Al-Mustaqbal University

جامعة المستقبل
AL MUSTAQBAL UNIVERSITY

College of Medical and Health Techniques

Medical Laboratories Techniques Department

Biochemistry Lectures for 2nd Year Students

(2 Credit Hrs. Theory + 2 Credit Hrs. Practice / Week = 3 Credit Unit

Academic Year: 2024 - 2025

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Second Semester

Lecture No. 6

Date: March, 9th, 2025

Lipid Metabolism

Metabolism of Cholesterol and Bile Acids

Objectives:

1. To study the chemical structure and biological role of cholesterol and its medical importance and various factors affecting cholesterol levels.
2. To study the metabolic pathway associated with cholesterol biosynthesis and the roles of various intermediates produced.
3. To study the regulatory mechanisms of cholesterol biosynthesis.
4. To study the metabolic roles of cytochrome P_{450} and intermediate produced in cholesterol biosynthesis.
5. To study the utilization of cholesterol and factors affecting its balance in tissues.
6. To study the catabolic products of cholesterol and bile acid biosynthesis.

Introduction:

Cholesterol is a wax-like substance found in every cell of the body. Liver naturally produces about 80% of the body's cholesterol and it is also consumed from the food sources like eggs, meat, fish and dairy products. Cholesterol, is transported in the blood in lipoproteins due to its absolute insolubility in water, serves as a stabilizing component of cell membranes and as a precursor of the various steroids. Precursors of cholesterol biosynthesis are converted to ubiquinone, dolichol, and, in the skin, to cholecalciferol, the active form of vitamin D3. Cholesterol can appear in its free, un-esterified form in the outer shell of lipoprotein macromolecules and as cholesterol esters in the lipoprotein core.

Structure and Biological Importance:

The structure of cholesterol (27-carbons) compound suggests a complex biosynthetic pathway. Cholesterol structure composed one of the steroidal compounds called cyclopentanophenanthrene nucleus, see **Figure 1.**

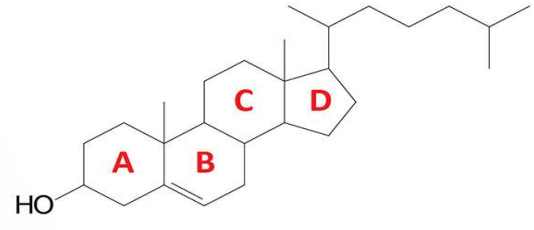

Fig. 1: Cholesterol structure

Cholesterol is an extremely important biological molecule and is most abundant steroid in human tissue (liver, 0.3%. skin, 0.3%, brain and nervous tissues, 2%, intestine, 0.2% and adrenal gland, 10%) that has roles in membrane structure as well as being a precursor for the biosynthesis of the steroid hormones, vitamin D3 and bile salts. Both dietary cholesterol (500-

700 mg/day), and that synthesized and also cholesteryl esters are transported through the circulation in lipoprotein particles (chylomicron, VLDL, LDL and HDL) in which cholesterol (free and esterified, the form in which cholesterol is stored in cells) combined with specific apo-proteins particles. Cholesterol in plasma or serum is present as free and esterified with long chain fatty acids.

Biomedical Significands:

The biosynthesis and utilization of cholesterol must be tightly regulated in order to prevent over-accumulation and abnormal deposition within the body. The clinical importance is the increased serum cholesterol levels and abnormal deposition of cholesterol and cholesterol-rich lipoproteins in the coronary arteries leading to atherosclerosis and other related diseases.

Absorption, elimination, and biosynthesis of cholesterol have been elucidated in patients with familial hypercholesterolemia, obesity, and diabetes, who are susceptible to the development of coronary artery diseases (CAD).

Functions of cholesterol:

The main biochemical functions of cholesterol include:

1. **Cell membranes:** Cholesterol is a component of membranes of cell walls and has a modulating effect on the fluid state of the membrane.
2. **Nerve conduction:** Cholesterol is used to insulate nerve fibers.
3. **Bile acids and bile salts:** Biosynthesis of digestive bile acids and bile salts in the intestine. Bile salts are important for fat absorption.
4. **Steroid hormones:** Cholesterol enables the body to synthesize glucocorticoids, androgens and estrogens.
5. Facilitate the body to biosynthesis of vitamin D3. Cholesterol is required for proper digestion and to improve immune system.

Factors Affecting the Cholesterol Levels:

Not only the dietary constituents but also several other factors can affect blood cholesterol levels, such as:

1. **Diet:** Saturated fat in the food increases the cholesterol levels.
2. **Weight:** Overweight increases the blood cholesterol.
3. **Exercise**: Regular exercise lowers the levels of LDL and raises the HDL levels.
4. **Age:** The cholesterol levels increase with age.
5. **Diabetes:** Poorly managed diabetes increases the blood cholesterol levels.
6. **Heredity:** High blood cholesterol can run in families.
7. **Other factors:** Some medications and medical conditions can cause high cholesterol levels.

