Lipid metabolism

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β-Oxidation of saturated fatty acid (Palmitic acid)

β-oxidation is the primary metabolic process by which fatty acids are broken down in the **mitochondria** to generate energy. For a saturated fatty acid like **Palmitic acid** (16 carbons), **the process follows these key stages:-**

1. Activation and Transport

Before oxidation, palmitic acid is activated in the cytosol into **Palmitoyl-CoA** by the enzyme fatty acyl-CoA synthetase. Since the inner mitochondrial membrane is impermeable to CoA, it is transported into the mitochondria via the **Carnitine shuttle**.

2. The Four Recurring Steps

Once inside the mitochondrial matrix, Palmitoyl-CoA undergoes a repeating cycle of four reactions:

a) **Oxidation:** Dehydrogenation by *acyl-CoA dehydrogenase* creates a double bond and produces **$FADH_2$**.

b) **Hydration:** Water is added across the double bond by *enoyl-CoA hydratase*.

c) **Oxidation:** The hydroxyl group is oxidized to a keto group by *3-hydroxyacyl-CoA dehydrogenase*, producing **NADH**.

d) **Thiolysis:** The enzyme *thiolase* cleaves the bond, releasing one **Acetyl-CoA** and a fatty acyl-CoA chain that is now two carbons shorter.

3. Net Yield for Palmitic Acid

To completely break down the 16-carbon Palmitic acid, the cycle runs **7 times**, resulting in:

a) **8 Acetyl-CoA** molecules (which enter the TCA cycle).

b) **7 $FADH_2$** molecules.

c) **7 NADH** molecules.

4. Energy Summary

After the electron transport chain and TCA cycle processing, the total net yield for one molecule of palmitic acid is approximately **106 ATP** (after accounting for the 2 ATP used during activation).

Ketone Bodies

Ketone bodies are water-soluble molecules generated in the liver as a result of fatty acid metabolism. They provide an alternative energy source for various tissues, particularly when carbohydrate intake is low, during extended fasting, or amid intense physical activity.

Synthesis of Ketone Bodies

a) The synthesis of ketone bodies in the liver mitochondria begins with condensing two molecules of acetyl CoA by thiolase (acetyl CoA acetyltransferase), forming acetoacetyl CoA.

b) The next step is a condensation of acetoacetyl CoA with another molecule of acetyl-CoA by HMG CoA synthase.

c) The condensation product, β-hydroxyβ-methylglutaryl-CoA (HMG-CoA), is then split by HMG-CoA lyase to acetyl-CoA and acetoacetate.

d) The lyase is present only in the mitochondria.

