short supply to the tissues, asobserved in starvation, and diabetes mellitus.

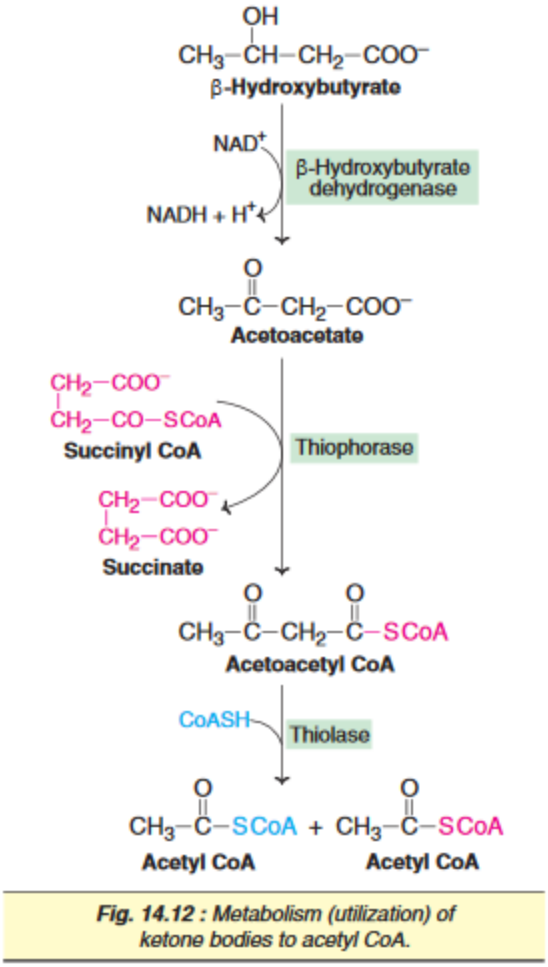


Fig. 14.12 : Metabolism (utilization) of ketone bodies to acetyl CoA.

During prolonged starvation, ketone bodies are the major fuel source for the brain and other parts of the central nervous system. It should be noted that the ability of the brain to utilize fatty acids for energy is very limited. The ketone bodies can meet 50-70% of the brain's energy needs. This is an adaptation for the survival ofthe organism during the periods of food deprivation.Reactions of ketone bodies : E-Hydroxy-butyrate is first converted to acetoacetate(reversal of synthesis) and metabolized.Acetoacetate is activated to acetoacetyl CoA by a mitochondrial enzyme thiophorase(succinyl CoA acetoacetate CoA transferase). The Coenzyme

A is donated by succinyl CoA, an intermediate in the citric acid cycle. Thiophorase is absent in the liver, hence ketone bodies are not utilized by the liver. Thiolase cleaves acetoacetylCoA to two moles of acetyl CoA (Fig.14.12).

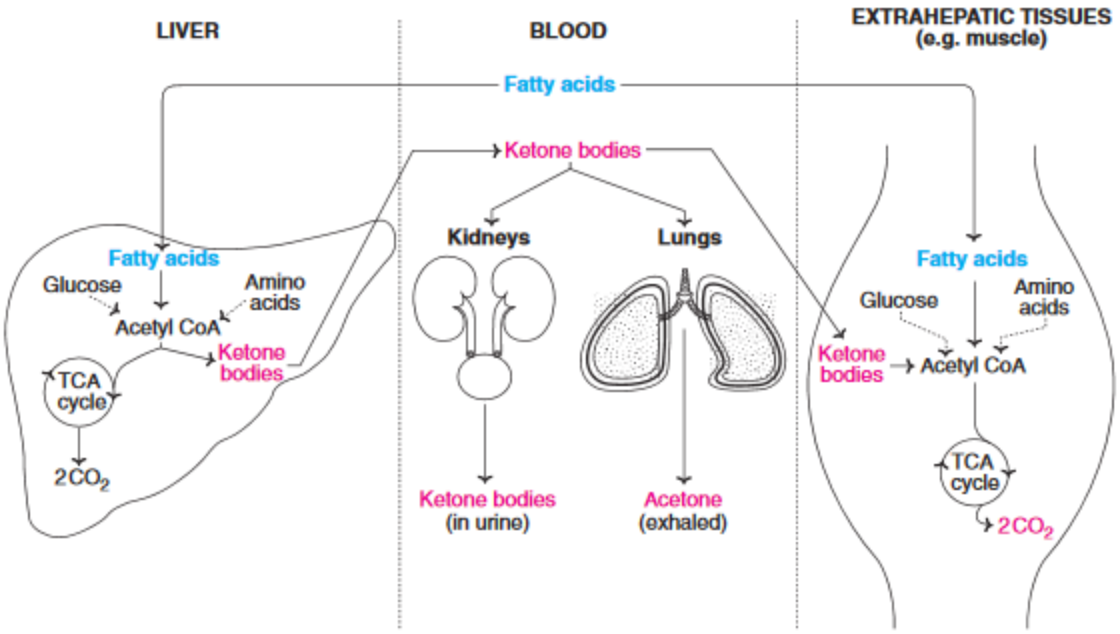


Fig. 14.13 : Summary of ketone body synthesis, utilization and excretion.

Ketoacidosis

Both acetoacetate and E-hydroxybutyrate are strong acids. Increase in their concentration in blood would cause acidosis. The carboxyl group has a pKa around 4. Therefore, the ketone bodies in the blood dissociate and release H+ ions which lower the pH. Diabetic ketoacidosis is dangerous—may result in coma, and even death,if not treated. Ketosis due to starvation is not usually accompanied by ketoacidosis.

Treatment of ketoacidosis : Rapid treatment of diabetic ketoacidosis is required to correct the metabolic abnormalities and the associated water and electrolyte imbalance. Administration Of insulin is necessary to stimulate uptake of glucose by tissues and inhibition of ketogenesis.

