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# BIOCHEMISTRY

## UNIT 3

TOPIC :

- **Lipid metabolism**

**$\beta$ -Oxidation of saturated fatty acid (Palmitic acid)**

**Formation and utilization of ketone bodies; ketoacidosis De novo synthesis of fatty acids (Palmitic acid)**

**Biological significance of cholesterol and conversion of cholesterol into bile acids, steroid hormone and vitamin D**

**Disorders of lipid metabolism: Hypercholesterolemia, atherosclerosis, fatty liver and obesity.**

## Lipid Metabolism

- Lipids are generally the esters of fatty acids and alcohols.
- Lipids constitute about 15–20% of the total body weight in humans.
- They are present in the body in various forms such as:
  - Triglycerides
  - Phospholipids
  - Fatty acids
  - Sterols (e.g., cholesterol)
- About 85–90% of the lipids in our body are triglycerides, which are stored in adipose tissue.
- These stored lipids serve as a major energy reserve.
- Lipid metabolism refers to the synthesis (lipogenesis) and breakdown (oxidation/lipolysis) of lipids in the body.
- It includes:
  - Lipogenesis: Formation of triglycerides and fatty acids from glucose or other sources.
  - $\beta$ -Oxidation: Breakdown of fatty acids to produce energy.
  - Ketogenesis: Formation of ketone bodies from excess acetyl-CoA during fasting.
  - Cholesterol and phospholipid metabolism

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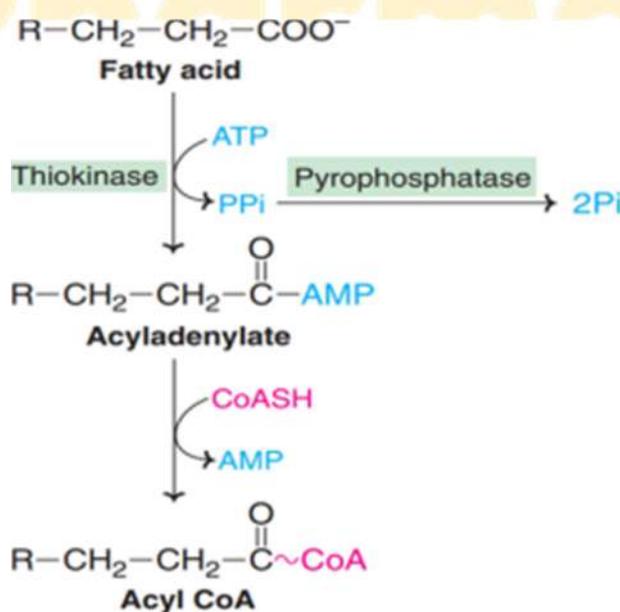
## $\beta$ -Oxidation of Fatty Acids

→  $\beta$ -Oxidation of fatty acid is a process by which fatty acids are broken down to produce energy . The beta oxidation of fatty acids occurs in three stages ;

- 1) Activation of fatty acids in the cytosol.
- 2) transport of activated fatty acids into mitochondria.
- 3) Beta oxidation of fatty acid in the matrix of mitochondria.

### 1. Activation of fatty acids

→ Fatty acids are activated to acyl CoA by thiokinase or acyl CoA synthetases. The reaction occurs in two steps and requires ATP, coenzyme A and  $Mg^{2+}$ . Fatty acid reacts with ATP to form acyladenylate which then combines with coenzyme A to produce acyl CoA. 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.

