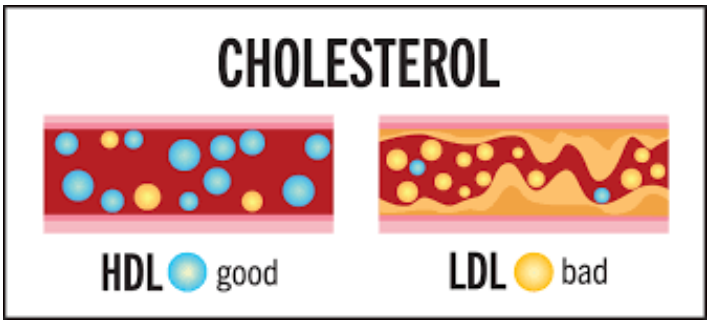
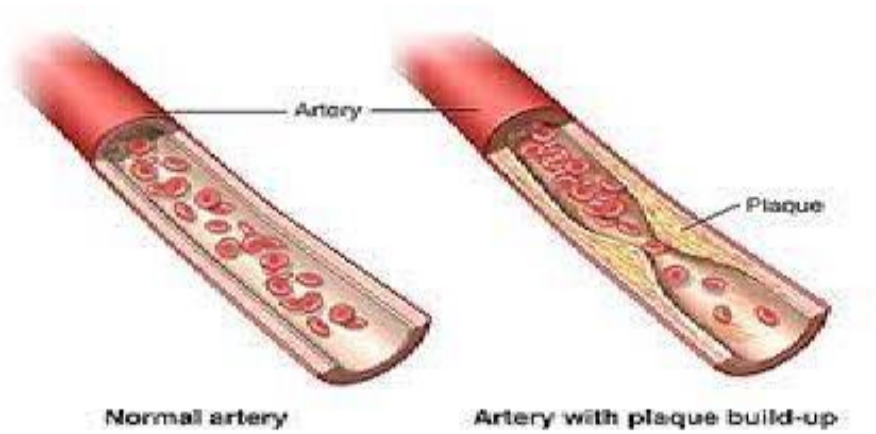
Cholesterol metabolism

- ***Cholesterol Significance:***
  - *Cholesterol is the **most important animal sterol**.*
  - *Cholesterol is the precursor of other steroids **(vitamin D, bile salts, sex hormones and corticosteroids).***
  - *Cholesterol is essential for **cell membranes**.*
  - *Cholesterol is transported to tissues in the form of **lipoproteins**.*
  - *Cholesterol is stored as **cholesterol ester**.*
  - ***High Denisty Lipoprotein (HDL)** transports excess cholesterol from tissues to the liver.*
  - ***Low Denisty Lipoprotein (LDL)** transports cholesterol from the liver to the peripheral tissues.*
  - *Excess peripheral cholesterol forms fatty deposits in arteries called **plaques** leading to **atherosclerosis**.*