Absorption of Cholesterol:

Cholesterol ester present in the diet is hydrolyzed by cholesterol-esterase. The free cholesterol is incorporated into bile salt micelle and absorbed into the mucosal cell. Absorption needs micellar formation. There is a specific protein which facilitates the transport of cholesterol into the mucosal cell from the micelle. Inside the mucosal cell, cholesterol is re-esterified and incorporated into chylomicrons. The chylomicrons reach the blood stream through lymphatics Then dietary cholesterol reaches the liver through chylomicron remnants.

Intestinal cholesterol is absorbed and transported to the liver, where it is mixed with hepatic cholesterol, followed by secretion into the circulatory lipoproteins, conversion to bile acids, or elimination in the feces by biliary secretion as cholesterol and bile acids. According to cholesterol homeostasis, cholesterol absorption and synthesis are interrelated, regulate LDL-receptor activities, and contribute accordingly to the regulation of serum cholesterol level.

Source of NADPH for Cholesterol Biosynthesis:

The oxidative reactions of the pentose phosphate pathway or HMP-shunt are the chief source of the hydrogen required for the reductive biosynthesis of each of cholesterol and fatty acids. Moreover, both metabolic pathways are found in the cytosol of the cell, so there are no membranes or permeability barriers against the transfer of NADPH + H^+. Other sources of NADPH + H^+ include the reaction that converts malate to pyruvate catalyzed by the “malic enzyme” ($NADP^+$ malate dehydrogenase) **(see Figure 2)** and the extramitochondrial isocitrate dehydrogenase reaction.

Sources of Acetyl-CoA for Cholesterol Biosynthesis:

The acetyl-CoA utilized for cholesterol biosynthesis is derived from an oxidation reaction (fatty acids or pyruvate or carbon skeleton of amino acids) in the mitochondria and is transported to the cytoplasm. Acetyl-CoA can also be synthesized from cytosolic acetate derived from cytoplasmic oxidation of ethanol which is initiated by cytoplasmic alcohol dehydrogenase (ADH). All the reduction reactions of cholesterol biosynthesis use NADPH + H^+ as a cofactor. The shuttle required for transfer of acetyl groups from mitochondria to the cytosol was indicated in **Figure 2.**

The mitochondrial outer membrane is freely permeable to all these compounds. Pyruvate derived from amino acid catabolism in the mitochondrial matrix, or from glucose by glycolysis in the cytosol, is converted to acetyl-CoA in the matrix. Acetyl groups pass out of the mitochondrion as citrate; in the cytosol they are delivered as acetyl-CoA for fatty acid synthesis. Oxaloacetate is reduced to malate, which returns to the

mitochondrial matrix and is converted to oxaloacetate. An alternative fate for cytosolic malate is oxidation by malic enzyme to generate cytosolic NADPH; the pyruvate produced returns to the mitochondrial matrix. Acetyl-CoA can also be derived from cytoplasmic oxidation of ethanol by acetyl-CoA synthetase. All the reduction reactions of cholesterol biosynthesis use NADPH + H^+ as a cofactor.