BIOSYNTHESIS OF FATTY ACIDS

The dietary carbohydrates and amino acids,when consumed in excess, can be converted to fatty acids and stored as triacylglycerols. Denovo (new) synthesis of fatty acids occurs predominantly in liver, kidney, adipose tissue and lactating mammary glands. The enzyme machinery for fatty acid production is located inthe cytosomal fraction of the cell. Acetyl CoA is the source of carbon atoms while NADPH provides the reducing equivalents and ATPsupplies energy for fatty acid formation.

The fatty acid synthesis may be learnt in 3 stages

I. Production of acetyl CoA and NADPH

II. Conversion of acetyl CoA to malonyl CoA

III. Reactions of fatty acid synthase complex.I.

I.Production of acetyl CoAand NADPH

Acetyl CoA and NADPH are the prerequisites for fatty acid synthesis. Acetyl CoA is produced in the mitochondria by the oxidation of pyruvate and fatty acids, degradation of carbon skeleton of certain amino acids, and from ketone bodies.Mitochondria, however, are not permeable to acetyl CoA. An alternate or a bypass arrangement is made for the transfer of acetylCoA to cytosol. Acetyl CoA condenses with oxaloacetate in mitochondria to form citrate.Citrate is freely transported to cytosol where it is cleaved by citrate lyase to liberate acetyl CoAand oxaloacetate. Oxaloacetate in the cytosol is converted to malate (Fig.14.14).

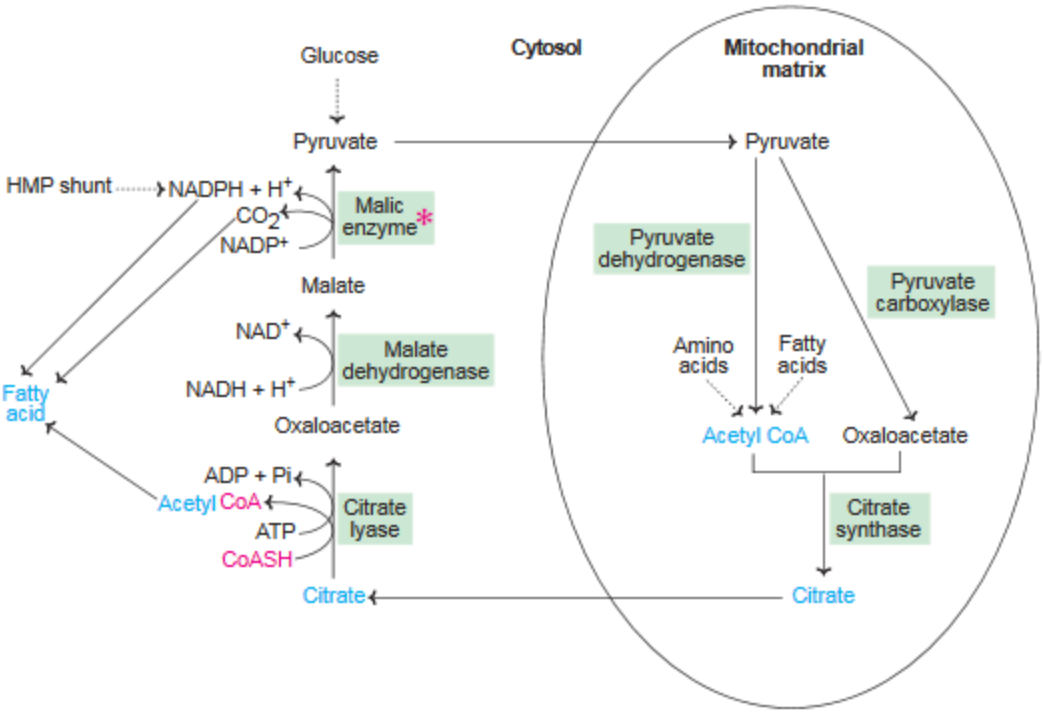


***Fig. 14.14 :** Transfer of acetyl CoA from mitochondria to cytosol*
*(HMP shunt—Hexose monophosphate shunt; *—also known as malate dehydrogenase).*

Malic enzyme converts malate to pyruvate.NADPH and CO2 are generated in this reaction.Both of them are utilized for fatty acid synthesis.

Advantages of coupled transport of acetylCoA and NADPH : The transport of acetyl CoAfrom mitochondria to cytosol is coupled with the cytosomal production of NADPH and CO2 which is highly advantageous to the cell for optimum synthesis of fatty acids.

II. Formation of malonyl CoA

Acetyl CoA is carboxylated to malonyl CoAby the enzyme acetyl CoA carboxylase(Fig.14.15). This is an ATP-dependent reaction and requires biotin for CO2 fixation. The Mechanism of action of acetyl CoA carboxylase is similar to that of pyruvate carboxylase(ReferChapter 7, Fig.7.29). Acetyl CoA carboxylase is a regulatory enzyme in fatty acid synthesis(details given later).

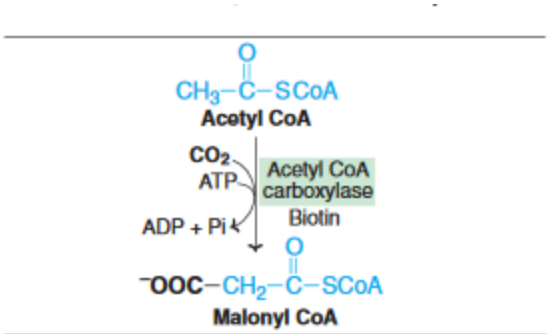


Fig. 14.15 : Conversion of acetyl CoA to malonyl CoA.

III. Reactions of fatty acid synthase complex

The remaining reactions of fatty acid synthesis are catalysed by a multifunctional enzyme known as fatty acid synthase (FAS) complex.

