CHOLESTEROL METABOLISM

Cholesterol is the major sterol in human and has *cyclopentanoperhydrophenanthrene* ring system as a parent structure **(Figure 13.33).**

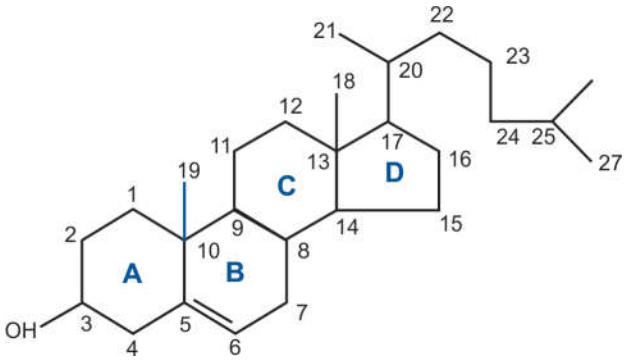

Figure 13.33: Structure of cholesterol

Cholesterol is an **amphipathic** lipid which can be synthesized by most cells of the body and it is obtained from the diet in foods of animal origin. ***It is not synthesized in plants.*** The major sources of dietary cholesterol are egg yolk and meat, particularly liver.

De Novo Synthesis of Cholesterol

Cholesterol is synthesized by a pathway that occurs in most cells of the body. *Liver* and *intestine* are major sites of cholesterol synthesis.

All 27-carbon atoms of cholesterol are derived from the **acetyl-CoA.** The enzyme system of cholesterol synthesis present in *cytosolic* and *microsomal* (endoplasmic reticulum) fractions. The reactions of cholesterol biosynthesis occurs into 5 stages **(Figures 13.34 and 13.35).**