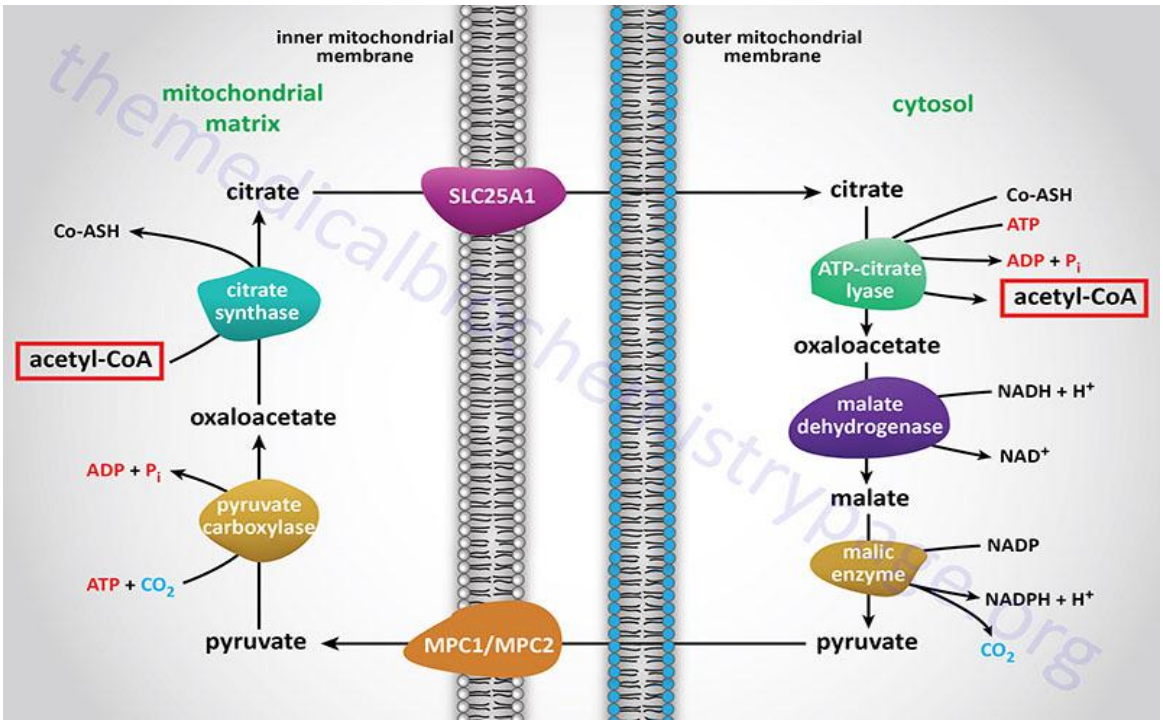

Fig. 2: Citrate-malate shuttle: Pathway for the movement of acetyl-CoA units from the mitochondrion to the cytoplasm.

Under high energy charge mitochondrial acetyl-CoA and citrate accumulate due to allosteric inhibition of the TCA cycle. Transport of citrate across the plasma membrane is catalyzed by the SLC16A1 protein (or monocarboxylic acid transporter-1, MCT1) and transport across the outer mitochondrial membrane involves a voltage-dependent porin transporter. Transport across the inner mitochondrial membrane requires a mitochondrial pyruvate carrier consisting of the MPC1 gene and encoded MPC2 proteins.

Biosynthesis of Cholesterol:

Cholesterol levels in the body come from two sources, dietary intake and biosynthesis. The majority of cholesterol utilized by healthy adults is synthesized in the liver, which produces ~70% of the total daily cholesterol requirement (~1 gm). The other 30% comes from dietary intake. All tissues in humans, although liver, intestine, adrenal cortex, and reproductive tissues including ovaries, testes and placenta make the largest contributions to the body cholesterol pool. The liver plays a central role in the regulation of the body cholesterol balance which is a series of transport, biosynthetic, and regulatory mechanism. Biosynthesis in the liver accounts for approximately 10%, and in the intestines approximately 15%, of the amount produced each

day. Cholesterol biosynthesis occurs in the cytoplasm and microsomes from the two-carbon acetate group of acetyl-CoA. It was estimated that nearly 50% of the daily cholesterol production is converted to bile acids and then bile salts and secreted in bile. Most of these were re-absorbed and re-used by way of entero-hepatic circulation. About 0.5 – 1.0 g/day is used for the biosynthesis of steroid hormones (about 40 mg/day). A small part of cholesterol (about 50 mg/day) in adult is excreted also from the surface of the skin.

Biosynthesis of cholesterol, like that of most biological lipids, begins from the two-carbon acetate group of acetyl-CoA and requires at least a total of 19 different enzymes. Several of the enzymes of cholesterol biosynthesis require NADPH + H^+ as a cofactor. **A total of 21 molecules of NADPH + H^+** are utilized for every molecule of cholesterol from acetyl-CoA synthesized.

Biosynthesis of cholesterol generally takes place in the endoplasmic reticulum of hepatic cells and begins with acetyl-CoA, which is mainly derived from an oxidation reaction in the mitochondria. Acetyl-CoA and acetoacetyl-CoA are converted to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) by HMG-CoA synthase. HMG-CoA is then converted to mevalonate by HMG-CoA reductase (HMGR). This reaction is completed with the aid of NADPH, which is used as a cofactor for all reduction reactions **see Figure 3.**

Mevalonate undergoes a series of phosphorylations and a decarboxylation yielding the isoprenoid, isopentenyl pyrophosphate (IPP). A series of condensing reactions occur, catalyzed by squalene synthase, leading to the production of squalene. From squalene, lanosterol, the first of the sterols is formed. The conversion of lanosterol to cholesterol requires 19 additional reaction steps.

HMG-CoA reductase is the target of compounds that are effective in lowering serum cholesterol levels. The process of cholesterol biosynthesis has five major steps according to each of **Figures 3:**

1. Three molecules of acetyl-CoA are condensed and converted to 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA).
2. HMG-CoA reductase catalyzed the conversion of HMG-CoA to mevalonate is the rate–limiting step in cholesterol biosynthesis in which cholesterol act as an allosteric inhibitor of gene expression of the enzyme, provides rapid feedback control of cholesterol biosynthesis within cells and also affected by different statin drugs as competitive inhibitors with mevalonate for bindings to HMG-CoA reductase (e.g. lovastatin and mevastatin which are used to decease high plasma cholesterol levels).

3. Mevalonate is converted in several enzymatic steps to isopentenyl pyrophosphate (IPP) and is the key five-carbon with the loss of CO_2. IPP is also precursors in the synthesis of coenzyme Q (ubiquinone of the oxidative phosphorylation pathway) and dolichol (used in the synthesis of N-linked glycoproteins) and another biomolecule such as vitamin E, K, side chain of heme A and carotinoids.
4. Squalene, a 30-carbon molecule is formed by several condensation reactions.
5. Conversion of squalene to cholesterol (a 27-carbon molecule) requires several reactions, some of them with unknown mechanism till now and involved the reducing equivalent NADPH and molecular oxygen (mixed – oxygenase system).

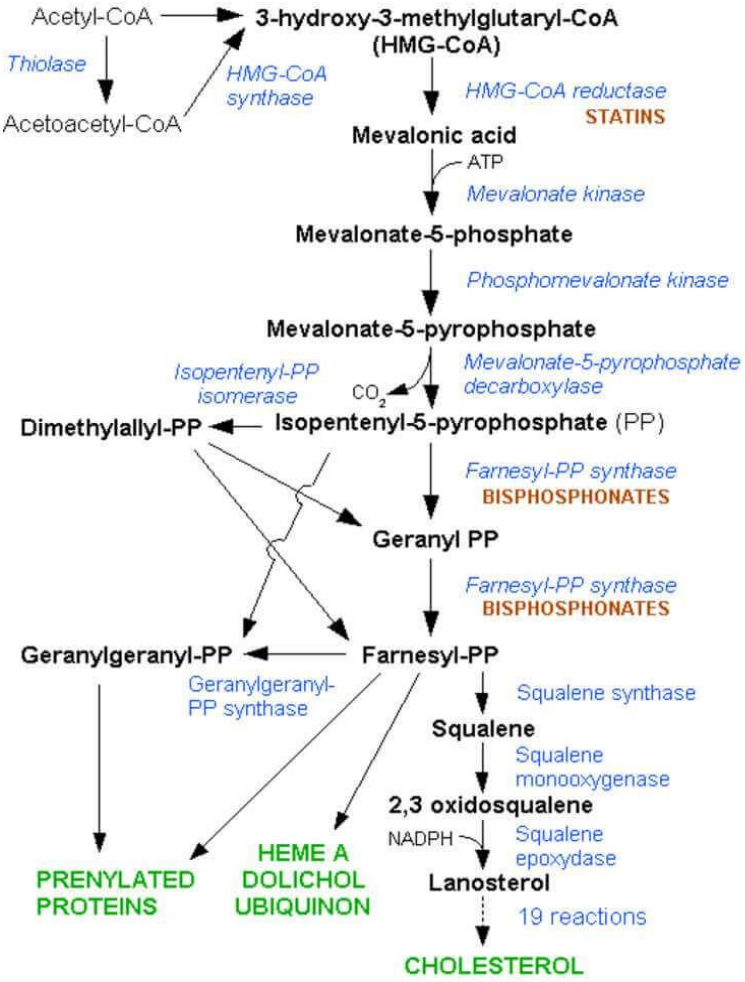

Fig. 3: Cholesterol biosynthetic pathway

The rate-limiting step occurs at the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase or HMGR catalyzed step. The phosphorylation reactions are required to solubilize the isoprenoid intermediates in the pathway.

Main Steps of Cholesterol Biosynthesis:

1. **HMG-CoA Biosynthesis:** Acetyl-CoA units are converted to mevalonate by a series of reactions that begins leading to HMG-CoA production.

Unlike the HMG-CoA formed during ketogenesis in the mitochondria, this intermediate is synthesized in the cytoplasm. Two molecules of acetyl-CoA are condensed in a reversal of the thiolase reaction, forming acetoacetyl-CoA. The cytoplasmic thiolase enzyme involved in cholesterol biosynthesis is acetyl-CoA acetyltransferase 2. Although the bulk of acetoacetyl-CoA is derived via this process, it is possible for some acetoacetate, generated during ketogenesis, to diffuse out of the mitochondria and be converted to acetoacetyl-CoA in the cytosol via the action of acetoacetyl-CoA synthetase (AACS).