In Eukaryotic cells, including man, the fatty acid synthase exists as a dimer with two identical units. Each monomer possesses the activities of seven different enzymes and an acyl carrier protein (ACP) bound to 4c-phosphopantetheine.Fatty acid synthase functions as a single unit catalysing all the seven reactions. Dissociation Of the synthase complex results in loss of the enzyme activities.

In the lower organisms(prokaryotes), the fatty acid synthesis is carried out by a multienzyme complex in association with a separate acyl carrier protein. This is in contrast to eukaryotes where ACP is a part of fatty acid synthase.The sequence of reactions of the extra—mitochondrial synthesis of fatty acids (palmitate)is depicted in Fig.14.16, and described in the next page.

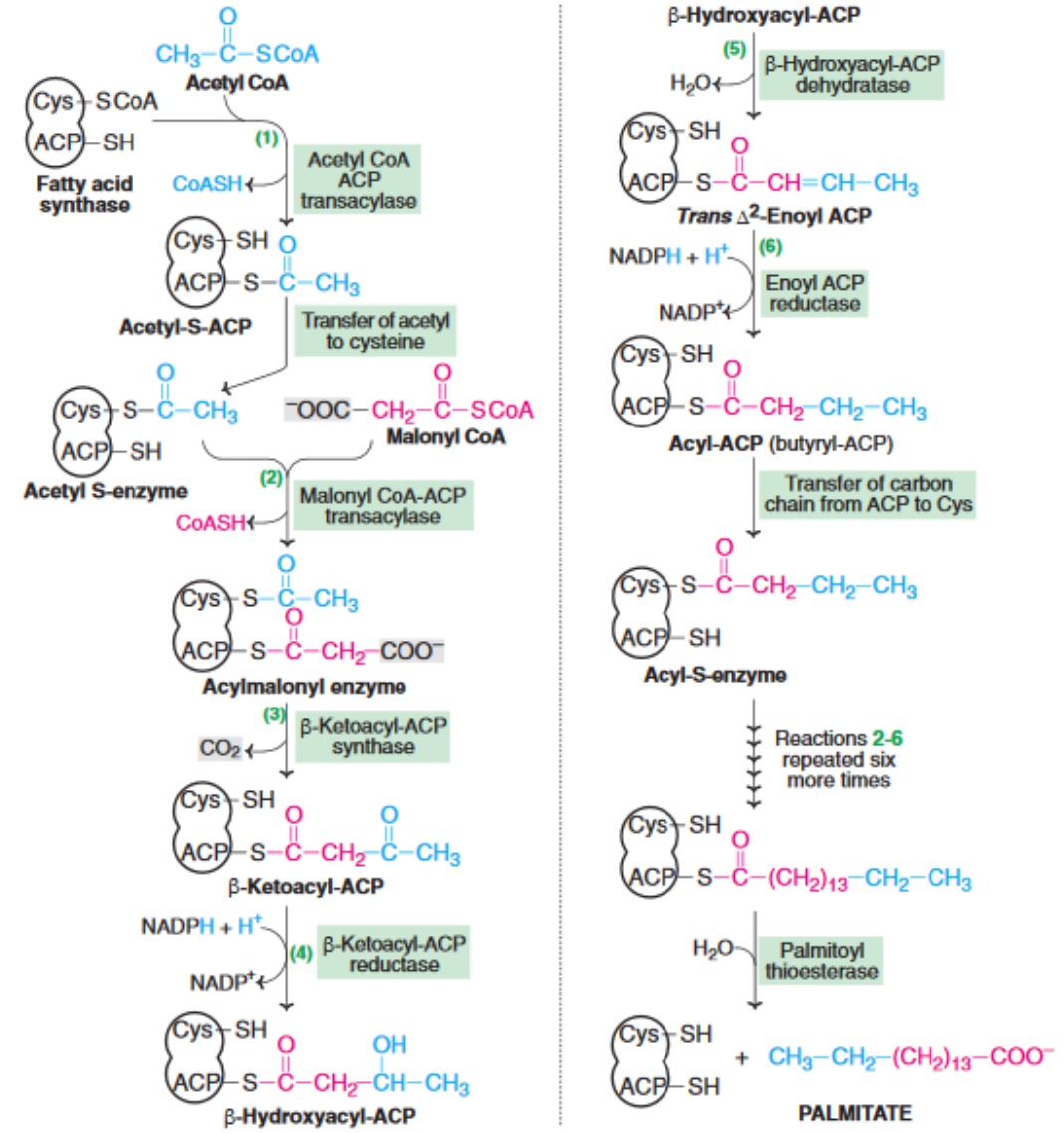


Fig. 14.16 contd. next column

Fig. 14.16 : Biosynthesis of long chain fatty acid-palmitate. (Cys–Cysteine; ACP–Acyl carrier protein; The pathway repeats 7 times to produce palmitate; the first two carbons at the methyl end are directly from acetyl CoA, the rest of the carbons come from malonyl CoA).

1. The two carbon fragments of acetyl CoA are transferred to ACP of fatty acid synthase,catalysed by the enzyme, acetyl CoA-ACPtransacylase. The acetyl unit is then transferredfrom ACP to cysteine residue of the enzyme.Thus ACP site falls vacant.
2. The enzyme malonyl CoA-ACPtransacylase transfers malonate from malonylCoA to bind to ACP.

3. The acetyl unit attached to cysteine is transferred to the malonyl group (bound to ACP).The malonyl moiety loses CO2 which was added by acetyl CoA carboxylase. Thus, CO2 is never incorporated into fatty acid carbon chains. The Decarboxylation is accompanied by loss of free energy which allows the reaction to proceed forward. This reaction is catalyzed byE-ketoacylACP synthase.

4.E-Ketoacyl ACP reductase reduces ketoacyl group to hydroxyacyl group. The Reducing equivalents are supplied by NADPH.

5.E-Hydroxyacyl ACP undergoes dehydration.A molecule of water is eliminated and a double bond is introduced between D and E carbons.

6. A second NADPH-dependent reduction,catalysed by enoyl-ACP reductase occurs to produce acyl-ACP. The four-carbon unit attached to ACP is butyryl group.The carbon chain attached to ACP istransferred to cysteine residue and the reactions 2-6 are repeated 6 more times. Each time, the fatty acid chain is lengthened by a two-carbon unit (obtained from malonyl CoA). At the end of7 cycles, the fatty acid synthesis is complete anda 16-carbon fully saturated fatty acid—namely palmitate—bound to ACP is produced.
7. The enzyme palmitoyl thioesterase separates palmitate from fatty acid synthase. This Completes the synthesis of palmitate.
Summary of palmitate synthesisOf the 16 carbons present in palmitate, only two come from acetyl CoA directly. The Remaining 14 are from malonyl CoA which, inturn, is produced by acetyl CoA. The overall reaction of palmitate synthesis is summarized8 Acetyl CoA + 7 ATP + 14 NADPH + 14 H+ o Palmitate + 8 CoA + 7 ADP + 7 Pi + 6H2O

Functions of cholesterol

Cholesterol is found exclusively in animals,hence it is often called as animal sterol.The total body content of cholesterol in an adult man weighing 70 kg is

about 140 g i.e.,around 2 g/kg body weight. Cholesterol is amphipathic in nature, since it possesses both hydrophilic and hydrophobic regions in the structure.

Cholesterol is essential to life, as it performs a number of important functions

1. It is a structural component of cell membrane.
2. Cholesterol is the precursor for the synthesis of all other steroids in the body. These Include steroid hormones, vitamin D and bile acids.
3. It is an essential ingredient in the structure of lipoproteins in which form the lipids in the body are transported.
4. Fatty acids are transported to the liver as cholesteryl esters for oxidation.

Plasma cholesterol—biomedical importanceIn healthy individuals, the total plasma cholesterol is in the range of 150-200 mg/dl.

In The newborn, it is less than 100 mg/dl and rises to about 150 mg/dl within a year. Women have relatively lower plasma cholesterol which is attributed to the hormones-estrogens.Cholesterol level increases with increasing age(in women particularly after menopause), andalso in pregnancy.

Plasma cholesterol is associated with different lipoprotein fractions (LDL, VLDL and HDL).Total cholesterol can be estimated by many methods such as Libermann-Burchard reaction,Carr and Dructor method and, more recently,cholesterol oxidase method.

HDL- cholesterol can be determined after precipitating LDL andVLDL by polyethylene glycol (PEG).

VLDLcholesterol is equivalent to 1/5thof plasma triacylglycerol (TG) in a fasting state. LDL-cholesterol can be calculated from Friedewaldformula given below.

LDL-cholesterol = Total cholesterol – (HDL-cholesterol + TG/5).The above formula is not valid if TGconcentration is above 400 mg/dl.In adults, the normal LDL-cholesterol is about 80-150 mg/dl while HDL-cholesterol is around 30-60 mg/dl. Elevation in plasma HDL-cholesterol is beneficial to the body, since it protects the body from atherosclerosis and coronary heart diseases (CHD). On the

other hand, increase in LDL-cholesterol is harmful to the body as it may lead to various complications,including CHD.

DEGRADATION OF CHOLESTEROL

The steroid nucleus (ring structure) of the cholesterol cannot be metabolized in humans.Cholesterol (50%) is converted to bile acids,excreted in feces, serves as a precursor for the synthesis of steroid hormones, vitamin D,coprostanol and cholestanol. The latter two are the fecal sterols, besides cholesterol.

I. Synthesis of bile acids

The bile acids possess 24 carbon atoms, 2 or3 hydroxyl groups in the steroid nucleus and aside chain ending in carboxyl group.

The bile acids are amphipathic in nature since they possess both polar and nonpolar groups. They Serve as emulsifying agents in the intestine and actively participate in the digestion and absorption of lipids.The synthesis of primary bile acids takes place in the liver and involves a series of reactions(Fig.14.29).

The step catalysed by 7D-hydroxy-lase is inhibited by bile acids and this is the rate limiting reaction. Cholic acid and chenodeo-xycholic acid are the primary bile acids and the former is found in the largest amount in bile. In Conjugation with glycine or taurine, conjugated bile acids (glycocholic acid, taurocholic acid etc.) are formed which are more efficient in their function as surfactants. In the bile, the conjugated bile acids exist as sodium and potassium salts which are known as bile salts.

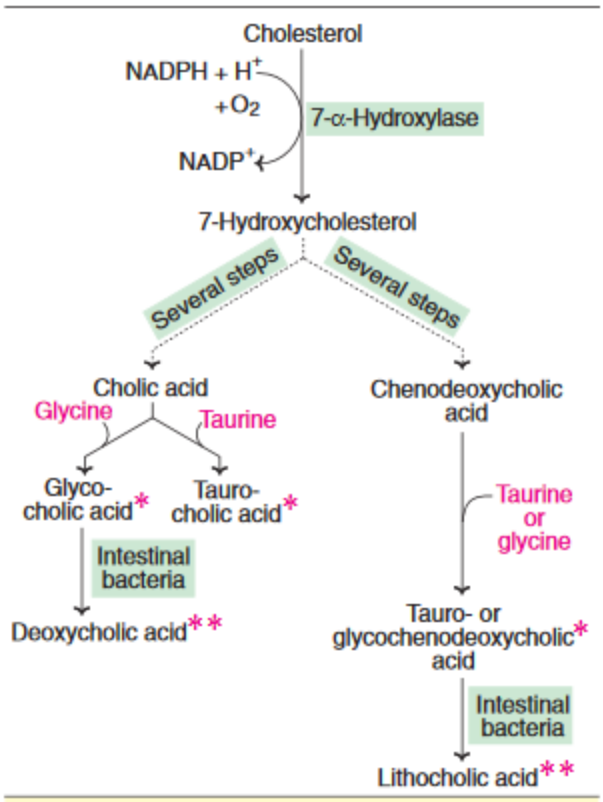


Fig. 14.29 : *Outline of bile acid synthesis (*–Primary bile acids, **–Secondary bile acids).*

In the intestine, a portion of primary bile acids undergoes deconjugation and dehydroxylation to form secondary bile acids (deoxycholic acid and lithocholic acid). These reactions are catalysed by bacterial enzymes in the intestine.