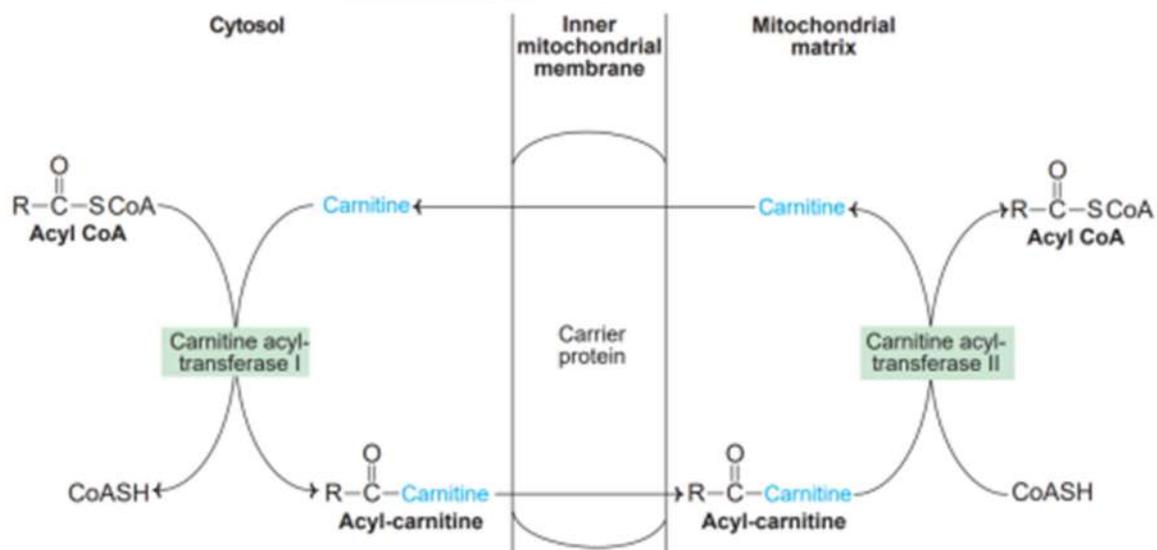


## 2. Transport of fatty acids into mitochondria

→ 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

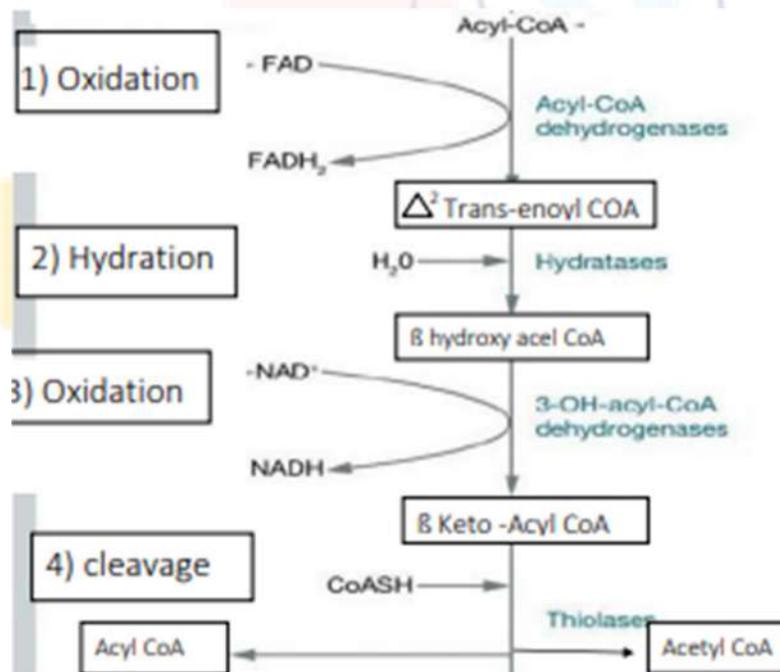
- Acyl group of acyl CoA is transferred to carnitine ( $\beta$ -hydroxy  $\gamma$ -trimethyl aminobutyrate), catalysed by carnitine acyltransferase I (present on the outer surface of inner mitochondrial membrane).
- The acyl-carnitine is transported across the membrane to mitochondrial matrix by a specific carrier protein.
- Carnitine acyl transferase II (found on the inner surface of inner mitochondrial membrane) converts acyl-carnitine to acyl CoA.
- The carnitine released returns to cytosol for reuse



### 3. $\beta$ -Oxidation proper in the mitochondrial matrix

→ Each cycle of  $\beta$ oxidation, liberating a two-carbon unit-acetyl CoA, occurs in a sequence of four reactions.

1. **Oxidation** — Acyl CoA undergoes dehydrogenation by an FADdependent flavoenzyme, acyl CoA dehydrogenase. A double bond is formed between  $\alpha$  and  $\beta$  carbons (i.e., 2 and 3 carbons).
2. **Hydration** — Enoyl CoA hydratase brings about the hydration of the double bond to form  $\beta$ -hydroxyacyl CoA.
3. **Oxidation** —  $\beta$ -Hydroxyacyl CoA dehydrogenase catalyses the second oxidation and generates NADH. The product formed is  $\beta$ -ketoacyl CoA.
4. **Cleavage** — The final reaction in  $\beta$ -oxidation is the liberation of a 2-carbon fragment, acetyl CoA from acyl CoA. This occurs by a thiolytic cleavage catalysed by  $\beta$ -ketoacyl CoA thiolase.



## Formation and Utilization of Ketone Bodies

**Ketone bodies** are water-soluble molecules produced in the **liver mitochondria** from **acetyl-CoA** during periods of:

- **Prolonged fasting**
- **Starvation**
- **Uncontrolled diabetes mellitus**
- **Low carbohydrate intake (e.g., ketogenic diet)**

There are **three main ketone bodies**:

Ketone Body	Nature	Fate
<b>Acetoacetate</b>	Primary ketone body	Used for energy or converted to others
<b><math>\beta</math>-hydroxybutyrate</b>	Reduced form of acetoacetate	Major circulating form
<b>Acetone</b>	Volatile, exhaled	Not metabolically useful

### Formation of Ketone Bodies (Ketogenesis)

- Fatty acids undergo  $\beta$ -oxidation → Produces excess acetyl-CoA
- Oxaloacetate is diverted to gluconeogenesis (in starvation), so acetyl-CoA cannot enter the TCA cycle.
- The liver converts this excess acetyl-CoA into ketone bodies.

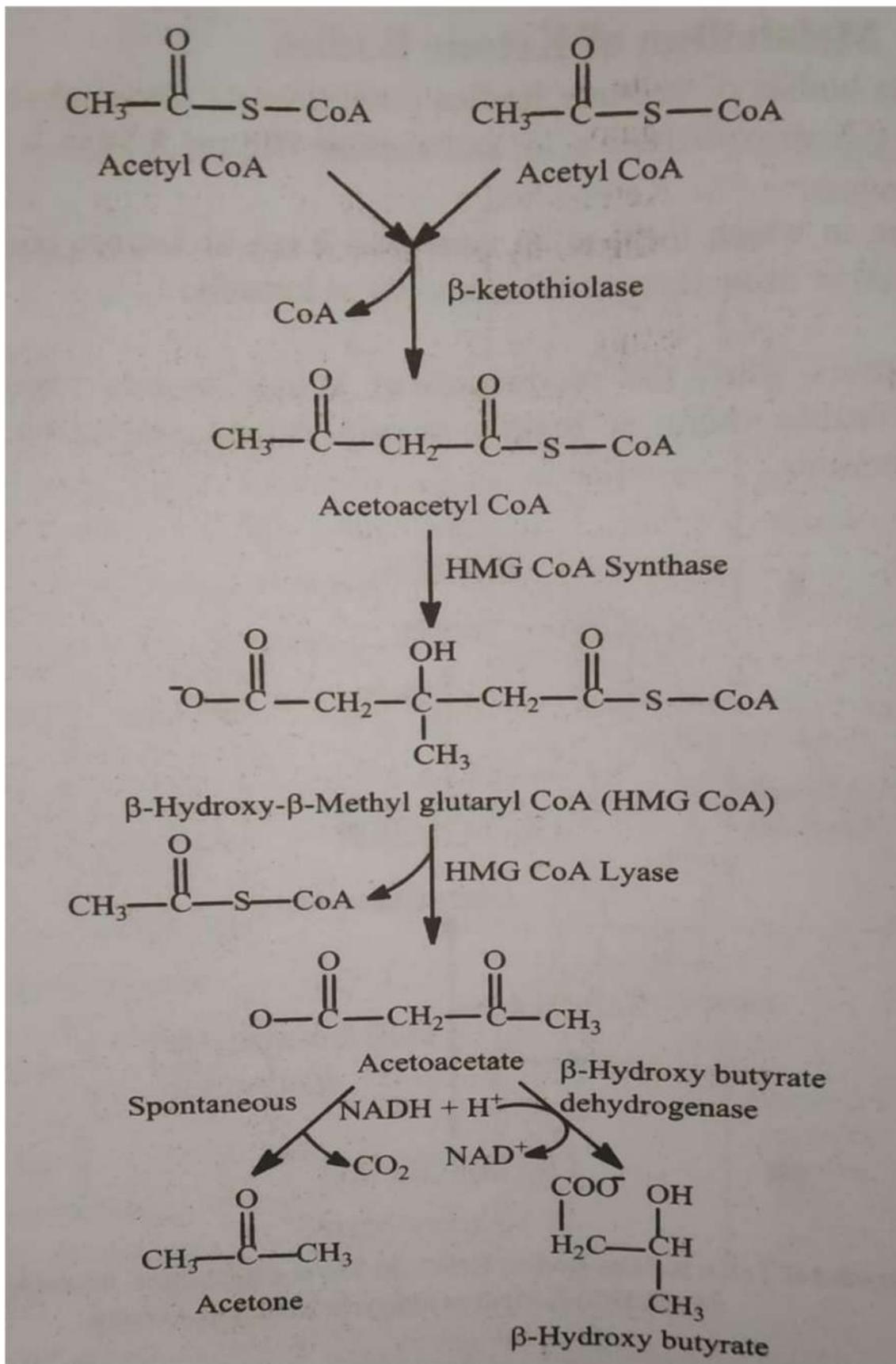
### Ketogenesis

- The synthesis of ketone bodies occurs in the liver. The enzymes for ketone body synthesis are located in the mitochondrial matrix. Ketone bodies are water-soluble and energy yielding. Acetyl CoA, formed by oxidation of fatty acids, pyruvate or some amino acids, is the precursor for ketone bodies.

- The three main types of ketone bodies produced are acetone, acetoacetate, and beta-hydroxybutyrate. Ketone bodies can be used by the brain and other tissues as an alternative energy source when glucose is scarce, and they are also involved in regulating blood glucose levels and reducing inflammation.
- However, excessive production of ketone bodies can lead to a condition known as ketoacidosis, which is a potentially lifethreatening metabolic state characterized by high levels of ketone bodies in the blood.

### **Ketogenesis occurs through the following reactions**

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  $\beta$ -hydroxy  $\beta$ -methyl glutaryl CoA (HMG CoA). HMG CoA synthase, catalysing this reaction, regulates the synthesis of ketone bodies.
3. HMG CoA lyase cleaves HMG CoA to produce acetoacetate and acetyl CoA.
3. Acetoacetate can undergo spontaneous decarboxylation to form acetone.
4. Acetoacetate can be reduced by a dehydrogenase to  $\beta$ -hydroxybutyrate.



## Utilization of Ketone Bodies (Ketolysis)

- Occurs in peripheral tissues like:
  - Brain (during starvation)
  - Skeletal muscles
  - Cardiac muscles
  - Kidney

## Ketolysis

- Ketolysis is the metabolic process by which ketone bodies are broken down and converted into energy in the body's cells. This process occurs primarily in the mitochondria of cells, where the ketone bodies are broken down into acetyl-CoA, which can then enter the citric acid cycle to produce ATP, the energy currency of cells.
- This process is important for individuals who rely on ketone bodies as their primary source of energy, such as those on a ketogenic diet or during periods of prolonged fasting.
- The rate of Ketolysis is influenced by several factors, including the availability of ketone bodies and the metabolic state of the cells.
- In some metabolic disorders, such as diabetes, there can be a disruption in the balance between ketone production and utilization, leading to an accumulation of ketone bodies in the blood and potentially causing ketoacidosis

## Ketoacidosis

Ketoacidosis is a **serious metabolic complication** caused by excessive production and accumulation of **ketone bodies**, leading to:

- **Lowered blood pH (acidosis)**
- **Electrolyte imbalance**
- **Potentially life-threatening condition**

Causes:

1. **Uncontrolled Type 1 Diabetes Mellitus**  
→ Insulin deficiency → ↑ Lipolysis → ↑ Fatty acid oxidation → ↑ Ketone production
2. **Starvation or prolonged fasting**
3. **Alcoholic Ketoacidosis**  
→ Excessive alcohol intake with poor nutrition

Pathophysiology:

- ❖ Excess lipolysis → ↑ Free fatty acids to liver
- ❖ ↑  $\beta$ -oxidation → ↑ Acetyl-CoA
- ❖ TCA cycle slows (due to low oxaloacetate)
- ❖ Acetyl-CoA diverted to ketogenesis
- ❖ Accumulated ketone bodies → Blood pH drops (below 7.35)  
→ Metabolic acidosis

Symptoms:

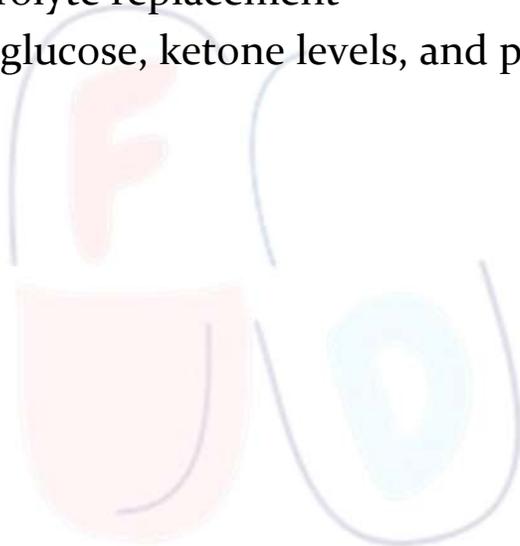
- ✚ Nausea, vomiting
- ✚ Rapid breathing (Kussmaul respiration)
- ✚ Abdominal pain
- ✚ Fruity breath (due to acetone)
- ✚ Confusion, coma (in severe cases)

### Diagnosis:

- ⇒ Blood ketone levels ↑
- ⇒ Blood pH ↓ (acidic)
- ⇒ Urine tests positive for ketones
- ⇒ High anion gap metabolic acidosis

### Treatment:

- ✓ Insulin therapy (especially in diabetic ketoacidosis)
- ✓ Fluid and electrolyte replacement
- ✓ Monitor blood glucose, ketone levels, and pH



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## De Novo Synthesis of Fatty Acids (Palmitic Acid)

- **De novo synthesis** is also known as the **biosynthesis of fatty acids**.
- It occurs in the **cytosol** of certain tissues such as the:
  - **Liver**
  - **Kidneys**
  - **Adipose tissue**
- The enzymes required for this process are present in the **cytosol (cytoplasm)**.
- The **most common fatty acid** synthesized during de novo synthesis is **palmitic acid (C<sub>16:0</sub>)**, a 16-carbon saturated fatty acid.

### Stages of De Novo Synthesis of Fatty Acids

#### Stage I: Production of Acetyl-CoA and NADPH

- **Acetyl-CoA** is produced in **mitochondria** from carbohydrate metabolism (glycolysis → pyruvate → acetyl-CoA).
- Acetyl-CoA combines with oxaloacetate → **Citrate** (crosses mitochondrial membrane).
- In cytosol, **citrate is cleaved** to form:

$\text{Citrate} \rightarrow \text{Acetyl-CoA} + \text{Oxaloacetate}$

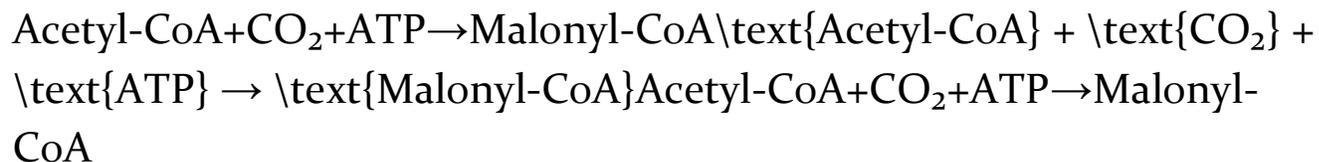
- Enzyme: **ATP-citrate lyase**
- **NADPH** is generated from:
  - **HMP shunt**
  - **Malic enzyme reaction** (oxaloacetate → malate → pyruvate + NADPH)