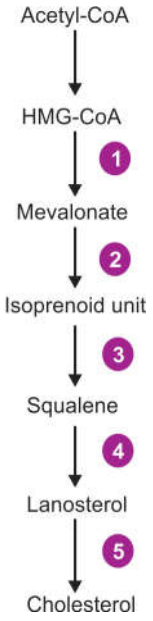

Figure 13.34: Five stages of cholesterol biosynthesis

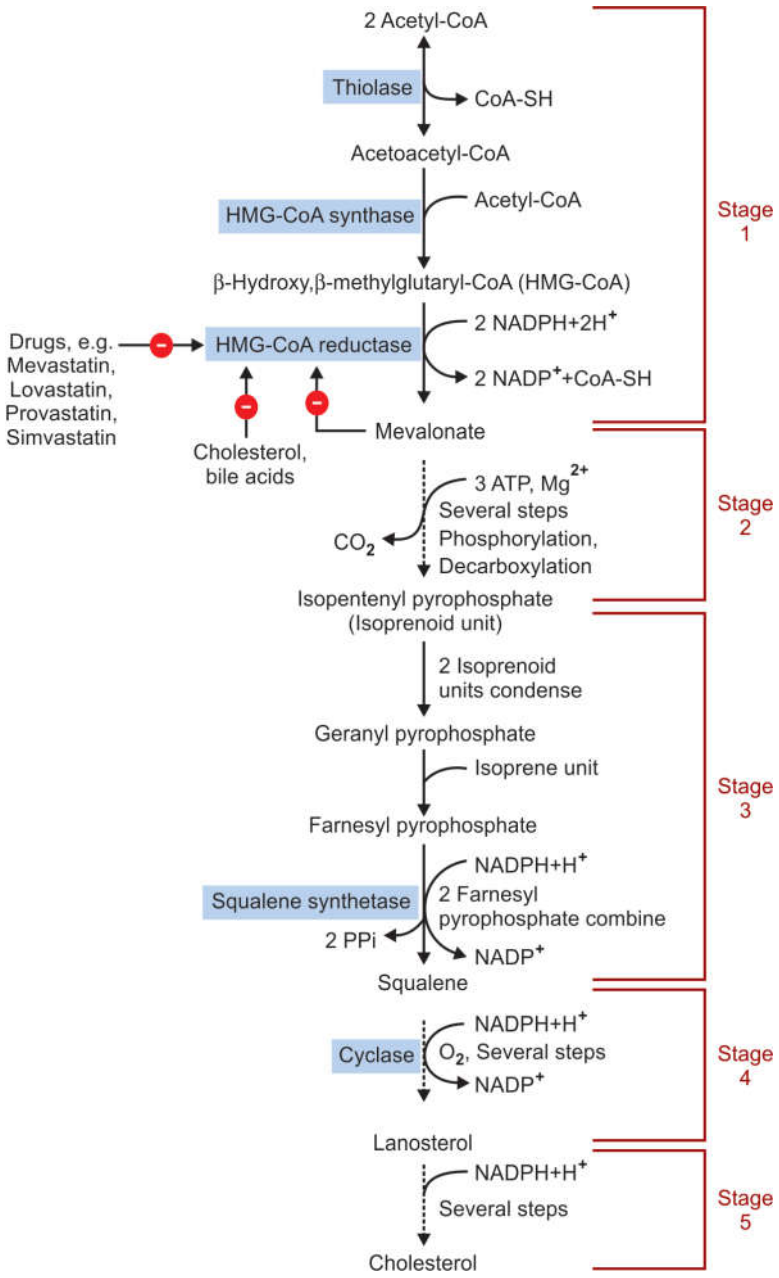

Figure 13.35: Biosynthesis of cholesterol, showing its five stages

Stage 1: Synthesis of Mevalonate from Acetyl-CoA through HMG-CoA

- First, two molecules of acetyl-CoA condense to form **acetoacetyl-CoA,** catalyzed by a cytosolic ***thiolase*** enzyme.
- Next, a third molecule of acetyl-CoA condenses with acetoacetyl-CoA catalyzed by ***HMG-CoA synthase*** *to* form **HMG-CoA.**

- This sequence of reactions in the cholesterol synthesis is similar to those for the synthesis of ketone bodies **(see Figure 13.11)** except that ketone body synthesis occurs in mitochondria and cholesterol is in the cytosol.
- The next step is catalyzed by ***HMG-CoA reductase.*** This enzyme uses two molecules of NADPH and converts HMG-CoA to **mevalonate.** This is the rate limiting step in the cholesterol synthesis.

Stage 2: Formation of Isoprenoid Unit by Decarboxylation of Mevalonate

Mevalonate is phosphorylated by ATP and subsequently decarboxylated to form a five carbon isoprene unit, ***isopentenyl pyrophosphate (IPP).***

Stage 3: Formation of squalene from condensation of six isoprenoid units

Six isopentenyl pyrophosphate molecules condense with loss of their pyrophosphate groups to yield the ***squalene*** (30-carbon atoms compound) through the formation of geranyl pyrophosphate and farnesyl pyrophosphate. ***Squalene was first isolated from the liver of sharks of genus Squalus.***

Stage 4: Cyclization of squalene to lanosterol

Squalene undergoes a series of complex enzymatic reactions, in which its linear structure is folded and cyclized to form lanosterol, which has the four condensed rings that form the steroid nucleus of cholesterol.

Stage 5: Formation of cholesterol from Lanosterol

The conversion of lanosterol to cholesterol is a multistep process, resulting in the

- Shortening of the carbon chain from 30 to 27
- Removal of the three methyl groups at C_4
- Migration of the double bond from C_8 to C_5
- Reduction of the one double bond between C_{24} and C_{25} by NADPH.

Regulation of De Novo Synthesis of Cholesterol (Figure 13.36)

HMG-CoA reductase is the rate limiting enzyme in cholesterol biosynthesis and is subjected to different kinds of metabolic control. The following are the different kinds of metabolic control.

Feedback Regulation

- *Cholesterol* the end product of the pathway, as well as ***mevalonate,*** repress the synthesis of ***HMG-CoA reductase.***
- It is also repressed by bile salts or bile acids, thus decreasing the cholesterol synthesis.

Hormonal Regulation

- Cholesterol synthesis is increased by **insulin** and **thyroid** hormone and is decreased by **glucagon** and **glucocorticoid** by stimulating and inhibiting HMG-CoA reductase enzyme respectively.

Nutritional Regulation

- Dietary cholesterol suppresses the synthesis of the HMG-CoA reductase in the liver.