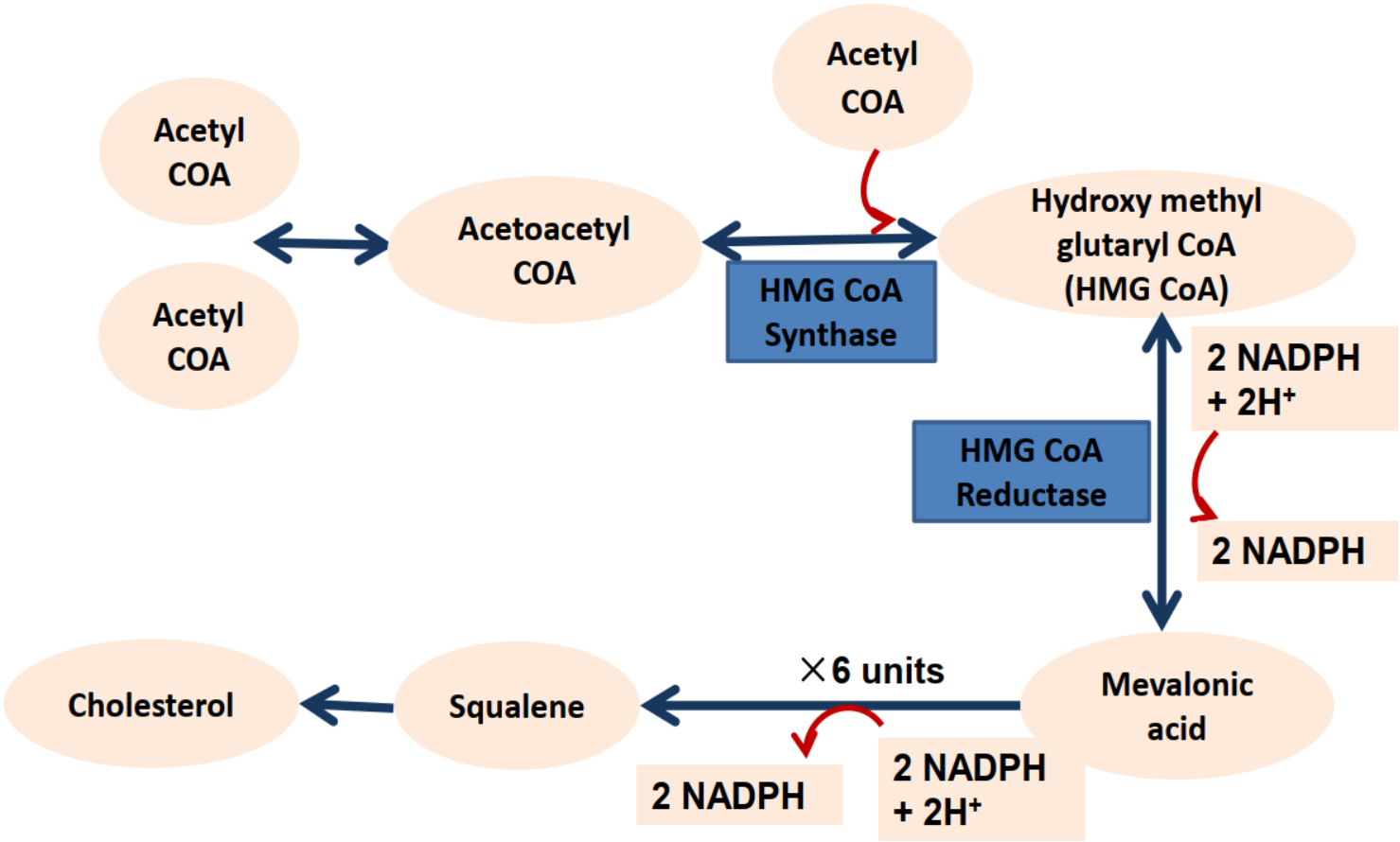




Cholesterol biosynthesis

- **Site:**
  - *Cholesterol is synthesized by the **cytosol** and **endoplasmic reticulum** of **all nucleated cells.***
  - ***Liver** is the main source of plasma cholesterol.*
  - *All carbon atoms of cholesterol are derived from **acetyl CoA.***