#### Stage II: Conversion of Acetyl-CoA to Malonyl-CoA

*(Rate-limiting step)*

- Enzyme: **Acetyl-CoA carboxylase (ACC)**

- Requires **biotin** and **ATP**
- Reaction:



**Malonyl-CoA** provides **2-carbon units** for elongation and is **essential for fatty acid synthesis**.

### Stage III: Action of Fatty Acid Synthase (FAS) Complex

- **Multifunctional enzyme** with 7 active sites
- Uses **Acetyl-CoA** as starter and **Malonyl-CoA** for chain extension
- Each cycle adds **2-carbon units** to the growing fatty acid chain
- **Reduction steps use NADPH**
- After **7 cycles**, the product is:

Palmitic Acid ( $C_{16}$ )

**Thioesterase** releases the final palmitic acid from the FAS complex.

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## Cholesterol

- Cholesterol primarily belongs to a group of compounds known as sterols.
- It is a major component of cell membranes in the human body, providing structural integrity and fluidity.
- Cholesterol is a type of lipid present naturally in our body.
- It is synthesized endogenously in the liver, but can also be obtained from external (dietary) sources.
- Cholesterol is present in foods of animal origin (e.g., meat, eggs, dairy), but is absent in foods of plant origin.

### Biological Significance of Cholesterol

- Cholesterol is a major structural component of cell membranes, contributing to membrane stability and fluidity.
- It is an essential component of lipoproteins, which are responsible for lipid transport in the blood.
- Cholesterol acts as a precursor for several important biological molecules:
  - Bile acids – which aid in the digestion and absorption of fats.
  - Vitamin D – synthesized in the skin from cholesterol upon exposure to sunlight.
  - Steroid hormones – including:
    - Progesterone
    - Androgens (e.g., testosterone)
    - Estrogens
    - Corticosteroids (e.g., cortisol and aldosterone)
- Fatty acids are transported to the liver in the form of cholesterol esters.
- It helps in maintaining nerve insulation (myelin sheath integrity).

## Conversion of Cholesterol into Bile Acids:

### *Step-by-step Conversion:*

1. Cholesterol is hydroxylated in the liver by cholesterol 7 $\alpha$ -hydroxylase (rate-limiting enzyme).
2. Forms primary bile acids:
  - o Cholic acid
  - o Chenodeoxycholic acid
3. These are conjugated with glycine or taurine to form bile salts (e.g., glycocholate, taurocholate).
4. Bile salts are secreted into bile and stored in the gallbladder.
5. They help in fat digestion by acting as emulsifiers in the intestine.

## Conversion of Cholesterol into Steroid Hormones:

### *Pathway Overview:*

1. In steroidogenic tissues (adrenal cortex, ovaries, testes), cholesterol is converted to **pregnenolone** in mitochondria.
  - o Enzyme: Cholesterol side-chain cleavage enzyme (P<sub>450</sub>scC)
2. Pregnenolone is then converted into:
  - o **Progesterone**
  - o **Cortisol** (glucocorticoid)
  - o **Aldosterone** (mineralocorticoid)
  - o **Androgens** (e.g., testosterone)
  - o **Estrogens** (e.g., estradiol)

These hormones are essential for:

- Metabolism regulation
- Immune response
- Water and salt balance
- Reproduction and sexual development

## Conversion of Cholesterol into Vitamin D:

### *Steps:*

- In the skin, 7-dehydrocholesterol (a cholesterol derivative) is exposed to UVB radiation.
- It is converted into previtamin D<sub>3</sub>, which is then thermally isomerized into cholecalciferol (Vitamin D<sub>3</sub>).
- In the liver, cholecalciferol is hydroxylated to 25-hydroxyvitamin D<sub>3</sub>.
- In the kidneys, further hydroxylation gives 1,25-dihydroxyvitamin D<sub>3</sub> (calcitriol), the active form.