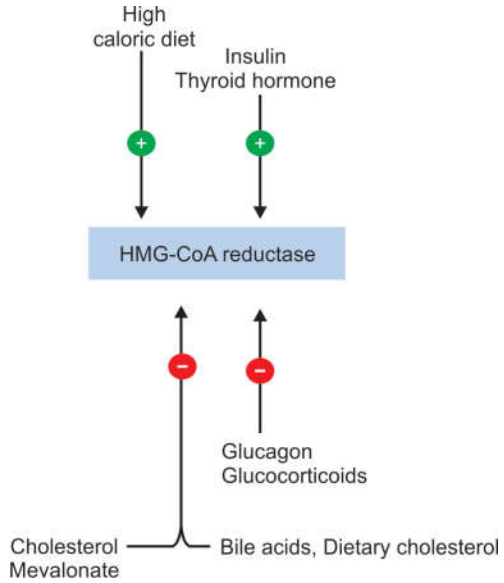

Figure 13.36: Regulation of cholesterol biosynthesis

- Increased caloric intake stimulates cholesterol synthesis primarily by increasing the availability of acetyl-CoA and NADPH.

Drugs like **mevastatin** and **lovastatin** inhibit cholesterol synthesis by acting as **competitive inhibitors** of HMG-CoA reductase. These drugs are used to decrease the serum cholesterol level in patients having elevated serum cholesterol concentration.

Transport of Cholesterol (Figure 13.37)

Transport of Dietary Cholesterol from Intestine

- After digestion, dietary cholesterol is absorbed into the intestinal mucosal cells, where much of it is subsequently reconverted into cholesterol esters.
- Cholesterol esters that are synthesized in the mucosal cells, together with some unesterified cholesterol are incorporated into ***chylomicrons,*** which transports cholesterol and other dietary lipids from intestine.
- When triacylglycerol of chylomicrons hydrolyzed by **lipoprotein lipase** in the peripheral tissue, only about 5% of the cholesterol ester is lost. The rest is taken up by the liver in the form of chylomicron remnants and is hydrolyzed to cholesterol.

Transport of Cholesterol from Liver to Peripheral Tissue

- Cholesterol from liver is transported in the form of VLDL into the plasma.
- Like chylomicrons VLDL triacylglycerol is hydrolyzed by lipoprotein lipase in the peripheral tissues and results with formation of cholesterol rich LDL.
- LDL cholesterol is taken up by the liver or extra-hepatic tissues by LDL receptors.

Transport of Cholesterol from Peripheral Tissue to Liver

- HDL picks up cholesterol from the peripheral tissues and converts it to cholesterol esters by LCAT enzyme
- These cholesterol esters are ultimately returned to the liver and thus HDL is said to participate in **"reverse *cholesterol transport.*"**

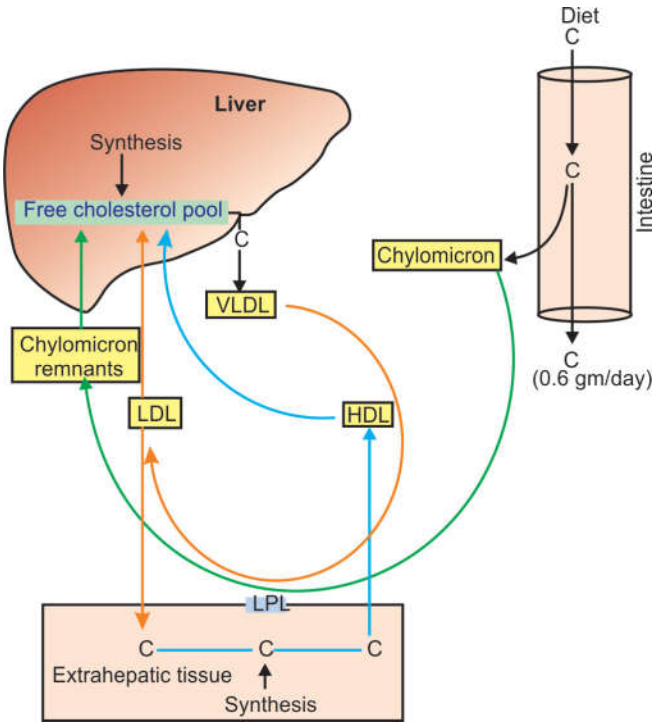

Figure 13.37: Transport of cholesterol
where, C:Cholesterol; LPL:Lipoprotein lipase

Degradation of Cholesterol

Cholesterol can undergo degradative reactions in humans with conversion of cholesterol to physiologically important products such as:

- Bile acids which is the main catabolic pathway
- Steroid hormones
- Vitamin D

Formation of Bile Acids

The primary bile acids ***cholic acid*** and ***chenodeoxycholic acid*** are synthesized in the liver from cholesterol (Figure 13.38).