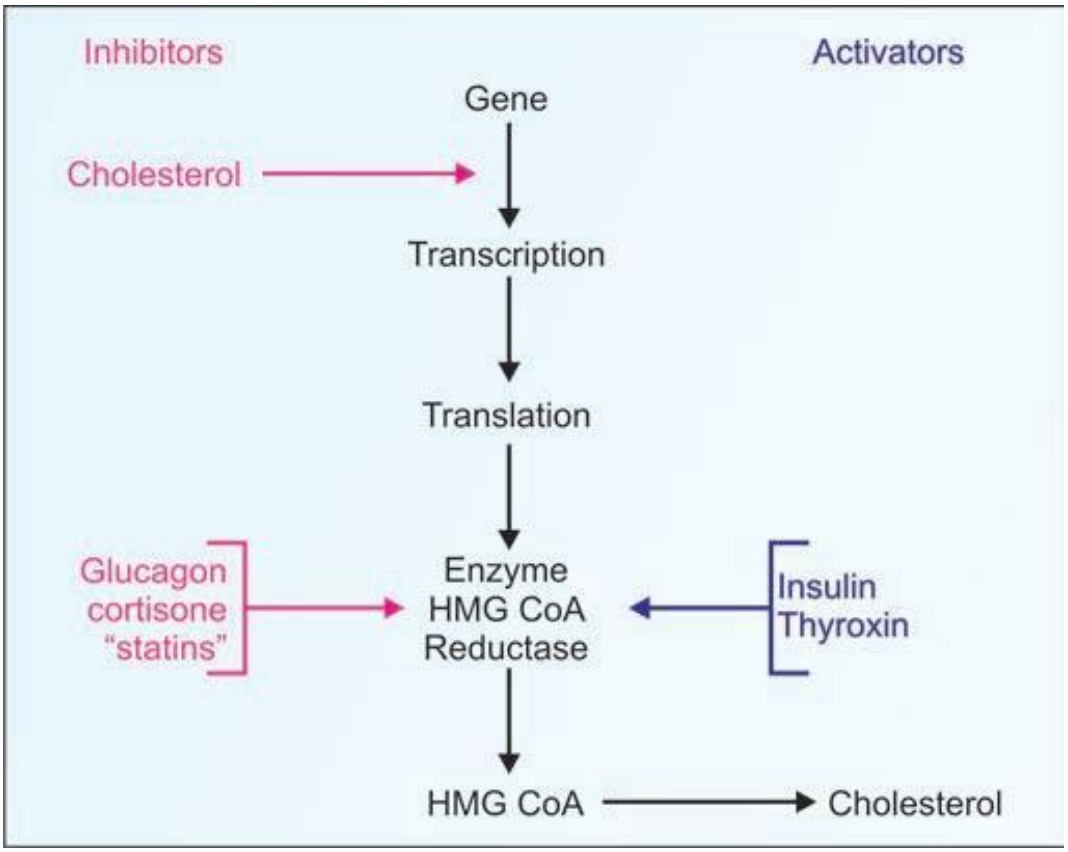
- **Steps:**



- ***Regulation of cholesterol biosynthesis:***

  - ***HMG CoA reductase is the rate-limiting enzyme and is controlled by:***

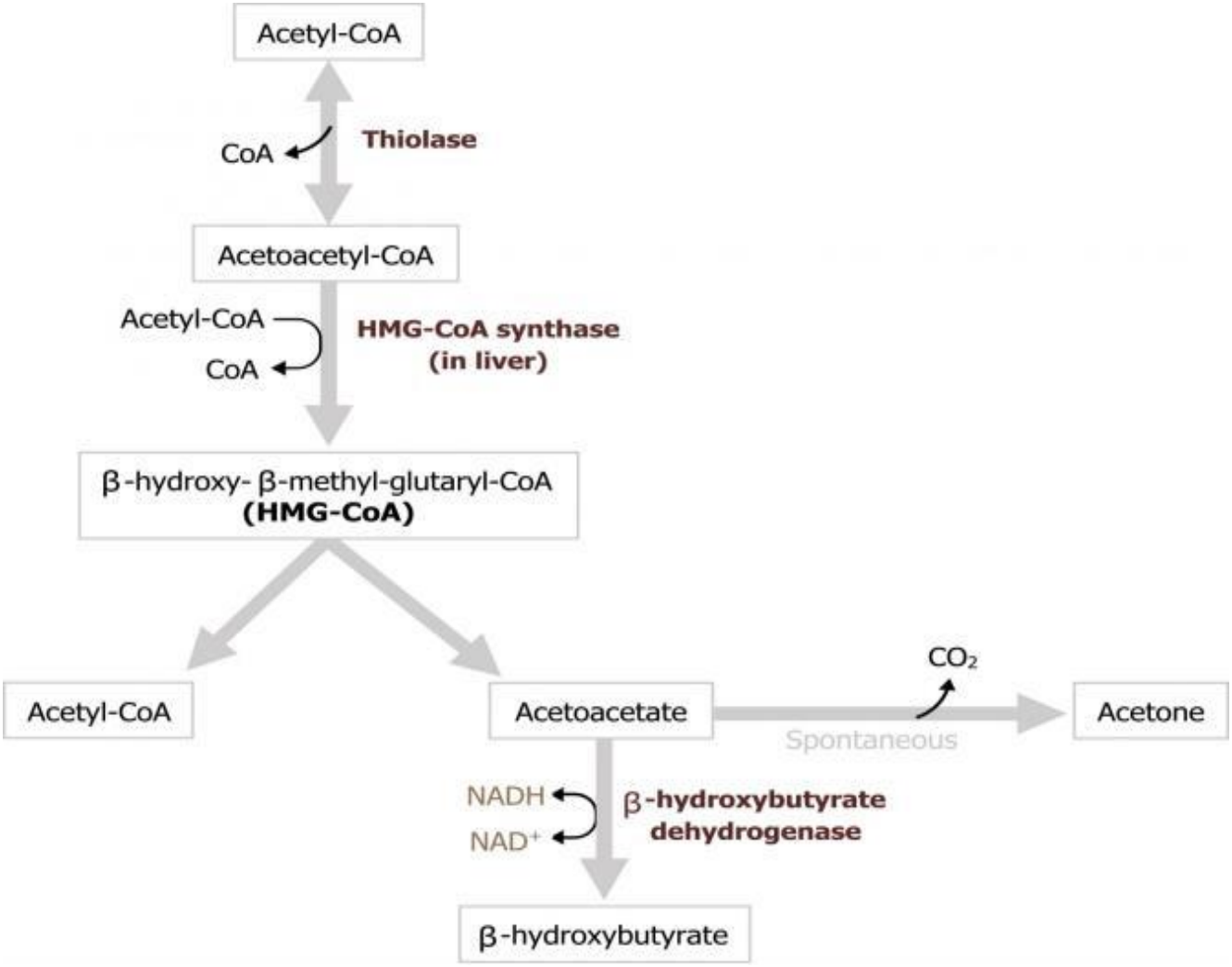
1. Regulation of transcription of the gene:	• *It is considered long-term regulation, when **sufficient cholesterol** is present, transcription of the gene is suppressed, and vice versa.*
2. Covalent modification:	• *It is considered short-term regulation.* • ***Insulin** and **thyroxine** activate the enzyme by dephosphorylation.* • ***Glucagon** & **cortisol** deactivate enzyme by phosphorylation.*
3. The rate of degradation of enzyme protein:	• *The rate of enzyme degradation is increased by the **increased sterols** level.*
4. Competitive inhibitors:	• ***Statins** are medications that function as competitive inhibitors of HMG-CoA reductase, thus reducing the serum level of cholesterol.*