### *Functions of Vitamin D:*

- ✓ Promotes calcium and phosphate absorption from the intestine.
- ✓ Maintains bone mineralization.
- ✓ Supports immune function and anti-inflammatory effects.

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## Disorders of Lipid Metabolism

Lipid metabolism disorders result from abnormalities in **lipid synthesis, transport, breakdown, or storage**, leading to various health conditions. These disorders often involve abnormal levels of:

- **Cholesterol**
- **Triglycerides**
- **Lipoproteins**
- **Fatty acids**

### 1. Hypercholesterolemia

- Hypercholesterolemia refers to abnormally high levels of cholesterol, particularly Low-Density Lipoprotein (LDL), in the blood.

#### *Causes:*

- **Genetic** (e.g., familial hypercholesterolemia)
- **Dietary intake** of saturated fats and cholesterol
- **Lack of physical activity**
- **Obesity and diabetes**
- **Hypothyroidism**

#### *Consequences:*

- Promotes **plaque formation in arteries**
- Increases risk of **atherosclerosis, heart attack, and stroke**

#### *Treatment:*

- **Statins** (HMG-CoA reductase inhibitors)
- Dietary changes (low saturated fat)
- Physical exercise
- Fiber intake and omega-3 fatty acids

## 2. Atherosclerosis

- Atherosclerosis is the hardening and narrowing of arteries due to the buildup of lipid-rich plaques (mostly LDL cholesterol) in the arterial wall.

### **Causes:**

- High levels of **LDL cholesterol**
- Smoking, hypertension, diabetes
- Inflammation and oxidative stress

### **Process:**

1. LDL deposits beneath arterial endothelium
2. Oxidation of LDL → triggers immune response
3. Foam cells form and accumulate → plaque buildup
4. Reduced blood flow or **artery blockage**

### **Consequences:**

- **Coronary artery disease (CAD)**
- **Stroke**
- **Peripheral vascular disease**

### **Prevention/Treatment:**

- Lipid-lowering drugs (statins, fibrates)
- Anti-inflammatory medications
- Lifestyle changes (diet, exercise, no smoking)

### 3. Fatty Liver (Hepatic Steatosis)

- Fatty liver is the accumulation of triglycerides in liver cells, often due to excessive fat metabolism or impaired fat export.

#### *Types:*

- **Alcoholic fatty liver disease (AFLD)** – due to chronic alcohol intake
- **Non-alcoholic fatty liver disease (NAFLD)** – due to obesity, insulin resistance

#### *Causes:*

- High-fat or high-sugar diet
- Obesity and insulin resistance
- Excess alcohol consumption
- Metabolic syndrome

#### *Symptoms:*

- Often **asymptomatic** in early stages
- Fatigue, mild abdominal discomfort
- May progress to **steatohepatitis, fibrosis, cirrhosis**

#### *Treatment:*

- Weight loss
- Healthy diet and regular exercise
- Controlling blood sugar and lipid levels
- Avoiding alcohol

#### 4. Obesity

- Obesity is a condition characterized by excessive accumulation of body fat, usually measured by Body Mass Index ( $BMI \geq 30 \text{ kg/m}^2$ ).

##### ***Causes:***

- **Overconsumption** of calories (especially fats and sugars)
- **Sedentary lifestyle**
- **Genetics and hormones**
- Psychological and environmental factors

##### ***Consequences:***

- Increases risk of:
  - **Type 2 diabetes**
  - **Cardiovascular diseases**
  - **Hypertension**
  - **Fatty liver disease**
  - **Certain cancers**
- Associated with **chronic inflammation and metabolic syndrome**

##### ***Management:***

- Balanced low-calorie diet
- Regular physical activity
- Behavior therapy
- Medications (e.g., orlistat)
- Bariatric surgery (in severe cases)