Importance of bile acids

- The bile acids required for the emulsification of the dietary lipids and facilitate the enzymatic digestion and absorption of dietary lipids.
- Conversion of cholesterol into bile acid in the liver prevents the body from becoming overloaded with cholesterol.
- As steroidal ring of cholesterol cannot be degraded in the body, the excretion of bile salts serves as a major route for removal of the steroid ring from the body.

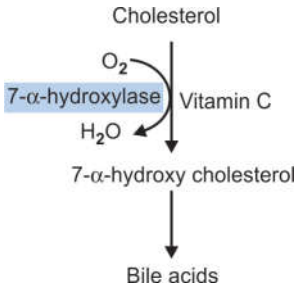

Figure 13.38: Synthesis of bile acid and its regulation

Formation of Steroid Hormones (Figure 13.39)

Cholesterol is the precursor of the five classes of steroid hormones:

1. Progesterone
2. Glucocorticoids
3. Mineralocorticoids
4. Sex hormones androgens
5. Estrogens.

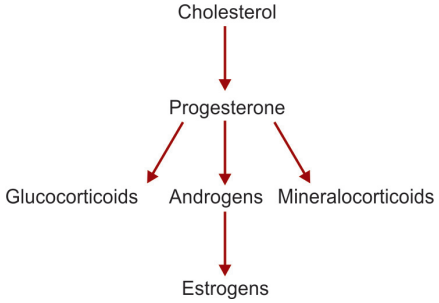

Figure 13.39: Formation of steroid hormones from cholesterol

Formation of Vitamin D

Cholesterol is also the precursor of vitamin D **(Figure 13.40)** which regulates calcium and phosphorus metabolism.

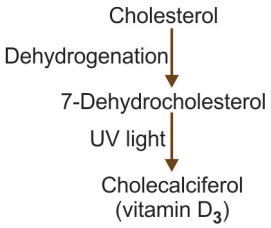

Figure 13.40: The formation of vitamin D_3 from cholesterol

Excretion of Cholesterol

- Cholesterol is excreted in feces
- Unlike many other metabolites, cholesterol cannot be destroyed by oxidation to CO_2 and H_2O, because of absence of enzymes capable of catabolizing the steroid ring.
- It is excreted in the bile either as cholesterol or after conversion to bile acids. About 1 gm of cholesterol is eliminated from the body per day. Roughly, half is excreted in the form of bile acids and half is in the form of cholesterol.
- Moreover, some dietary cholesterol is excreted in feces without being absorbed.
- Some of the cholesterol in the intestine is acted on by intestinal bacterial enzymes and converted to neutral sterols, coprostanol, cholestanol and excreted through feces.

Blood Cholesterol

The normal total plasma cholesterol lies between **150–250 mg per 100 ml.** Cholesterol present in blood occurs both free and as ester form. The hydroxyl group at position three of cholesterol can be esterified with fatty acids producing cholesterol esters. About 70% of the plasma cholesterol is esterified with fatty acids to form cholesterol ester, remaining 30% is free cholesterol.

Good cholesterol and bad cholesterol

- HDL cholesterol is considered to be the good cholesterol, because it removes excess cholesterol from peripheral tissues and transport it to the liver where it is degraded or excreted in the bile. HDL thus tends to lower blood cholesterol level.
- On the other hand LDL cholesterol is called bad cholesterol, because it transports cholesterol from liver

Contd.

to the peripheral tissue. Whereas for excretion, cholesterol must enter the liver **(Figure 13.37).** The risk of coronary heart disease (CHD) is related to plasma levels of total cholesterol and LDL-cholesterol.