2. **Mevalonate Biosynthesis:** HMG-CoA produced is then converted to mevalonate by HMG-CoA reductase bound in the endoplasmic reticulum (ER) and absolutely requires NADPH + H^+ as a cofactor and two molecules of NADPH + H^+ are consumed during the conversion of HMG-CoA to mevalonate. The reaction catalyzed by 3-hydroxy methyl glutaryl-CoA reductase (HMGR) which is the rate-controlling step of cholesterol biosynthesis, and this enzyme is subject to complex regulatory controls mechanism.
3. Mevalonate is then activated by two successive phosphorylations catalyzed by peroxisomal enzymes mevalonate kinase, and phospho-mevalonate kinase yielding, sequentially, mevalonate-5-phosphate and then mevalonate-5-diphosphate. The latter compound is also called 5-pyrophosphomevalonate or mevalonate 5-pyrophosphate.
4. **Isopentenylpyrophosphate Biosynthesis:** Following the formation of mevalonate-5-diphosphate, an ATP-dependent decarboxylation yields isopentenyl pyro-phosphate (IPP) which is an activated isoprenoid molecule. The synthesis of IPP is catalyzed by diphosphomevalonate decarboxylase Isopentenyl pyrophosphate is in equilibrium with its isomer, dimethylallyl pyrophosphate (DMAPP) via the action of isopentenyl-diphosphate delta isomerase (also called isopentenyl pyrophosphate isomerase).
5. **Squalene Biosynthesis:** One molecule of IPP condenses with one molecule of dimethylallyl pyrophosphate (DMAPP) to generate geranyl pyrophosphate, GPP which further condenses with another IPP molecule to yield farnesyl pyrophosphate (FPP). Biosynthesis of both GPP and FPP is catalyzed by the enzyme, farnesyl diphosphate synthase. The synthesis of squalene, from FPP, represents the first cholesterol/sterol-specific step in the cholesterol synthesis pathway. The synthesis of squalene is catalyzed by the NADPH-requiring enzyme called squalene synthase).

6. **Conversion of Squalene to Lanosterol:** Squalene then undergoes a two-step cyclization to yield lanosterol. The first reaction in this two-step cyclization is catalyzed by squalene monooxygenase. This enzyme uses NADPH + H^+ as a cofactor to introduce molecular oxygen as an epoxide at the 2,3 positions of squalene forming the intermediate, 2,3-oxidosqualene. In the second step, this epoxide intermediate is converted to lanosterol through the action of lanosterol synthase.
7. **Conversion of Lanosterol to 7-Dehydrocholesterol:** The actual fate of lanosterol is determined by the cell in which it is synthesized as well as by the need for various steroids other than cholesterol. There are two pathways that utilize lanosterol for the biosynthesis of sterols as indicated below:
   - **A.** One pathway is called the **Bloch pathway** which terminates with the biosynthesis of desmosterol. Desmosterol can be converted to cholesterol via the action of the NADPH-requiring enzyme, 24-dehydrocholesterol reductase.
   - **B.** The other pathway is called the **Kandutsch-Russell pathway** and this represents the major pathway for the conversion of lanosterol to 7-dehydrocholesterol in humans. Kandutsch-Russell pathway, is a series of 17 reactions converts lanosterol to 7-dehydrocholesterol and they are catalyzed by eight different enzymes that are integral membrane proteins of the endoplasmic reticulum.
8. **Conversion of Dehydrocholesterol to Cholesterol:** The terminal reaction in cholesterol biosynthesis is catalyzed by the NADPH-dependent enzyme, 7-dehydrocholesterol reductase (DHCR7). Deficiency in activity of this enzyme (due to gene mutations) results reduced levels (15% to 27% of normal) of cholesterol resulting in multiple developmental malformations and behavioral problems.

Regulation of Cholesterol Biosynthesis:

A relatively constant level of cholesterol in the body (150 - 200 mg/dL) is maintained primarily by controlling the level of *de novo* biosynthesis. The level of cholesterol synthesis is regulated in part by the dietary intake of cholesterol. Cholesterol from both diet and synthesis is utilized in the formation of membranes and in the synthesis of the steroid hormones and bile acids. The greatest proportion of cholesterol is used in bile acid synthesis (50%). HMG-CoA reductase is the major control point for cholesterol biosynthesis and is subject to different kinds of metabolic control. The cellular supply of cholesterol is maintained at a steady level by three distinct mechanisms:

1. Regulation of HMG-CoA reductase activity and levels.

2. Regulation of excess intracellular free cholesterol through the activity of sterol *O*-acyltransferases or acyl-CoA: cholesterol acyltransferase (ACAT).
3. Regulation of plasma cholesterol levels via LDL receptor-mediated uptake and HDL-mediated reverse transport.

Regulation of HMG-CoA reductase activity is the primary means for controlling the level of cholesterol biosynthesis. The enzyme is controlled by four distinct mechanisms:

A. Feed-back inhibition
B. Control of gene expression
C. Rate of enzyme degradation
D. Phosphorylation-dephosphorylation.