Enterohepatic circulation : The conjugated bile salts synthesized in the liver accumulate in gallbladder. From there they are secreted into the small intestine where they serve as emulsifying agents for the digestion and absorption of fats and fat soluble vitamins. A Large portion of the bile salts (primary and secondary) are reabsorbed and returned to the liver through portal vein. Thus the bile salts are recycled and reused several times in a day. This Is known as enterohepatic circulation. About 15-30 g of bile salts are secreted into the intestine each day and reabsorbed. However, a small portion of about 0.5 g/day is lost in the feces. An Equal amount (0.5 g/day) is synthesized in liverto replace the lost bile salts. The fecal excretion of bile salts is the only route for the removal of cholesterol from the body.

Cholelithiasis : Bile salts and phospholipids are responsible for keeping the cholesterol in bile in a soluble state. Due to their deficiency(particularly bile salts), cholesterol crystalsprecipitate in the gall bladder often resulting incholelithiasis—cholesterol gall stone disease.Cholelithiasis may be due to defective absorption of bile salts from the intestine, impairment in liver function, obstruction of biliary tract etc.The patients of cholelithiasis respond to the administration of bile acid chenodeoxycholic acid, commonly known as chenodiol. It is believed that a slow but gradual dissolution of stones occurs due to chenodiol. For severe cases of cholelithiasis, surgical removal of gallbladder is the only remedy.

II. Synthesis of steroid hormones from cholesterolCholesterol is the precursor for the synthesis of all the five classes of steroid hormones

(a) Glucocorticoids (e.g. cortisol)
(b) Mineralocorticoids (e.g. aldosterone)
(c) Progestins (e.g. progesterone)
d) Androgens (e.g. testosterone)
(e) Estrogens (e.g. estradiol).

A brief outline of steroid hormone synthesis is given in Fig.14.30 and more details are discussed under ‘Hormones’

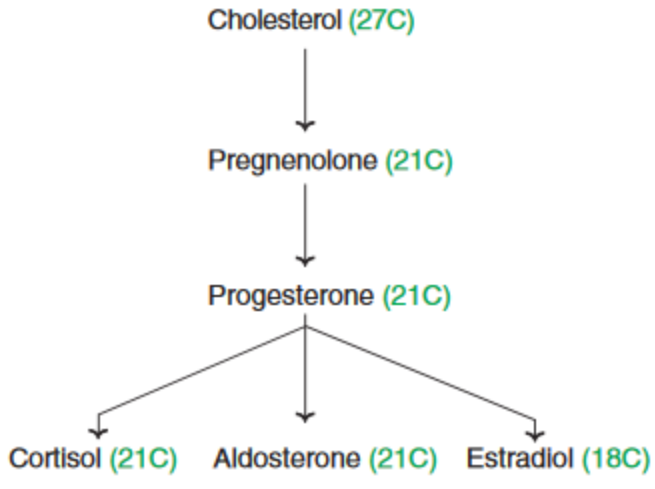


Fig. 14.30 : *Outline of steroid hormone synthesis from cholesterol (Numbers in the brackets represent the number of carbon atoms).*

III. Synthesis of vitamin D

7-Dehydrocholesterol, an intermediate in the synthesis of cholesterol, is converted to chole-calciferol (vitamin D3) by ultraviolet rays in the skin.A brief summary of prominent sources and the major pathways for utilization of cholesterol with the liver as the central metabolic organ is depicted in Fig.14.31.

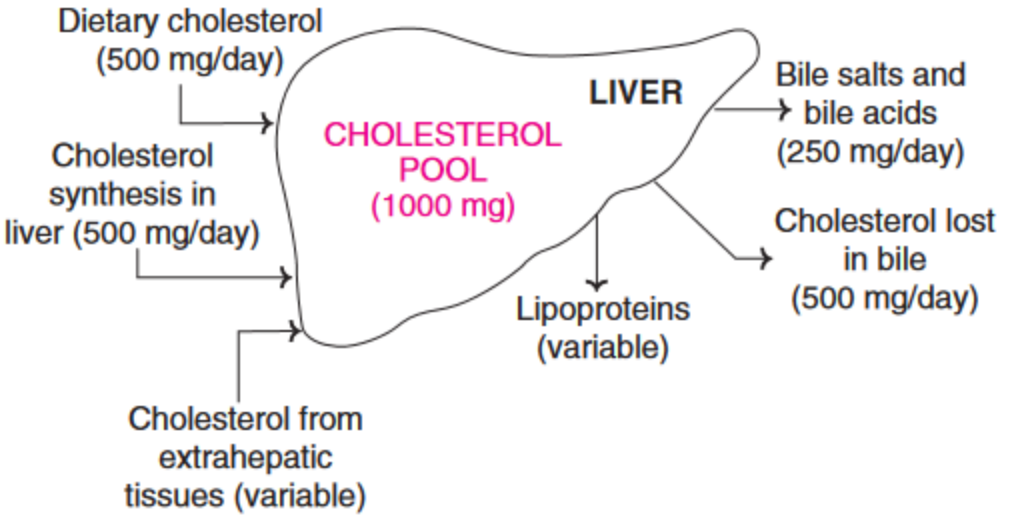


Fig. 14.31 Summary of major sources of liver cholesterol and its utilization (values given in brackets are variable).

Disorders of lipid metabolism:

HYPERCHOLESTEROLEMIA

Increase in plasma cholesterol (> 200 mg/dl)concentration is known as hypercholesterolemia and is observed in many disorders

1.Diabetes mellitus : Due to increased cholesterol synthesis since the availability of acetyl CoA is increased

2.Hypothyroidism (myxoedema) : This is believed to be due to decrease in the HDLreceptors on hepatocytes.

3.Obstructive jaundice : Due to an obstruction in the excretion of cholesterol through bile.

4.Nephrotic syndrome : Increase in plasma globulin concentration is the characteristic feature of nephrotic syndrome. Cholesterol Elevation is due to increase in plasma lipoprotein fractions in this disorder.Hypercholesterolemia is associated with atherosclerosis and coronary heart disease(CHD). More specifically, LDL-cholesterol is positively correlated, whereas HDL-cholesterol is negatively correlated with CHD.

Bad cholesterol and good cholesterol : Cholesterol is a natural metabolite performing awide range of functions (membrane structure,precursor for steroid hormones, bile acids). The usages good and bad to cholesterol, although inappropriate, are still in use. The cholesterol in high concentration, present in LDL, is considered bad due to its involvement in atherosclerosis related complications. Thus, LDL may be regarded as lethally dangerous lipoprotein. Small Dense LDL (sdLDL) is considered to be the most dangerous fraction of LDL associated with CHD.On the other hand, HDL cholesterol is good since its high concentration counteracts atherogenesis. HDL may be considered as highly desirable lipoprotein.

Effects of lifestyles on serum cholesterol level : Individual lifestyles and habits certainly influence serum cholesterol, and thus play a significant role in the development of coronary heart disease. The parameters such as high blood pressure, emotional stress, smoking, drinking of soft water (against hard water), coffee drinking,lack of exercise, obesity (particularly of abdomen)elevate serum cholesterol level.Control of hypercholesterolemiaSeveral measures are advocated to lower the plasma cholesterol level.

1.Consumption of PUFA : Dietary intake of polyunsaturated fatty acids (PUFA) reduces the plasma cholesterol level. PUFA will help in transport of cholesterol by LCAT mechanism(described earlier) and its excretion from the body. The oils with rich PUFA content include cottonseed oil, soya bean oil, sunflower oil, corn oil, fish oils etc. Ghee and coconut oil are poor sources of PUFA.

2.Dietary cholesterol : Dietary cholesterol influence on plasma cholesterol is minimal.However, avoidance of cholesterol-rich foods is advocated, and a dietary

intake of <300 mg/day is advised. Certain drugs (e.g. ezetimibe) inhibit intestinal cholesterol absorption.

3.Plant sterols : Certain plant sterols and their esters (e.g. sitostanol esters) reduce plasma cholesterol levels. They inhibit the intestinal absorption of dietary cholesterol.

4.Dietary fiber : Fiber present in vegetables decreases the cholesterol absorption from the intestine.

5.Avoiding high carbohydrate diet : Diets Rich in carbohydrates (e.g. sucrose) should be avoided to control hypercholesterolemia.

6.Impact of lifestyles : Elevation in plasma cholesterol is observed in people with smoking,abdominal obesity, lack of exercise, stress, high blood pressure, consumption of soft water etc.Therefore, adequate changes in the lifestyles will bring down plasma cholesterol.

7.Moderate alcohol consumption : The Beneficial effects of moderate alcohol intake are masked by the ill effects of chronic alcoholism.Red wine is particularly beneficial due to its antioxidants, besides low alcohol content.

8.Use of drugs : Drugs such as lovastatin which inhibit HMG CoA reductase and decrease cholesterol synthesis are used. Statins currently in use include atorvastatin, simvastatin,fluvastatin and pravastatin. Statins are usually taken at night to ensure maximum effect (HMGCoA reductase activity at peak about 6 hours after dark). Certain drugs—cholestyramine and colestipol—bind with bile acids and decrease their intestinal reabsorption. This helps in the conversion of more cholesterol to bile acids and its excretion through feces. Clofibrate increases the activity of lipoprotein lipase and reduces the plasma cholesterol and triacylglycerols.

FATTY LIVER

The normal concentration of lipid (mostly phospholipid) in the liver is around 5%. Liver is not a storage organ for fat, unlike adipose tissue.However, in certain conditions, lipids—especially the triacylglycerols—accumulate excessively in the liver, resulting in fatty liver(Fig.14.37). In the normal liver, Kupffer cells contain lipids in the form of droplets. In fatty liver, droplets of triacylglycerols are found in the entire cytoplasm of hepatic cells. This causes impairment in metabolic functions of the liver. Fattyliver is associated with fibrotic changes and cirrhosis, Fatty liver may occur due to two main causes.

1. Increased synthesis of triacylglycerols
2. Impairment in lipoprotein synthesis.

1.Increased triacylglycerol synthesis :Mobilization of free fatty acids from adipose tissue and their influx into liver is much higher than their utilization.