Hypercholesterolemia

In a normal adult, the total plasma cholesterol ranges form **150–250 mg/100 ml.** An increase in plasma cholesterol more than 250 mg/100 ml is known as **hypercholesterolemia** and is seen in the following conditions:

1. **Diabetes mellitus:** This is due to deficiency of insulin, rate of lipolysis is increased. Increased rate of lipolysis results in more release of free fatty acids in circulation which increases acetyl-CoA. Excess of acetyl-CoA are diverted for cholesterol biosynthesis.
2. **Hypothyroidism:** This is due to decrease in the **HDL receptors** on hepatocyte in hypothyroidism and due to decreased synthesis of **7-α-hydroxylase** that requires for the conversion of cholesterol to bile acids. Thyroid hormone induces the synthesis of 7-α-hydroxylase.
3. **Obstructive jaundice:** Due to decreased excretion of cholesterol through bile.
4. **Familial hypercholesterolemia:** It is a genetic disease caused by deficiency or malfunction of the LDL receptors. In the absence of these receptors, the liver cannot take LDL and there is no release of cholesterol of LDL into the liver. Therefore, they do not cause feedback inhibition of cholesterol synthesis and lead to increased cholesterol formation.

ATHEROSCLEROSIS

High level of serum cholesterol results in atherosclerosis. The **atherosclerosis** is characterized by hardening and narrowing of the arteries due to deposition of cholesterol and other lipids in the inner arterial wall. Deposition of cholesterol and other lipids in the inner arterial wall leads to formation of plaque (sticky deposite) and results in the endothelial damage and norrowing of the arterial lumen. The hardening and narrowing of coronary arteries results in coronary heart disease (CHD).

Factors responsible for development of atherosclerosis

Age

Aging brings about changes in the blood vessel wall due to decreased metabolism of cholesterol. As age advances, the elasticity of the vessel wall decreases and formation of plaques progresses. The plaques are composed of smooth muscle cells, connective tissue, lipids and debris that accumulate in the inner side of the arterial wall. Formation of plaque leads to narrowing of the lumen and invites atherosclerosis.

Sex
Males are affected more than females, female incidence increases after menopause. Suggesting that male sex hormone might be atherogenic or conversely that female sex hormones might be protective.

Genetic factor
Hereditary genetic derangement of lipoprotein metabolism leads to high blood lipid level and familial hypercholesterolemia.

Hyperlipidemia
Increased levels of the following components of plasma lipids are associated with increased risk of atherosclerosis

- Total serum cholesterol and triacylglycerol.
- Low density lipoprotein (LDL) is richest in cholesterol and deposits it in tissues and has maximum association with atherosclerosis.
- **Lipoprotein(a) (LPa):** Some people have a special type of abnormal LDL called LP(a) containing an additional protein, ***apoprotein-a.*** Elevated LPa levels are associated with an increased risk of coronary heart disease.

Level of HDL
Low level of HDL is associated with atherosclerosis. HDL has protective effect against atherosclerosis. HDL participates in reverse transport of cholesterol, i.e. it transports cholesterol from cells to the liver for excretion in the bile. The higher the levels of HDL, the lower is the risk of ischemic heart disease. Consequently, high ratio of HDL/LDL reduces the development of atherosclerosis. There is an inverse relationship between cardiovascular risks and HDL concentration.

Hypertension
Hypertension is the major risk factor in patients over 45 years of age. It acts probably by mechanical injury of the arterial wall due to increased blood pressure.

Cigarette smoking
Ten cigarettes per day increase the risk three-fold due to reduced level of HDL and accumulating carbon monoxide that may cause endothelial cell injury. Cessation of smoking decreases risk to normal after 1 year.

Diabetes mellitus
The risk is due to the coexistence of other risk factors such as obesity, hypertension, and hyperlipidemia.

Minor or soft risk factors
These include lack of exercise, stress, obesity, high caloric intake, diet containing large quantities of saturated fats, use of oral contraceptive, alcoholism and hyperuricemia, etc. The risk is due to increased LDL and decreased HDL levels.

Prevention of atherosclerosis

- The most important preventive measure against the development of atherosclerosis is to eat a low fat diet that contains mainly unsaturated fat with low cholesterol content.
- Natural antioxidants such as vitamin E, C or β-carotene may decrease the risk of cardiovascular disease by protecting LDL against oxidation.
- Moderate consumption of alcohol and exercise appears to have a slightly beneficial effect by raising the level of HDL.
- Drug therapy, e.g. Lovastatin, clofibrate, cholestyramine which inhibit cholesterol synthesis.