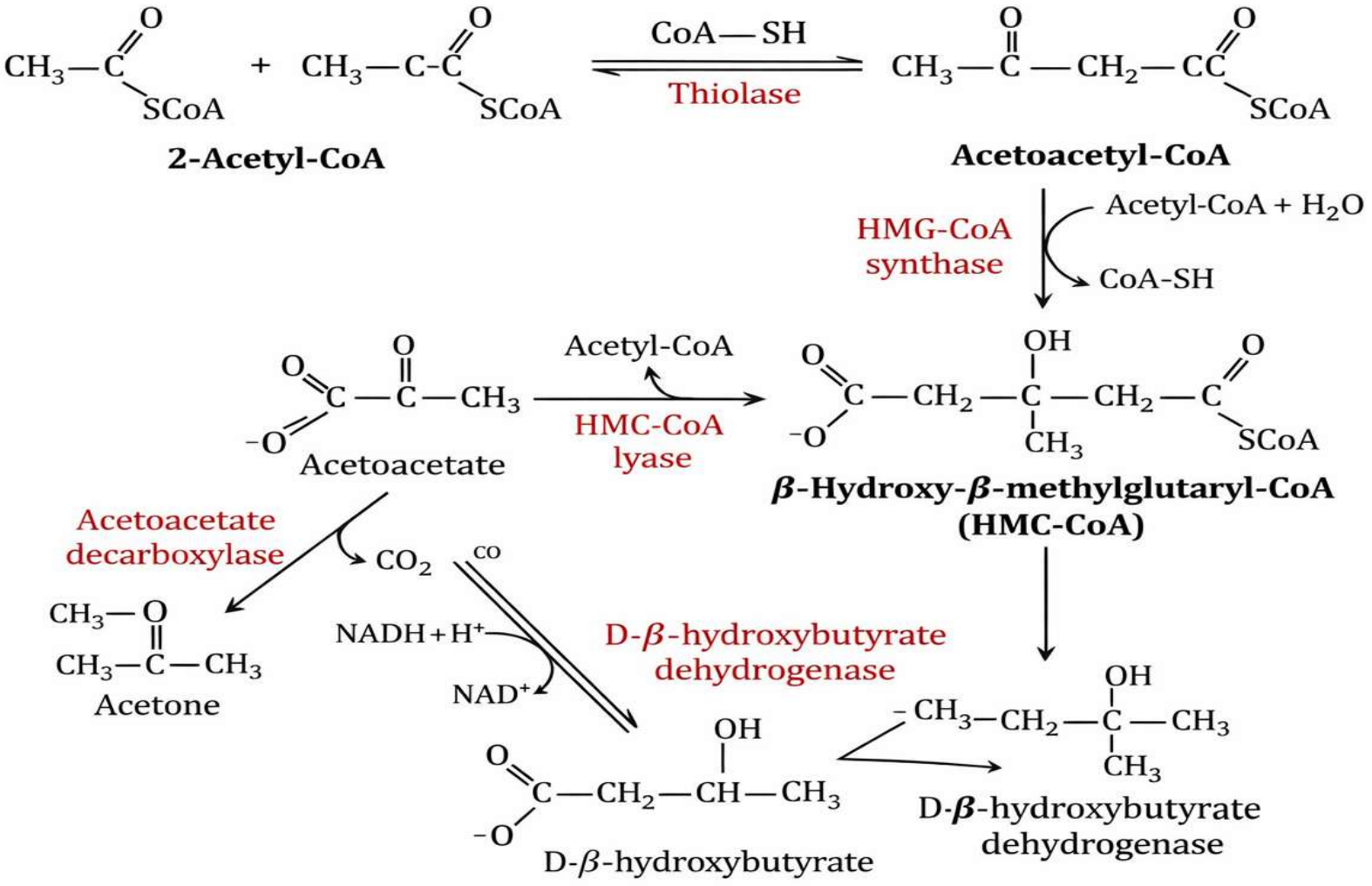
e) The other two ketone bodies can be synthesized from acetoacetate.

f) It may be reduced by β-hydroxybutyrate dehydrogenase to D- β-hydroxy butyrate.

g) Recall that β-oxidation of fatty acids produces the L-stereoisomer of D-hydroxy acyl CoA.

h) Finally, acetoacetate may be decarboxylated non-enzymatically or by acetoacetate decarboxylase to acetone, an exhaled volatile compound.

i) The liver releases acetoacetate and β-hydroxy butyrate into circulation to be picked up by extrahepatic tissues.



The pathway of ketogenesis

Utilization of Ketone Bodies

a) The extrahepatic tissues convert ketone bodies back to acetyl CoA in the mitochondria.