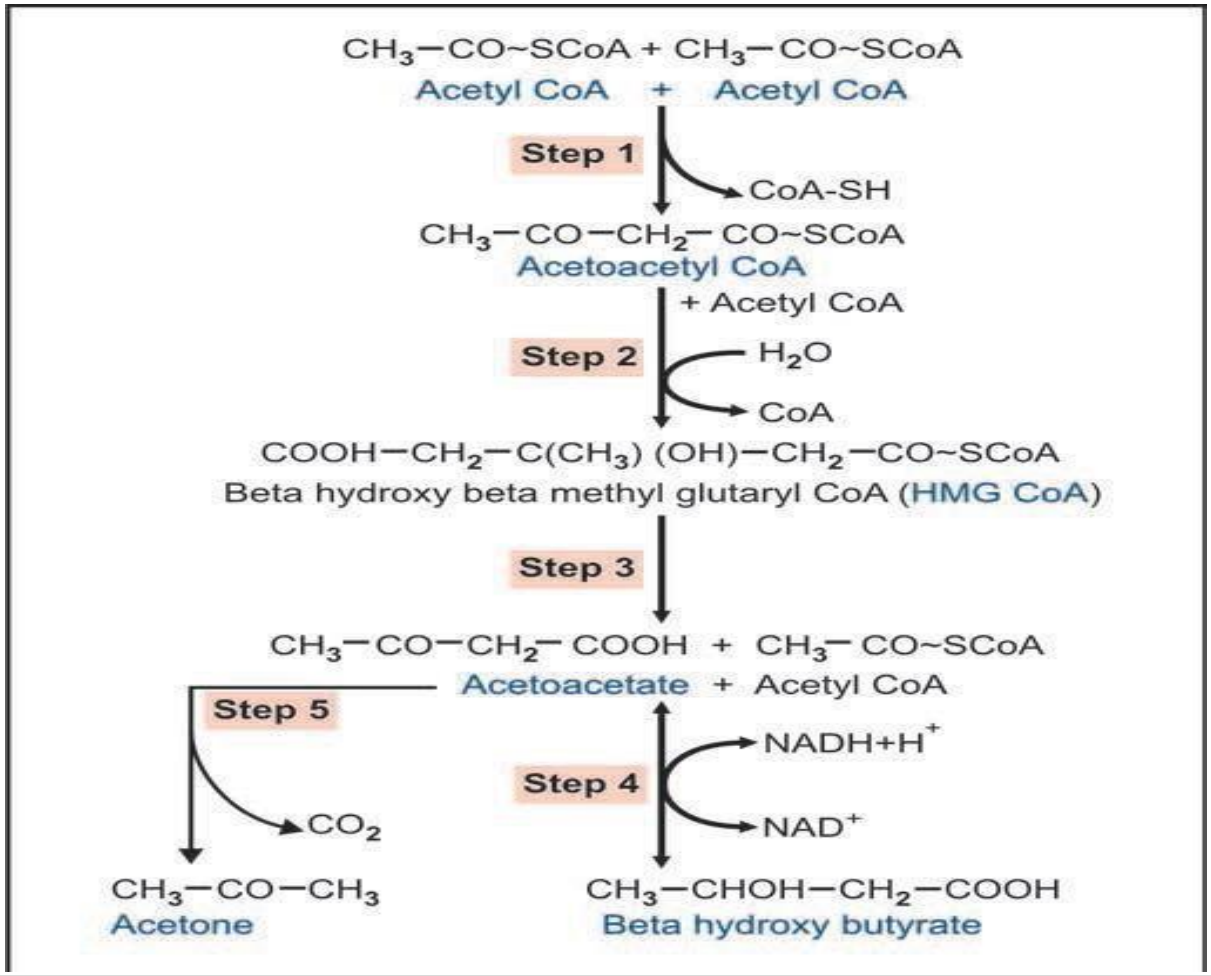


Ketone body metabolism

Ketogenesis

Definition:	• *Ketogenesis is the formation of ketone bodies (KB) from acetyl COA resulting from B oxidation of fatty acids* ***in excess of optimal function of Krebs cycle.***
Types of KB:	• ***Acetoacetic acid, β- hydroxyl butyric acid and acetone.***
Site:	• *The* ***mitochondria*** *of the* ***liver.***
Importance:	***1)*** *The acetyl CoA formed from fatty acids can enter and get oxidized in TCA cycle only when carbohydrates are available.* ***2)*** *During* ***starvation and diabetes mellitus****, the acetyl CoA takes the alternate fate of formation of ketone bodies in the liver.* ***3)*** *Ketone bodies* ***go via blood to extrahepatic tissues*** *where they become oxidized to energy, CO2 and water (****ketolysis****).* ***4)*** *Ketogenesis may be considered as* ***a preparatory step*** *performed in the liver to facilitate the oxidation of FA by extrahepatic tissues as most tissues can more easily oxidize ketone bodies than FAs.*
Steps:	***1) Two molecules of acetyl CoA condense*** *to produce* ***acetoacetyl CoA*** *in a reaction catalyzed by* ***thiolase.*** ***2) Formation of hydroxymethylglutaryl CoA:*** ➢ *(HMG-CoA) from acetoacetyl CoA and acetyl CoA in a reaction catalyzed by* ***mitochondrial HMG-CoA synthase.*** ***3) Cleavage of HMG-CoA*** *by HMG-CoA lyase to form acetyl CoA and acetoacetate.* ***4) Reduction of acetoacetate*** *to* ***B-hydroxybutyrate.*** ***5) Spontaneous decarboxylation*** *of acetoacetate to* ***acetone*** *(the source of the odor on the breath of ketotic diabetic patients)*

