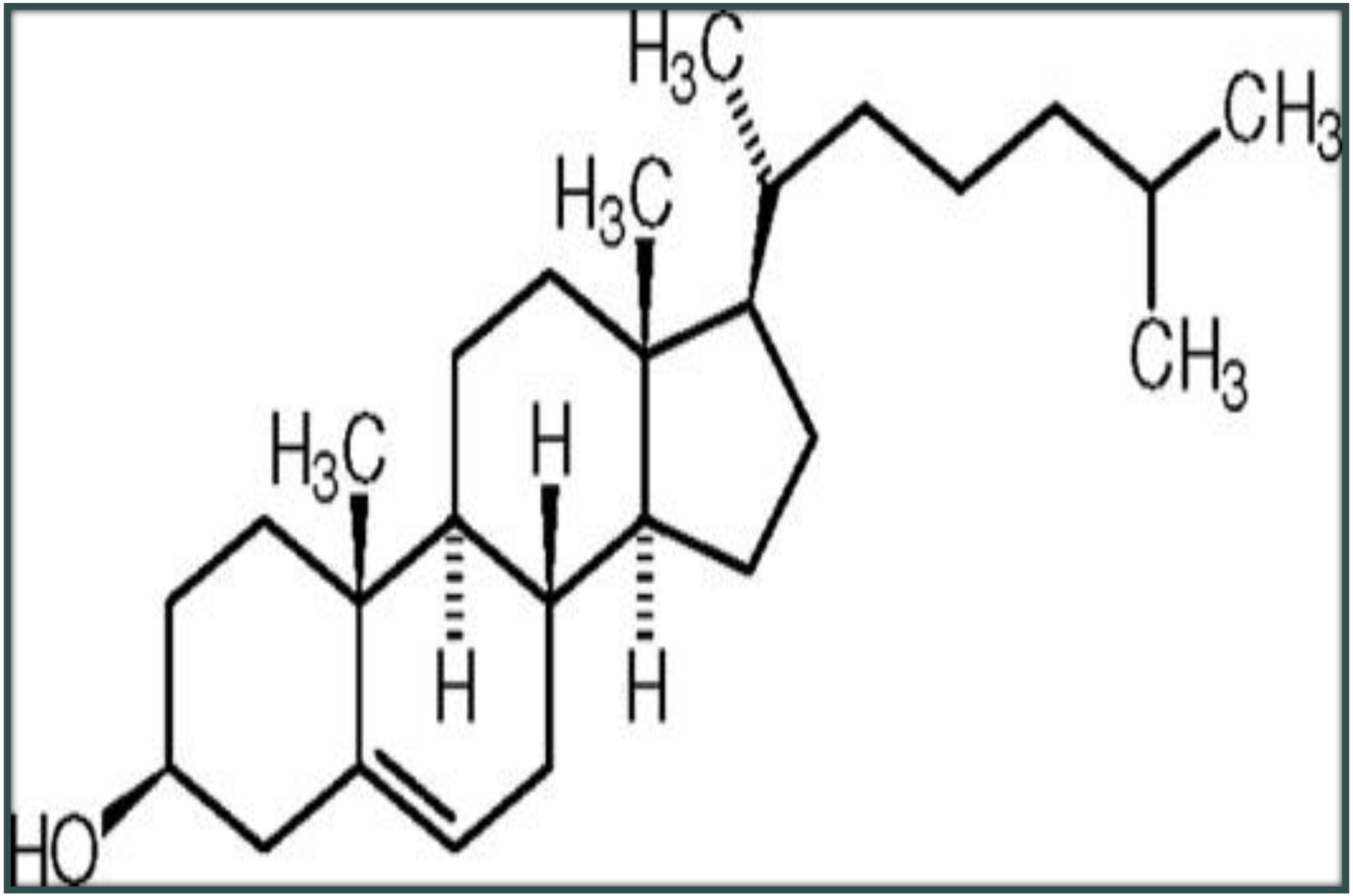
Biochemistry

Lipid Metabolism

Cholesterol : **is a fat-like substance found in the blood stream and in all the cells. It is used in the body in the synthesis of the cell membranes, protecting nerves, digesting dietary fats. It produces certain hormones such as the sexual hormones. Around 75% of cholesterol of the body needs is made naturally by the liver and other cells of the body and can be effected by heredity while the 25% comes from foods such as eggs, meats, butter, and dairy products (Stein *et al.*, 1994).**