Hormonal regulation:

The activity of HMG-CoA reductase is controlled hormonally. An increase in insulin favors dephosphorylation (activation) of the HMG-CoA *reductase*, whereas an increase in glucagon and epinephrine has the opposite effect. Insulin or thyroid hormone increases HMG-CoA reductase activity, whereas glucagon, cortisol or glucocorticoids decrease its activity. Activity is reversibly modified by phosphorylation-dephosphorylation mechanisms, some of which may be cAMP-dependent and therefore immediately responsive to glucagon.

Diet and Cholesterol Levels:

Attempts to lower plasma cholesterol in humans by reducing the amount of cholesterol in the diet produce variable results. The ability of insulin to stimulate, and glucagon to inhibit, HMG-CoA reductase activity is consistent with the effects of these hormones on other metabolic pathways. The basic function of these two hormones is to control the availability and delivery of energy to all cells of the body. Generally, a decrease of 100 mg in dietary cholesterol causes a decrease of approximately 0.13 mmol/L of serum.

Reductions in circulating cholesterol levels can have profound positive impacts on cardiovascular disease, particularly on atherosclerosis, as well as other metabolic disruptions of the vasculature. Control of dietary intake is one of the easiest and least cost intensive means to achieve reductions in cholesterol. It was observed that reductions in dietary cholesterol not only resulted in decreased serum VLDL and LDL, and increased HDL but DNA synthesis was also shown to be increased in the thymus and spleen. Upon histological examination of the spleen, thymus and lymph nodes it was found that there was an increased number of immature cells and enhanced mitotic activity indicative of enhanced proliferation. These results suggest that a

marked reduction in serum LDL, induced by reduced cholesterol intake, stimulates enhanced DNA synthesis and cell proliferation.

Effect of Drugs on Cholesterol Levels:

Drug treatment to lower plasma lipoproteins and/or cholesterol is primarily aimed at reducing the risk of atherosclerosis and subsequent coronary artery disease that exists in patients with elevated circulating lipids. Drug therapy usually is considered as an option only if non-pharmacologic interventions (altered diet and exercise) have failed to lower plasma lipids. Lovastatin and other "statin" group of drugs are used in clinical practice to reduce cholesterol level in blood. The statin drugs (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) are structural analogs of HMG-CoA and / or metabolized to reversible, competitive inhibitors of HMG-CoA reductase. They are used to decrease plasma cholesterol levels in patients with hyper-cholesterolemia.

The Utilization of Cholesterol:

Cholesterol is transported in the plasma predominantly as cholesteryl esters associated with lipoproteins. Dietary cholesterol is transported from the small intestine to the liver within chylomicrons. Cholesterol synthesized by the liver, as well as any dietary cholesterol in the liver that exceeds hepatic needs, is transported in the serum within LDLs. The liver synthesizes VLDLs and these are converted to LDLs through the action of endothelial cell-associated lipoprotein lipase. Cholesterol found in plasma membranes can be extracted by HDLs and esterified by the HDL-associated enzyme LCAT. The cholesterol acquired from peripheral tissues by HDLs can then be transferred to VLDLs and LDLs via the action of cholesteryl ester transfer protein (apo-D) which is associated with HDLs. Reverse cholesterol transport allows peripheral cholesterol to be returned to the liver in LDLs. Ultimately, cholesterol is excreted in the bile as free cholesterol or as bile salts following conversion to bile acids in the liver.

Cholesterol Pool:

The total body cholesterol content varies from 130–150 grams. Low density lipoprotein transports cholesterol from the liver to the peripheral tissues and high-density lipoprotein transports cholesterol from tissues to liver. Cells of extrahepatic tissues take up cholesterol from LDL, **Figure 4.** The free cholesterol released within the cell has the following fates:

1. Incorporated into cell membranes.
2. Metabolized to steroid hormones, especially in adrenal cortex and gonads.
3. Esterified with saturated fatty acids and stored in the cell. The enzyme ACAT (acyl cholesterol acyl transferase) helps in this reaction.

4. Esterified with poly-unsaturated fatty acids (PUFA) by the action of LCAT (lecithin cholesterol acyl transferase) and finally excreted through liver.

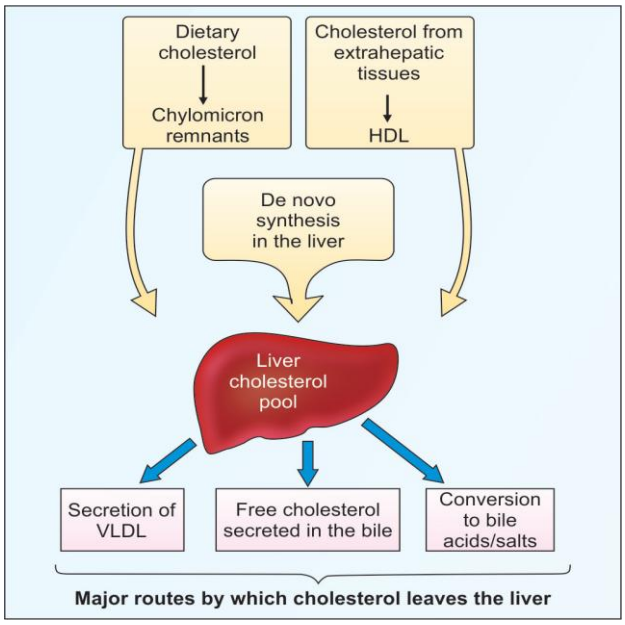

Fig. 4: Cholesterol pool in the liver

Bile Acids Biosynthesis and Utilization:

The ring structure of cholesterol cannot be metabolized to CO_2 and water in humans. Rather, the intact sterol ring is eliminated from the body by:

1. Conversion to bile acids, which are excreted in feces.
2. Secretion of cholesterol into the bile, which transports it to the intestine for elimination.

Bile salts are primarily used to emulsify fatty acids and monoacylglycerols and package them into micelles, along with fat-soluble vitamins, phospholipids and cholesteryl esters, for re-absorption by villi in the small bowel. The end products of cholesterol utilization are the bile acids, synthesized in the liver (primary bile acid; cholic and chenodeoxycholic acid), as in **Figure 5.**

Bile acids contain 24 carbons with two or three hydroxyl groups and a side chain that terminates in a carboxyl group. The bile acids are amphipathic in that all the -OH groups are in α- orientation (lie above the plane of the ring) and the methyl group are β- orientation (lie below the plane of the ring). Therefore, the molecules have both a polar and a non-polar face and can acts as emulsifying agents in the intestine, helping to prepare dietary TG and other lipids for degradation by pancreatic digestive enzymes, **Figure 5.** Biosynthesis of bile acids is one of the predominant mechanisms for the excretion of excess cholesterol.

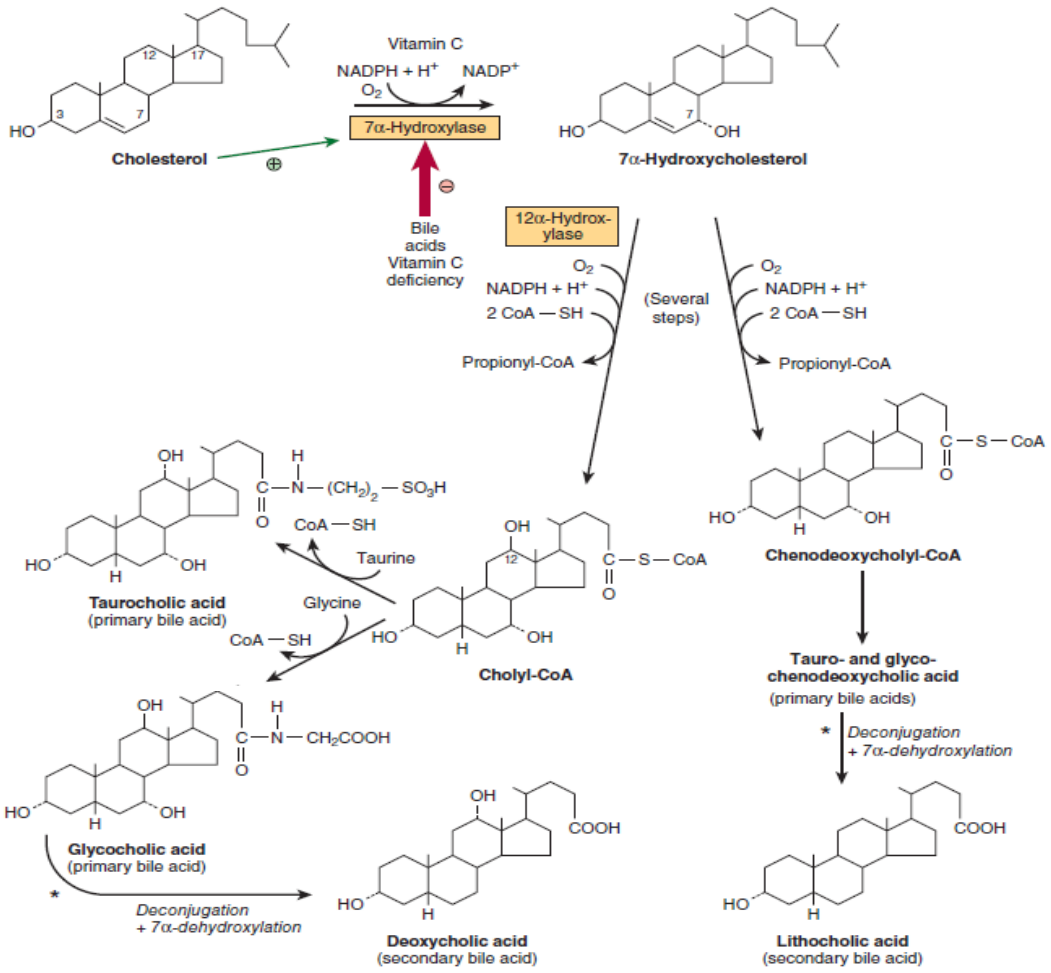

Fig. 5. Biosynthesis and degradation of bile acids. A second pathway in mitochondria involves hydroxylation of cholesterol by sterol 27-hydroxylase.