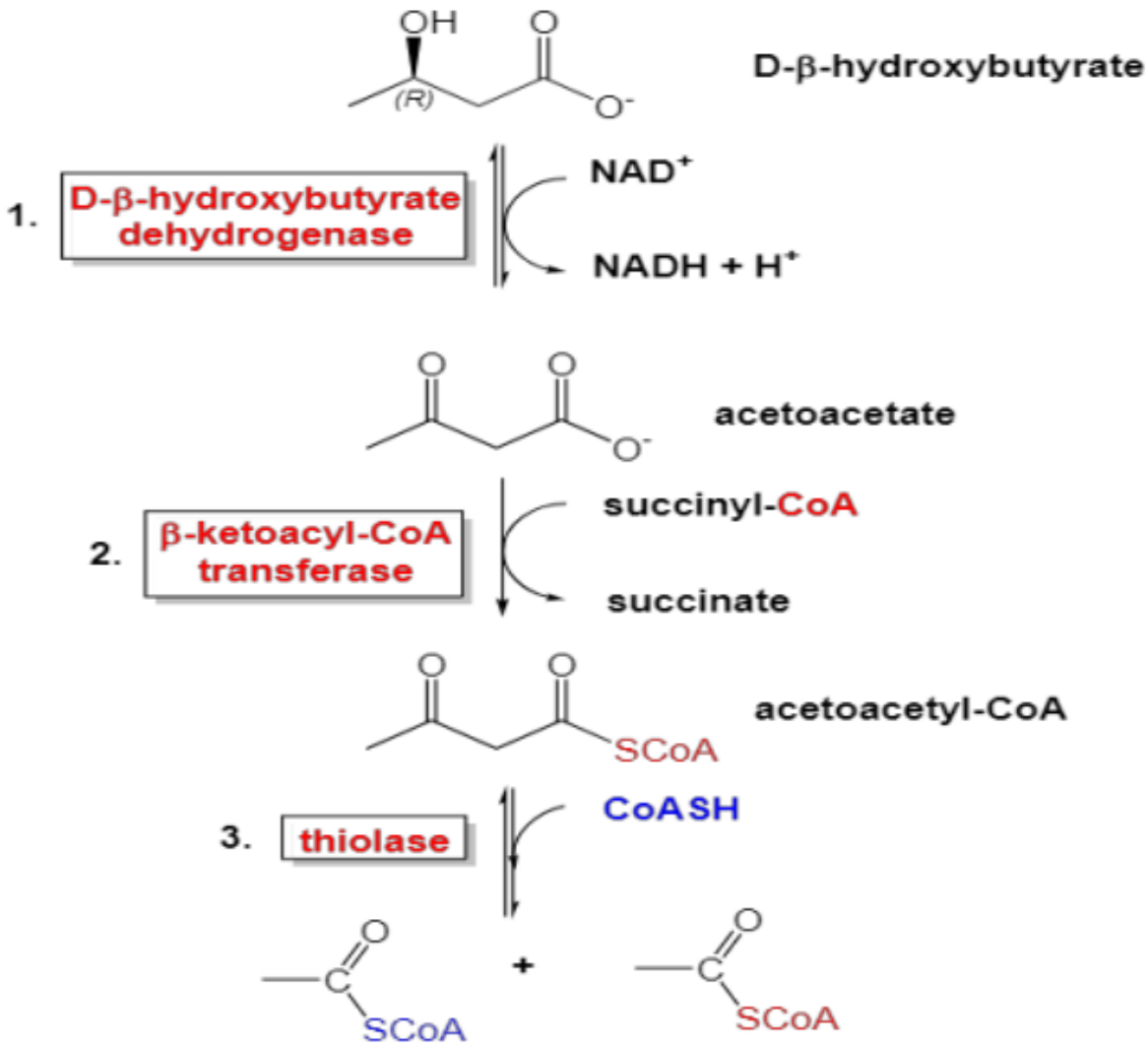

Acetyl-CoA
CoA
Thiolase
Acetoacetyl-CoA
Acetyl-CoA
CoA
HMG-CoA synthase
(in liver)
β-hydroxy- β-methyl-glutaryl-CoA
(HMG-CoA)
Acetyl-CoA
Acetoacetate
CO2
Spontaneous
Acetone
NADH
NAD+
β-hydroxybutyrate
dehydrogenase
β-hydroxybutyrate