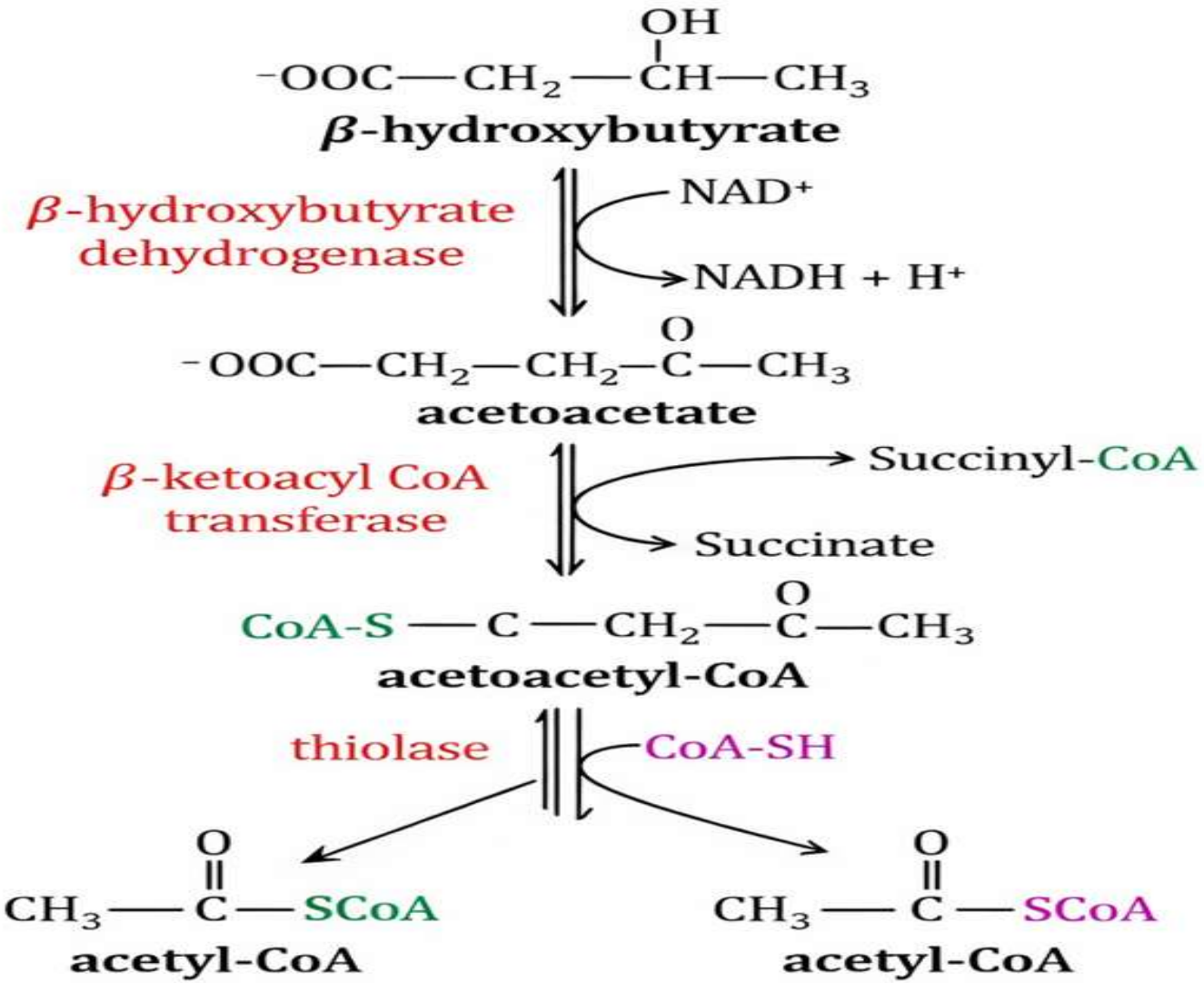
b) An enzyme missing in the liver and present in all tissues holds the key to the utilization of ketone bodies.

c) The enzyme is βketoacyl CoA transferase (or thiophorase) that activates acetoacetate by transferring the CoA group from succinyl CoA.

d) The next step is the thiolytic cleavage by acetoacetyl CoA thiolase. In the case of β-hydroxybutyrate, it is first oxidized to acetoacetate by β-hydroxybutyrate dehydrogenase.

e) The resultant acetyl-CoA units can now enter the TCA cycle for complete oxidation.

f) The dehydrogenase and thiolase function in both synthesis and utilization of ketone bodies.