The most abundant bile acids in human bile are chenodeoxycholic acid (45%) and cholic acid (31%). These are referred to as the primary bile acids. Within the intestines the primary bile acids are acted upon by bacteria and converted to the secondary bile acids, identified as deoxycholate (from cholate) and lithocholate (from chenodeoxycholate). Both primary and secondary bile acids are reabsorbed by the intestines and delivered back to the liver via the portal circulation, **Figure 6.**

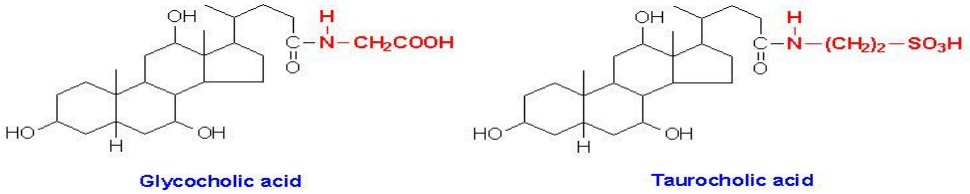

Fig. 6. Structure of the conjugated cholic acids

Within the liver the carboxyl group of primary and secondary bile acids is conjugated via an amide bond to either glycine or taurine before their being re-secreted into the bile canaliculi. Taurine is an end product of cysteine catabolism. It is abundant in the retina and the CNS and is also found in the liver. The ratio of the glycine to taurine forms in the bile is approximately (3:1) and is called bile salts. Bile salts are more effective detergents than

bile acids because of their enhanced amphipathic nature. These conjugation reactions yield glycoconjugates and tauro-conjugates, respectively. Bile acids are carried from the liver through these ducts to the gallbladder, where they are stored for future use. The ultimate fate of bile acids is secretion into the intestine, where they aid in the emulsification of dietary lipids. In the gut the glycine and taurine residues are removed and the bile acids are either excreted (only a small percentage) or reabsorbed by the gut and returned to the liver. This process of secretion from the liver to the gallbladder, to the intestines and finally re-absorption is termed the entero-hepatic circulation.

Liver and Cholesterol:

The liver has a major role in controlling the plasma levels of low-density lipoprotein-cholesterol (LDL-C), see **Figure 7.**

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

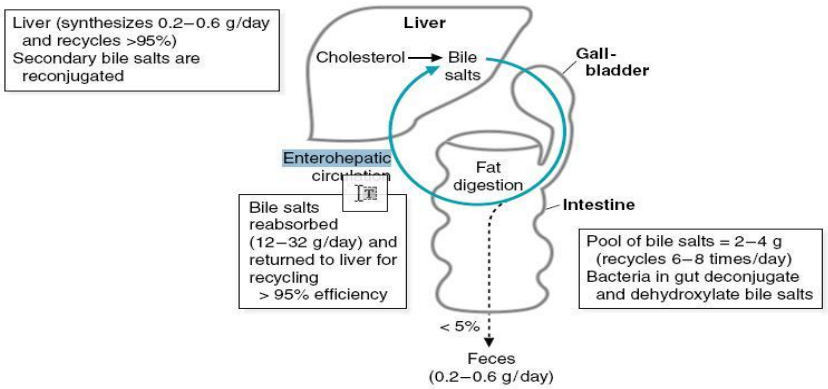

Fig. 7: An overview of bile salt metabolism.

Clinical Significance of Bile Acid Biosynthesis:

Bile acids perform four physiologically significant functions:

1. Their synthesis and subsequent excretion in the feces represent the only significant mechanism for the elimination of excess cholesterol.
2. Bile acids and phospholipids solubilize cholesterol in the bile, thereby preventing the precipitation of cholesterol in the gallbladder.
3. They facilitate the digestion of dietary triacylglycerols by acting as emulsifying agents that render fats accessible to pancreatic lipases.
4. They facilitate the intestinal absorption of fat-soluble vitamins.

The movement of cholesterol from the liver into the bile must be accompanied by the simultaneous secretion of phospholipids and bile salts. If this coupled process is disrupted and more cholesterol enters the bile than can be solubilized by the bile salts and lecithin present, the cholesterol may be precipitated in the gallbladder initiating the occurrence of cholesterol gallstone disease (the disease is called cholethiasis).