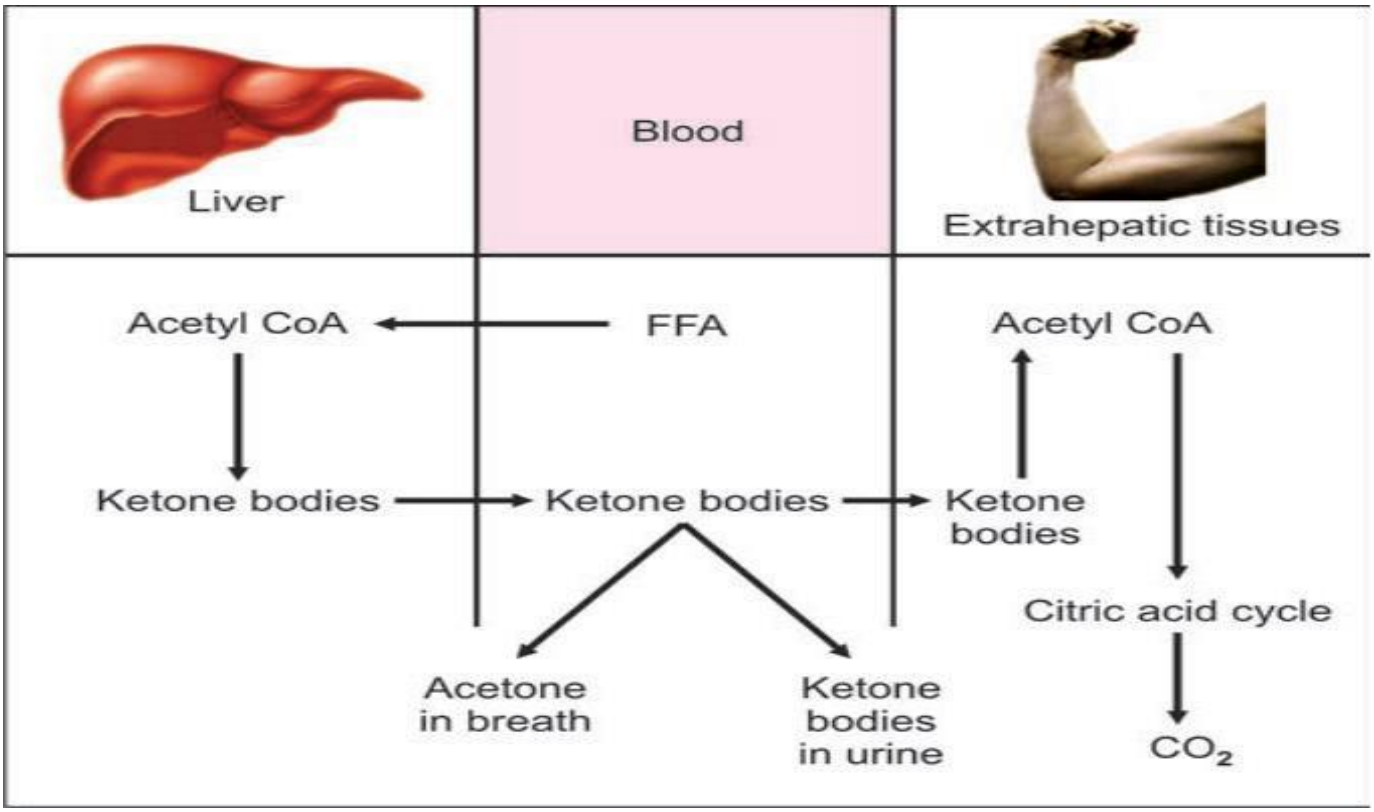

CH3—CO~SCoA + CH3—CO~SCoA
Acetyl CoA + Acetyl CoA
Step 1
CoA-SH
CH3—CO—CH2— CO~SCoA
Acetoacetyl CoA
+ Acetyl CoA
Step 2
H2O
CoA
COOH—CH2—C(CH3) (OH)—CH2—CO~SCoA
Beta hydroxy beta methyl glutaryl CoA (HMG CoA)
Step 3
CH3—CO—CH2— COOH + CH3— CO~SCoA
Acetoacetate + Acetyl CoA
Step 5
CO2
Step 4
NADH+H+
NAD+
CH3—CO—CH3
Acetone
CH3—CHOH—CH2—COOH
Beta hydroxy butyrate

Ketolysis

Definition:	• *Oxidation of ketone bodies for production of energy.*
Site:	• *Mitochondria of **extrahepatic tissues** such as muscle and kidney not in liver due to deficiency of the required enzymes.* • ***During starvation**, ketone bodies in the blood increase to a level that permits entry into **brain cells**, where they are oxidized.*
Importance:	• *Ketolysis **completes the oxidation of FA,** which started in the liver.* • *It is a major source of energy to extrahepatic tissues during **starvation**.*
Steps:	*1) Acetoacetate can **enter cells directly**, or it can be **produced from** the oxidation of Bhydroxybutyrate.* ➢ *NADH is produced by this reaction and can generate adenosine triphosphate (ATP).* *2) Acetoacetate is activated by reacting with succinyl CoA to **form acetoacetyl CoA** and succinate.* ➢ *This reaction is catalyzed by thiophorase enzyme also called CoA transferase.* *3) **Acetoacetyl CoA is cleaved by thiolase** to form two molecules of acetyl CoA, which enter the TCA cycle.*

KETONE BODY UTILIZATION





Ketosis

- **Definitions:**