This leads to the overproduction of triacylglycerols and their accumulation in the liver. Diabetes mellitus,starvation, alcoholism and high fat diet associated with increased mobilization of fatty acids that often cause fatty liver. Alcohol also inhibits fatty acid oxidation and, thus, promote fat synthesis and its deposition

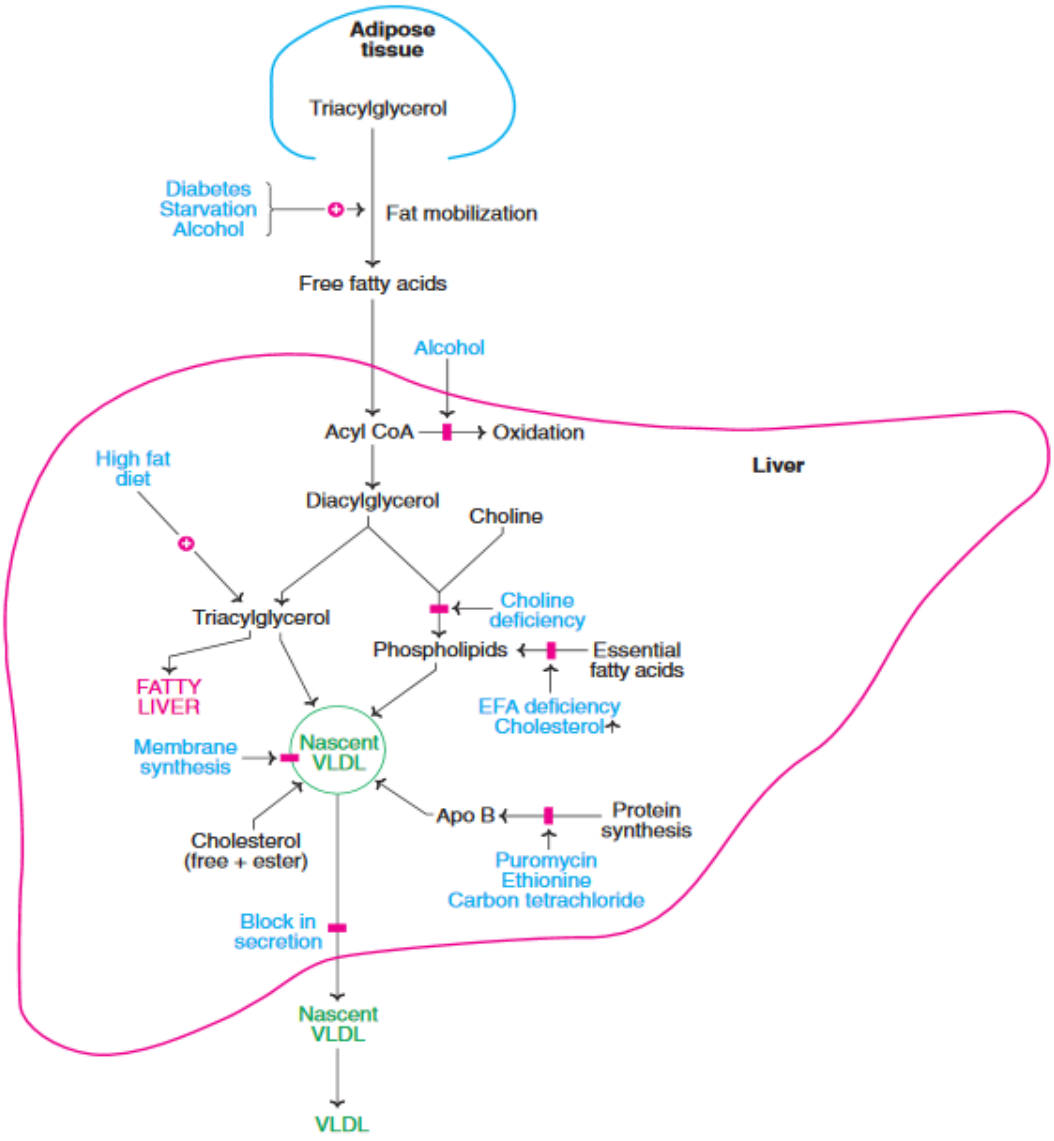


Fig. 14.37 : Development of fatty liver along with responsible factors.

2.Impaired synthesis of lipoproteins : The Synthesis of very low density lipoproteins (VLDL)actively takes place in the liver. VLDL formation requires phospholipids and apoprotein B. Fatty Liver caused by impaired lipoprotein synthesis may be due to :

- ❖ a defect in phospholipid synthesis;
- ❖ a block in apoprotein formation;
- ❖ a failure in the formation/secretion of lipo-protein.

Among the three causes, fatty liver due to impairment in phospholipid synthesis has been studied in some detail. This is usually associated with the dietary deficiency of lipotropic factors such as choline, betaine, inositol etc. (more details given later). Deficiency of essential fatty acids leads to a decreased formation of phospholipids. Further, excessive consumption of cholesterol competes with essential fatty acids and impairs phospholipid synthesis.

Certain chemicals (e.g. puromycin, ethionine,carbon tetrachloride, chloroform, lead,phosphorus etc.) that inhibit protein synthesis cause fatty liver. This is due to a blockade in the synthesis of apoprotein B required for VLDLproduction.

Lipoprotein synthesis and their secretion require ATP. Decrease in the availability of ATP,sometimes found in pyridoxine and pantothenic acid deficiency, impairs lipoprotein formation.The action of ethionine in the development of fatty liver is believed to be due to a reduction in the availability of ATP. Ethionine competes with methionine and traps the available adenosine(s adenosylmethionine)—thereby reducing ATPlevels.

Deficiency of vitamin E is associated with fatty liver. Selenium acts as a protective agent in such a condition.
Endocrine factors : Certain hormones likeACTH, insulin, thyroid hormones, adreno-corticoids promote deposition of fat in the liver.

OBESITY

Obesity is an abnormal increase in the body weight due to excessive fat deposition.Nutritional basisMen and women are considered as obese iftheir weight due to fat (in adipose tissue),respectively, exceeds more than 20% and 25%of body weight. Obesity is basically a disorder of excess calorie intake, in simple language—overeating. It has to be remembered that every 7calories of excess consumption leads to 1 g fat deposit and increase in body weight.Overeating—coupled with lack of physical exercise—contribute to obesity.Obesity due to virus infection : It was found that around 15% of people weighing more than120 kg had antibodies to adenovirus-36 in their blood,

implying that this virus infection(causes cold, diarrhea etc.), by an unknown mechanism contributes to obesity. Surprisingly,adenovirus-36 infected individuals have normal serum cholesterol and other lipid parameters.