- **Cholesterol doesn’t contain fatty acids, its sterol nucleus is synthesized from degradation products of fatty acid molecules, and thus giving it different physical and chemical properties to other lipid substances .Cholesterol can be obtained from the diet and it can be synthesized in the body. The liver is the major site of cholesterol synthesis in mammals, although the intestine also forms significant amounts. The rate of cholesterol formation by these organs is highly responsive to the cellular level of cholesterol.**

- **Acetyl-CoA is a building unite of cholesterol, this unit produced from degradation complex organic compounds (like carbohydrates, fatty acids and amino acids) to simple substances .**
- **Cholesterol and triglycerides are transported in the body fluids in the form of lipoprotein particles. Thus, all lipoproteins contain cholesterol so that an increase in any of them will elevate the plasma total cholesterol concentration**



cholesterol structure

Lipoprotein:

A lipoprotein is a complex of protein and lipid with a characteristic density, size and chemical composition. Lipoproteins transport lipids in blood between the sites of their absorption, the liver and various tissues that utilize lipids. The major lipoprotein classes are :

A-<u>Chylomicrons</u>:

Which are large lipoprotein of extremely low density and secreted by the small intestine, transport dietary triglycerides and cholesterol esters from the intestine to the tissues. Chylomicrons may be atherogenic when their concentrations in plasma is chronically elevated.

Chylomicrons elevations, which are exacerbated by a high-fat diet, do not appear to be a risk factor for atherosclerosis.

B-*Very low-density lipoprotein (VLDL):*

This type of lipoprotein are synthesized in the liver and are associated with Chylomicrons . Lipid synthesized by the liver are carried by VLDL to tissues.VLDL secretion may be converted by cholesteryl ester availability. It is important to mention an increase in VLDL does not consider a serious risk factor for atherosclerosis

C- *Low density lipoprotein (LDL):*

people often refer to it as *bad cholesterol*

This kind of lipoprotein is responsible for carrying cholesterol from liver to tissues. LDL is engulfed by cells after binding to LDL receptors. Higher LDL increases risk factor of heart disease.

The more extreme LDL elevations usually are genetic in origin, and dietary restriction produces little improvement . LDL lipoproteins carry cholesterol from the liver into the body because these cells having LDL-receptors on their surfaces.

D-*High-density lipoprotein (HDL):*

people often refer to it as good cholesterol.

HDL lipoproteins carry cholesterol from liver and circulate in the blood to pick up excess cholesterol from the body and carry it back to the liver to be removed from the body . HDL are relatively small lipoproteins rich in cholesteryl esters, phospholipids and apoprotein A . Two types of HDL can be isolated from plasma, HDL_2 and HDL_3


HDL
LDL


LDL
HDL

- ***E-<u>Intermediate-density lipoprotein (IDL)</u>:***
- IDL is product of VLDL catabolism in the bed of capillary, from which a large share of the triglyceride have been removed. IDL is converted to LDL and undetectable in normal plasma

Cholesterol synthesis, transport and excretion

Importance and uses

1- It is a precursors for all steroids, such as, Vit.D, corticosteroids, sex HS, and bile salts.

2- His an essential structure of cell membranes and outer layer of LP.

3- Chol ester is a storage form of chol. in tissue.

4- LDL is mediator for chol.

5- It is a major consistituents of gall stone.

6- In the genes of atherosclerosis.

- More than 5% of chol. is synthesized (700 mg/day) and the remainder is provide from the diet.
- In human 10% synthesis by liver, 10% by small intestine, and tissue contain nucleated cell are capable to form chol.

Cholesterol synthesis

- Acetyl CoA is the source of all carbon atom in cholesterol
- The synthesis involve 5 stage:

1- The synthesis of mevalonate 6 carbon compound from acetyl CoA.

2- Isoprenoid to formed from mevalonate by loss of CO2

3- Six isoprenoid to form squaline

4- Squaline cyclizes to give rise lanosterol.

5- Lanosterol loss 3- methyl group to form cholesterol .

Cholesterol synthesis in extra mitochondria:

In extra mitochondria: step 1. $2\text{molecule of acetyl CoA} \xrightarrow{thiolase} \text{acetoacetyl CoA}$

In liver mitochondria: acetoacetate synthesize inside mitochondria as in ketogenesis, and diffuse into cytosol, then activated to acetoacetyl CoASH by acetoacetyl CoA synthase, and ATP to give acetoacetyl CoA.

acetoacetyl CoA+acetyl CoA B-hydroxy-3methyl glutaryl CoA by enzyme HMGCoA synthase.

$$HMGCoA + 2NADPH + 2H^{+} \xrightarrow{HMGCoA\ reductase} Mevalonicaiol + 2NADP^{+} + CoASH$$

This is the rate limiting step in cholesterol synthesis.