Ketonemia:	• Condition characterized by **increased production** of excessive amounts of **ketone bodies** in **blood**.
Ketonuria:	• Condition characterized by **increased production** of excessive amounts of **ketone bodies** in **urine**.
Ketosis:	• Condition characterized by a **combination** of **ketonemia**, **ketonuria** and smell of acetone in breath.

NB:

- The utilization of ketone bodies by the extrahepatic tissues is considerable.
- They are **oxidized proportionately to their concentration** in the blood.
- If the blood level is raised, **oxidation of ketone bodies increases** until at a concentration of approx. **70 mg/100 ml**, they saturate oxidative machinery and any further increase in the rate of ketogenesis raises the blood and urine concentration.

Clinical correlate

- ***A 20-year-old man is brought to the emergency department with nausea, and vomiting with increasing polyuria, polydipsia, and drowsiness since the day before.***
- ***He was diagnosed with type 1 diabetes 2 years previously. He mentions that he ran out of insulin 2 days ago.***
- ***On examination he is drowsy, Kussmaul breathing with acetone odor.***
- ***Chemical investigations on blood showed elevated levels of glucose, H ion concentrations and serum ketones.***
- ***Urine examination reveals presence of ketone bodies.***

➢ ***What is your provisional diagnosis?***

- *The patient has* ***diabetic ketoacidosis (DKA).***
- *High glucose is due to* ***diabetes Mellitus.***
- ***Ketoacidosis*** *is confirmed by presence of ketone bodies in urine sample.*