The conversion of ketone bodies to acetyl CoA in extrahhepatic tissues.

Ketoacidosis

S.No	Aspect	Details
1	**Definition**	Ketoacidosis is a metabolic condition characterized by excess production and accumulation of ketone bodies in blood, leading to metabolic acidosis.
2	**Types**	Diabetic ketoacidosis (DKA) – most common Alcoholic ketoacidosis Starvation ketoacidosis
3	**Etiology (Causes)**	Diabetes (Type 1): Insulin deficiency (major cause) Infection, stress, trauma Missed insulin dose Alcohol abuse Prolonged fasting/starvation
4	**Pathogenesis**	Insulin deficiency → ↑ lipolysis → ↑ free fatty acids → liver converts to ketone bodies (acetoacetate, β-hydroxybutyrate, acetone) → accumulation in blood → ↓ pH → metabolic acidosis
5	**Clinical Features**	Polyuria, polydipsia Nausea, vomiting Fruity breath (acetone smell) Kussmaul breathing (deep, rapid breathing) Dehydration, confusion
6	**Diagnostic Tests**	Blood glucose: ↑ (in DKA) Ketone bodies: ↑ in blood & urine Arterial blood gas (ABG): ↓ pH, ↓ bicarbonate Electrolytes: altered (especially K^+)
7	**Treatment – Emergency Management**	IV fluids (rehydration) Insulin therapy Electrolyte correction (especially potassium) Treat underlying cause (infection, etc.)
8	**Complications**	Severe dehydration Electrolyte imbalance Coma Death (if untreated)

Biological significance of cholesterol

1. Structural Role in Cell Membranes

- Cholesterol is an essential component of **cell membranes**.
- It maintains **membrane fluidity and stability**.
- Prevents membranes from becoming too rigid (at low temperatures) or too fluid (at high temperatures).

2. Precursor of Steroid Hormones

- Cholesterol acts as a starting material for synthesis of several important hormones:
- **Glucocorticoids** (e.g., cortisol)
- **Mineralocorticoids** (e.g., aldosterone)
- **Sex hormones** (e.g., estrogen, progesterone, testosterone)

☞ These hormones regulate metabolism, electrolyte balance, and reproduction.

3. Formation of Bile Acids and Bile Salts

- Cholesterol is converted in the liver into **bile acids** (e.g., cholic acid).
- Bile salts help in:
  - **Digestion and absorption of fats**
  - Absorption of fat-soluble vitamins (A, D, E, K)

Biological significance of cholesterol

4. Precursor of Vitamin D

- Cholesterol (7-dehydrocholesterol in skin) is converted into **Vitamin D** upon exposure to sunlight.
- Vitamin D is essential for:
  - Calcium absorption
  - Bone formation