Step 2: Mevalonate + ATP $\xrightarrow{Kinase}$ to form active isoperenoid units.
CO_2

The activation by ATP and decarboxylation give isopentenyl pyrophosphate.

Step 3: Six isoprenoid units form squalene.

a- isomerization of isopentenyl PP. ⟶ dimethyl allyl PP.

b- condensation + isopentenyl PP. ⟶ 10 intermediate.

c- condense + isopentenyl PP. ⟶ 15 carbon: farnesyl PP.

d- two molecule of farnesyl PP. condense and eliminate of PP to give presqualene PP.

e- reduction with NADPH with elimination PP to give squalene.

Step 4: Squalene converted to lanosterol

1. Squlalene $\xrightarrow[epoxidase\ oxidize]{squalene}$ Methyl group on $C_{14} \longrightarrow C_{13}$, and on $C_8 \longrightarrow C_{14}$ then cyclization by oxido squalene : lanosterol cyclase.

Step 5: lanosterol $\longrightarrow$ cholesterol involve

1. the methyl gr. on C_{14} oxidize to CO_2
2. two methyl gr. on C_4 are removed to give zymosterol.
3. cholestadienol formed by moving double bond C_8-C_9 C_8-C_7. and Desmosterol formed at this point by shift double bond on ring B to take a position C_5-C_6.
   The cholesterol formed by reduce the double bond on C_{24}.

The synthesis of cholesterol utilize

1- 18 mole of acetate: each mole of mevalonic acid produce by 3 M of acetate, 6 mole of mevalonat produce cholesterol.

2- 6 mole of CO2 are eliminated from conversion of mevalonic acid ⟶ 3- isopentyl PP.

3- 3 mole of CO2 are eliminated in conversion of lanosterol to cholesterol. chol. is 27 C atom.

4- Required 18 mole of ATP.

5- Required 13 mole of NADPH.

- HMG CoA reductase: this inhibited by elevated level of cholesterol, blocking the excessive synthesis when high cholesterol is taken in diet.

Regulation of cholesterol synthesis

- Regulation of chol. is near the beginning of pathway at HMGCoA reductase.

1- Mark decrease in the activity of enzyme in fasting.

2- There is feed bake mechanism, the enzyme inhibited by mevaloante, and cholesterol., cholesterol ester it is metabolite may act either:

a- Repression قمع the synthesis of new reductase.

b- Inducing the enzyme degrade the existing reductase.

3- Inhibited by cholesterol taken up via LDL receptor (apo B100, E receptors) which effect on chol. synthesis and on reductase activity.

4- Insulin, thyroid HS increase HMG CoA reductase activity, whereas glucagon and glucocorticoids decrease activity of the enzyme.

5- Variation of cholesterol in diet, when there is only 0.05%. in the diet, 70-80% of chol. synthesis in liver, adrenal gland, in the body. When dietary intake reside up to 2%. The endogenous production decrease and the hepatic synthesis is inhibited by cholesterol-rich chylomicrons remnants, taken by liver inhibited sterol synthesis.

Disorder of lipid metabolism

- Serum cholesterol and its relation to atherosclerosis
- Atherosclerosis characterize the presentation of chol. Ester of LP containing apo B100 i.e. VLDL, TDL and LDL. Any disease cause high amount or elevated in these lipoprotein cause atherosclerosis. Such diseases are:

1- lipid nephrosis 2- hypothyroidism 3- another condition of hyperlipemia

Factors affect serum cholesterol level

1- Hereditary factors, which is the greatest factor affected blood chol. Conce.

2- Diet and envirment factor also affected.

- The substance of poly unsaturated, Mono unsat. F.A is good and leads to reduce serum cholesterol levels. These acids present in sunflower, cotton seeds, soybean oil, but butter, beef fat, contain high amount of saturated F.A.
- The reason for poly unsaturated F.A lower S. chol. Is not clear , however several hypothesis as:

1- Stimulation chol. Excretion 2- stimulation chol. Oxidation to bile acid.

- It is possible that chol. Ester of poly unsat. F.A are more rapidly metabolize by the liver and other tissue and enhance their excretion or oxidation. The important thing is by increase distribution of cholesterol from plasma to tissue due to increase catabolic rate of LDL due to the regulation of LDL receptor by poly unsat. F.A and reduce regulation in presence of sat. F.A, because of formation small VLDL that contain more chol. Which is metabolize at slower rate than large partical.
- Sucrose, fructose have greater effect in raising blood lipid than other carbohydrate.


Thank You