Body mass index (BMI)Clinical obesity is represented by body mass index. BMI is calculated as the weight (in kilograms) divided by the height (in meters2).

$$\text{BMI (kg/m}^2\text{)} = \frac{\text{Weight (kg)}}{\text{[height (m)}^2\text{]}}$$

Healthy reference range for BMI is between 8.5–24.9 kg/m^2.

Grade I obesity or overweight – BMI 25–30 kg/m^2

Grade II or clinical obesity – BMI > 30 kg/m^2

Grade III or morbid obesity – BMI > 40 kg/m^2

Obesity is associated with many health complications e.g. type II diabetes, CHD,hypertension, stroke, arthritis, gallbladder disease.

In recent years, the ratio between waist and hip sizes (for men < 0.9 and for women < 0.85)is considered as more effective than BMI,particularly with regard to the risk of heart diseases. The lower is the waist to hip ratio, the lower the risk for health complications, and therefore better is the health.

Genetics, obesity and leptin

There is strong evidence to suggest that obesity has a genetic basis. Thus, a child born totwo obese people has about 75% chances ofbeing obese. One gene namely ob gene,expressed in adipocytes (of white adipose tissue)producing a protein called leptin (mol. wt.16,000 daltons), is associated with obesity.Leptin is regarded as a body weight regulatory hormone. It binds to a specific receptor in the brain and functions as a lipostat.When the fat stores in the adipose tissue are adequate, leptin levels are high. This signals to restrict the feeding behaviour and limit fat deposition. Further, leptin stimulates lipolysis and inhibits lipogenesis. Any genetic

defect in leptin or its receptor will lead to extreme overeating and obesity. Treatment of such obeseindividuals with leptin has been shown to reverse obesity. During starvation, leptin levels fall which promote feeding, and fat production and its deposition.
Obesity and adipose tissueObesity is due to an increase in both the number and size of adipocytes (of adipose tissue). There are two types of adipose tissues

1.White adipose tissue : The fat is mostly stored and this tissue is metabolically less active.
2.Brown adipose tissue : The stored fat is less but the tissue is metabolically very active.
Brown adipose tissue possesses a high proportion of mitochondria and cytochromes butlow activity of ATP synthase. This is an active centre for the oxidation of fat and glucose and is responsible for the diet-induced thermogenesis.

The peculiarity of mitochondria of brown adipose tissue is that the oxidation and phosphorylation are not coupled. Mitochondrial Oxidation produces more heat and less ATP.A specific protein—namely thermogenin—has been isolated in the inner membrane of the mitochondria. Thermogenin functions like an uncoupler and dissipates the energy in the form of heat, and thus blocks the formation of ATP.

Brown adipose tissue is mostly found in hibernating animals, and the animals exposed to cold, besides the newborn. In adult humans,though not a prominent tissue, it is located in the thoracic region. It is significant to note that brown adipose tissue is almost absent in obesepersons. Some individuals are fortunate to have active brown adipose tissue. They eat and liberateit as heat, and therefore do not become obese.

Pharmacological treatment of obesity : Inrecent years, synthetic lipids such as Olestra andOrlistat are used to treat obesity. They taste like natural lipids but cannot be digested, and excreted unchanged.

ATHEROSCLEROSIS

Atherosclerosis (Greek: athere—mush) is a complex disease characterized by thickening or hardening of arteries due to the accumulation of lipids (particularly cholesterol, free, andesterified) collagen, fibrous tissue, proteoglycans,calcium deposits etc. in the inner arterial wall.Atherosclerosis is a progressive disorder that narrows and ultimately blocks the arteries.Infarction is the term used to indicate the stoppage of blood flow resulting in the death of affected tissue. Coronary arteries—the arteries supplying blood to heart—are the most commonly affected leading to myocardial infarction or heart attacks.

Causes of atherosclerosis and CHD : The Development of atherosclerosis and the risk for.
Coronary heart disease (CHD) is directly correlated with plasma cholesterol and LDL. On The other hand, plasma HDL is inversely correlated with CHD.

Disorders that may cause atherosclerosis

Certain diseases are associated with atheros-clerosis. These include diabetes mellitus,hyperlipoproteinemias, nephrotic syndrome,hypothyroidism etc. Many other factors like obesity, high consumption of saturated fat,excessive smoking, lack of physical exercise,hypertension, stress etc., are the probable causes of atherosclerosis.

Relation between HDL and CHD

The increased levels of plasma HDL (good cholesterol) are correlated with a low incidence of cardiovascular disorders. Women have higherHDL and are less prone to heart disease compared to men. This is attributed to estrogen in women. Strenuous physical exercise,moderate alcohol intake, consumption of unsaturated fatty acids (vegetable and fish oils),reduction in body weight—all tend to increase HDL levels and reduce the risk CHD (see hyper-cholesterolemia, p-315).

Lipoprotein a and CHD

Lipoprotein a (Lp-a) is almost identical in structure to LDL. Lp-a contains an additional apoprotein, apo-a. Lp-a inhibits fibrinolysis.Recent studies have shown that elevation of lipoprotein-a in the plasma (>30 mg/dl) suggests increased risk of CHD. It is hypothesized that elevated Lp-a reduces the breakdown of blood clots by interfering with plasminogen activation.This results in intravascular thrombosis, an increased risk of heart attacks. Indians have higher levels of Lp-a compared to Westernpopulation.

Antioxidants and atherosclerosis

Antioxidants, in general, decrease the oxidation of LDL. There is some evidence, based on epidemiological studies, that taking antioxidants (vitamins E and C or E-carotene)reduces the risk of atherosclerosis, and CHD.