5. Insulation and Protection

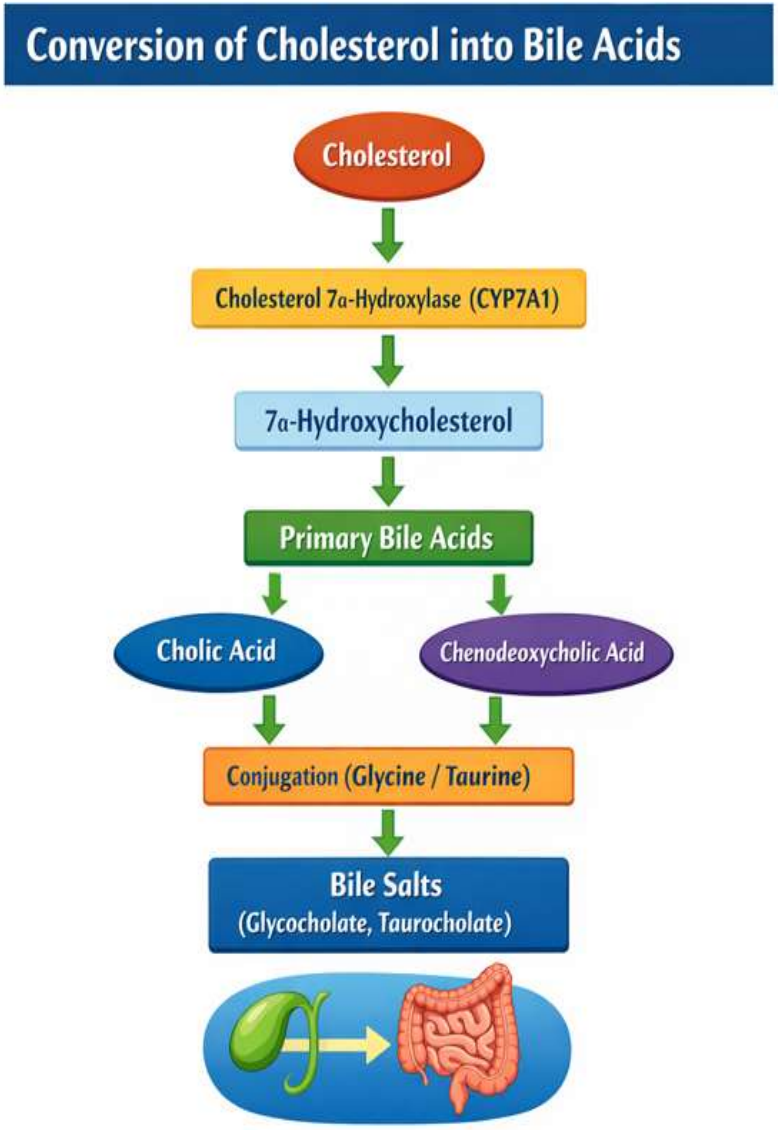
- Cholesterol is present in **myelin sheath** of nerve fibers.
- Helps in:
  - Proper nerve conduction
  - Protection of neurons

6. Lipoprotein Formation and Transport

- Cholesterol is transported in blood via **lipoproteins**:
  - LDL (Low Density Lipoprotein)
  - HDL (High Density Lipoprotein)
- Maintains lipid transport and distribution in the body

Conversion Of Cholesterol Into Bile Acids

1. The conversion of cholesterol into bile acids occurs in the **liver** and represents the primary pathway for the elimination of excess cholesterol from the body. This process is essential for lipid digestion and maintaining cholesterol balance.
2. The first and rate-limiting step is the hydroxylation of cholesterol to form **7α-hydroxycholesterol**, catalyzed by the enzyme **cholesterol 7α-hydroxylase (CYP7A1)**. This step requires NADPH and oxygen and is tightly regulated.
3. Through a series of enzymatic reactions involving oxidation, hydroxylation, and shortening of the side chain, cholesterol is converted into the primary bile acids:
   - **Cholic acid**
   - **Chenodeoxycholic acid**
4. These bile acids are then conjugated with amino acids **glycine** or **taurine** to form bile salts (e.g., glycocholate and taurocholate), which are more water-soluble and effective in digestion.
5. Bile salts are secreted into bile, stored in the gallbladder, and released into the small intestine, where they play a crucial role in:
   - Emulsification of fats
   - Absorption of fat-soluble vitamins (A, D, E, K)
6. In the intestine, some primary bile acids are converted by bacteria into secondary bile acids such as **deoxycholic acid** and **lithocholic acid**. Most bile acids are reabsorbed and returned to the liver via enterohepatic circulation.
7. Thus, this pathway is vital for both digestion and regulation of cholesterol levels in the body.



Steroid Hormones

S.No	Feature	Description
1	**Definition**	Lipid-soluble hormones derived from cholesterol
2	**Site of Synthesis**	Adrenal cortex, testes, ovaries, placenta
3	**Types**	Glucocorticoids (cortisol), Mineralocorticoids (aldosterone), Sex hormones (testosterone, estrogen, progesterone)
4	**Precursor**	Cholesterol
5	**Solubility**	Lipid soluble
6	**Transport in Blood**	Bound to plasma proteins
7	**Receptor Type**	Intracellular (cytoplasmic/nuclear receptors)
8	**Mechanism of Action**	Regulate gene transcription (slow but long-lasting)
9	**Functions**	Metabolism regulation, electrolyte balance, reproduction, anti-inflammatory action
10	**Examples**	Cortisol, Aldosterone, Testosterone, Estrogen

Vitamin D

S.No	Feature	Description
1	**Definition**	Fat-soluble vitamin with hormone-like action (secosteroid)
2	**Source**	Sunlight (UV rays), diet (fish, egg yolk, fortified milk)
3	**Precursor**	7-dehydrocholesterol (cholesterol derivative)
4	**Site of Synthesis**	Skin → Liver → Kidney
5	**Active Form**	Calcitriol (1,25-dihydroxycholecalciferol)
6	**Solubility**	Lipid soluble
7	**Transport in Blood**	Bound to vitamin D binding protein
8	**Receptor Type**	Intracellular (nuclear receptor)
9	**Mechanism of Action**	Regulates gene expression
10	**Functions**	Calcium & phosphate absorption, bone mineralization
11	**Deficiency Diseases**	Rickets (children), Osteomalacia (adults)

Disorders of lipid metabolism

1. Hypercholesterolemia
2. atherosclerosis
3. fatty liver
4. obesity

1.Hypercholesterolemia

S.No	Aspect	Details
1	**Definition**	A disorder of lipid metabolism characterized by elevated blood cholesterol levels, especially LDL cholesterol, increasing the risk of cardiovascular diseases.
2	**Etiology (Causes)**	Primary (Genetic): Familial hypercholesterolemia (LDL receptor defect), Apo-B mutation, PCSK9 mutation Secondary (Acquired): High-fat diet, obesity, sedentary lifestyle, diabetes mellitus, hypothyroidism, nephrotic syndrome, liver disease, drugs (steroids, diuretics)
3	**Pathogenesis**	↑ LDL in blood → LDL enters arterial wall → oxidation of LDL → macrophage uptake → foam cell formation → fatty streaks → atherosclerotic plaque → narrowing of arteries → reduced blood flow
4	**Diagnostic Tests**	Lipid Profile: ↑ Total cholesterol (>200 mg/dL), ↑ LDL (>100 mg/dL), ↓ HDL Other Tests: Apo-B, Lipoprotein (a), thyroid function test Genetic Testing: Familial cases Imaging: Carotid ultrasound, coronary angiography
5	**Treatment – Lifestyle**	Low-fat diet, high fiber intake, regular exercise, weight reduction, avoid smoking and alcohol
6	**Treatment – Drugs**	Statins: Atorvastatin, Rosuvastatin Bile Acid Sequestrants: Cholestyramine Absorption Inhibitor: Ezetimibe Others: PCSK9 inhibitors, fibrates
7	**Advanced Treatment**	LDL apheresis (in severe cases)
8	**Complications**	Atherosclerosis, coronary artery disease, myocardial infarction, stroke

2.Atherosclerosis

S.No	Aspect	Details
1	**Definition**	A chronic condition characterized by deposition of lipids (cholesterol), fibrous tissue, and inflammatory cells in arterial walls, leading to plaque formation and narrowing of arteries.
2	**Etiology (Risk Factors)**	Modifiable: Hypercholesterolemia, smoking, hypertension, diabetes mellitus, obesity, sedentary lifestyle Non-modifiable: Age, male gender, genetic predisposition
3	**Pathogenesis**	Endothelial injury → ↑ LDL entry → LDL oxidation → macrophage uptake → foam cells → fatty streaks → smooth muscle proliferation → fibrous plaque → plaque rupture → thrombosis
4	**Diagnostic Tests**	Blood Tests: Lipid profile (↑ LDL, ↓ HDL) Imaging: Angiography (gold standard), CT, MRI, Doppler ultrasound Others: ECG, stress test
5	**Treatment – Lifestyle**	Low-fat diet, regular exercise, smoking cessation, weight control
6	**Treatment – Drugs**	Statins: Atorvastatin, Rosuvastatin Antiplatelet: Aspirin Antihypertensives, antidiabetics
7	**Surgical Treatment**	Angioplasty, stent placement, coronary artery bypass graft (CABG)
8	**Complications**	Coronary artery disease, myocardial infarction, stroke, peripheral arterial disease

3.Fatty Liver

S.No	Aspect	Details
1	**Definition**	Fatty liver (hepatic steatosis) is a condition characterized by excess accumulation of triglycerides in liver cells (hepatocytes).
2	**Types**	Alcoholic fatty liver disease (AFLD) Non-alcoholic fatty liver disease (NAFLD)
3	**Etiology (Causes)**	Alcoholic: Chronic alcohol consumption Non-alcoholic: Obesity, diabetes mellitus, insulin resistance, hyperlipidemia, malnutrition, drugs (e.g., steroids)
4	**Pathogenesis**	↑ Free fatty acids in liver → ↑ triglyceride synthesis → ↓ β-oxidation → ↓ lipoprotein export → fat accumulation in hepatocytes → liver enlargement
5	**Clinical Features**	Often asymptomatic Fatigue Mild abdominal discomfort Hepatomegaly (enlarged liver)
6	**Diagnostic Tests**	Blood tests: ↑ liver enzymes (ALT, AST) Imaging: Ultrasound (most common), CT scan, MRI Liver biopsy: Gold standard
7	**Treatment – Lifestyle**	Weight reduction, balanced diet, exercise, avoid alcohol
8	**Treatment – Medical**	Control diabetes and lipids Vitamin E (in some cases) Insulin sensitizers
9	**Complications**	Steatohepatitis (NASH), fibrosis, cirrhosis, liver failure

4.Obesity

S.No	Aspect	Details
1	**Definition**	Obesity is a condition characterized by excess accumulation of body fat, usually defined as Body Mass Index (BMI) ≥ 30 kg/m².
2	**Classification (BMI)**	Normal: 18.5–24.9 kg/m² Overweight: 25–29.9 kg/m² Obesity Class I: 30–34.9 kg/m² Class II: 35–39.9 kg/m² Class III (Severe): ≥ 40 kg/m²
3	**Etiology (Causes)**	Primary: Excess calorie intake, sedentary lifestyle Secondary: Genetic factors, endocrine disorders (hypothyroidism, Cushing's syndrome), drugs (steroids, antidepressants)
4	**Pathogenesis**	Energy intake > energy expenditure → excess calories stored as fat → adipocyte hypertrophy & hyperplasia → hormonal imbalance (leptin resistance, insulin resistance) → further fat accumulation
5	**Risk Factors**	Poor diet, lack of exercise, genetics, psychological factors, urban lifestyle
6	**Clinical Features**	Increased body weight, fatigue, breathlessness, joint pain, reduced mobility
7	**Diagnostic Tests**	BMI calculation Waist circumference Lipid profile Blood glucose levels
8	**Treatment – Lifestyle**	Low-calorie diet, regular physical activity, behavioral therapy
9	**Treatment – Drugs**	Appetite suppressants Lipase inhibitors like Orlistat
10	**Surgical Treatment**	Bariatric surgery (gastric bypass, sleeve gastrectomy)
11	**Complications**	Type 2 diabetes, hypertension, cardiovascular disease, fatty liver, osteoarthritis

THANK YOU

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