Cholesterol biosynthesis & Breakdown

Cholesterol metabolism

- Cholesterol is the most important animal steroid
- Brain & egg yolk is very rich sources. The liver, kidney and red meat are rich sources.
- Average diet supplies about 0.5 - 1 g/day.
- Maximum dietary intake should not exceed 300mg.

Extremely important biological molecule being a precursor for the synthesis of the steroid hormones and bile acids and Vitamin D₃

- Cholesteryl esters, are the form in which Cholesterol is stored in the cells.

The synthesis and utilization of Cholesterol must be tightly regulated in order to prevent over-accumulation and abnormal deposition within the body

- Such deposition, eventually leading to atherosclerosis, is the leading contributing factor for CVD
- Most plasma cholesterol is in an esterified form, which is more hydrophobic than free cholesterol.

FATE OF CHOLESTEROL

Plasma lipid profile (normal values)

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total plasma lipids</td>
<td>400-600 mg/dl</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>140-200 mg/dl</td>
</tr>
<tr>
<td>HDL cholesterol, male</td>
<td>30-60 mg/dl</td>
</tr>
<tr>
<td>HDL cholesterol, female</td>
<td>35-70 mg/dl</td>
</tr>
<tr>
<td>LDL cholesterol, 30-39 yrs</td>
<td>80-130 mg/dl</td>
</tr>
<tr>
<td>Triglycerides, male</td>
<td>50-150 mg/dl</td>
</tr>
<tr>
<td>Triglycerides, female</td>
<td>40-150 mg/dl</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>150-200 mg/dl</td>
</tr>
<tr>
<td>Free fatty acids (FFA)</td>
<td>10-20 mg/dl</td>
</tr>
</tbody>
</table>
**FUNCTION OF CHOLESTEROL**

- Cell membranes
- Nerve conduction
- Bile acids and Bile salts derived
- Steroid Hormones synthesis
- Vitamin D
- Esterification of fatty acids

**BIOSYNTHESIS OF CHOLESTEROL**

- The *major sites of synthesis* of cholesterol are *liver, adrenal cortex, testes, ovaries and intestine.*

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**a. HMG-CoA synthase** is common to sterol and Ketone body synthesis. HMG-CoA reductase makes Mevalonate (MVA), the key and first intermediate of sterol biosynthesis. This is a highly regulated step.

**b.** An “active isoprene” is made which may combine with another C5 unit to make C10 and C15 products.
Steps of Biosynthesis

I. Synthesis of mevalonate: A 6-C compound from acetyl-CoA.
II. II. Formation of “Iso-Prenoid units” (C-5) from Mevalonate:
   By successive phosphorylations and followed by loss of CO2.
   Note: The isoprenoid units are regarded as the building blocks of the steroid nucleus.
III. Formation of Squalene: A 30-carbon aliphatic chain,
   formed by condensation of six isoprenoid units.
IV. Cyclisation of Squalene to form Lanosterol.
V. Conversion of Lanosterol → to form cholesterol.

Steps in Biosynthesis of Cholesterol

1. Synthesis of HMG Co A
2. Formation of Mevalonate (6c)
3. Production of isoprenoid units (5c)
4. Synthesis of squalene (30c)
5. Conversion of squalene to cholesterol (27c).

REGULATION OF CHOLESTEROL BIOSYNTHESIS

Regulation of cholesterol synthesis is exerted near the beginning of the pathway, at the HMG-CoA reductase step.
Following mechanisms are involved at the regulatory step-
○ Competitive inhibition
○ Feed back inhibition
○ Covalent modification (Role of hormones)
○ Sterol mediated regulation of transcription

Regulation of Cholesterol Synthesis

• Regulation at transcription: The regulatory enzyme is HMG CoA reductase. Long-term regulation involves regulation of transcription of the gene for HMG CoA reductase.
• When sufficient cholesterol is present in the cell, transcription of the gene for HMG CoA reductase is suppressed, and cellular synthesis of cholesterol is decreased.
• When cholesterol in diet is low, synthesis is increased

Sterol regulatory element binding protein (SREBP)

• A specific recognition sequence known as the sterol regulatory element (SRE) is present in DNA.
• SRE binding by sterol regulatory element binding protein (SREBP) is essential for the transcription if these genes. When cholesterol level are sufficiently high, the SREBP remains as an inactive precursor.
Covalent modification

- Short-term regulation is by covalent modification of the enzyme.
- Cyclic AMP-mediated cascade phosphorylates the enzyme which is inactive.
- Dephosphorylated from is active further is, the activity of HMG CoA reductase is also regulated by the rate of degradation of enzyme protein.

Regulation of HMG CoA reductase

- Insulin and thyroxine increase the activity of HMG CoA reductase.
- Cortisol and glucagon decrease its activity.

Degradation of cholesterol

- Cholesterol (50%) is converted to bile acids (excreted in feces), serves as a precursor for the synthesis of steroid hormones, vitamin D.
- The bile acids are synthesized in the liver from cholesterol.
- Bile acids are amphiphatic in nature.
- Possess both polar & non-polar groups.
- Serve as emulsifying agents in the intestine.
- Participate in digestion & absorption of lipids.

Synthesis of steroid hormone from cholesterol

- Cholesterol is the precursor for the synthesis of all the five classes of steroid hormones
- Glucocorticoids (Cortisol)
- Mineralocorticoids (Aldosterone)
- Progestins (Progesterone)
- Androgens (Testosterone)
- Estrogens (Estradiol)
**Synthesis of Vitamin D**

- 7-Dehydrocholesterol, an intermediate in the synthesis of cholesterol, is converted to cholecalciferol (vitamin D3) UV rays in the skin.

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**Plasma cholesterol & its significance**

- Cholesterol level associated with CAD
- **Good level:** below 200 mg/dl (low risk of heart disease).
- **Border line:** 200-240 mg/dl (if higher, at high risk)
- **Hypercholesterolemia:** Increase in plasma cholesterol (>200 mg/dl) is known as Hypercholesterolemia.
- It is observed in Diabetes mellitus:

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- Due to increased cholesterol synthesis. The availability of acetyl CoA is increased.
- **Obstructive jaundice:** Due to an obstruction in the excretion of cholesterol through bile.
- **Nephrotic syndrome:** Due to increase in plasma lipoprotein fractions.
- **Hypercholesterolemia** is associated with atherosclerosis & coronary heart disease.

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- Deposition of cholesterol esters & lipids in the intima of arterial walls leading to hardening of coronary arteries & cerebral blood vessels.
- **Bad cholesterol & good cholesterol:** LDL Cholesterol is considered bad due to its involvement in atherosclerosis & related complications. carry cholesterol from liver to blood then to organs

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- HDL Cholesterol is good cholesterol. carry cholesterol from peripheral organs and blood to liver to get rid of it
- It removes excess cholesterol from tissues (it cleans blood).
Control of hypercholesterolemia

➢ Consumption of PUFA: Dietary intake of PUFA reduces the plasma cholesterol levels.

➢ Avoidance of cholesterol-rich foods is advocated to be on the safe side.

➢ Plant sterols: Certain plant sterols (sitostanol esters) & their esters reduce plasma cholesterol levels. They inhibit the intestinal absorption of dietary cholesterol.

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

➢ Avoiding high carbohydrate diet.

➢ Elevation in plasma cholesterol is observed in people with smoking, abdominal obesity, lack of exercise, stress, high blood pressure, consumption of soft water. Lifestyle changes will reduce cholesterol levels.

➢ Moderate alcohol consumption: