Biochemistry
2nd stage

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ILO:K2,S11,A1

Objectives:

The students are learned to understand the Ketone Bodies Metabolism including the following points:

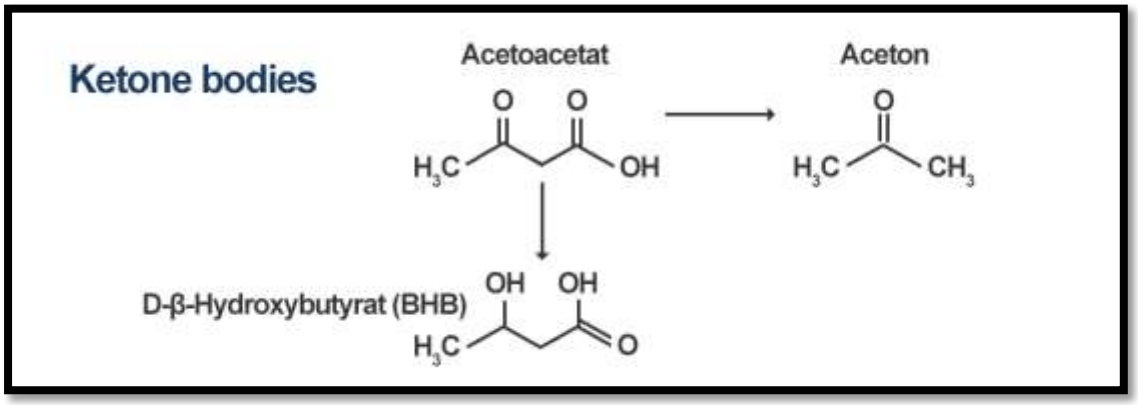
- **Definition**
- **Ketogenesis**
- **Utilization**
- **Mechanism of Ketosis**

KETONE BODIES METABOLISM

Ketone body metabolism occurs during the high rates of fatty acid oxidation, primarily in the liver. The large amount of acetyl-CoA generated, which exceeds the capacity of the TCA cycle, results in the synthesis of ketone bodies.

Ketogenesis

Acetoacetate is the **primary ketone body** while beta-hydroxy butyrate and acetone are **secondary ketone** bodies. They are synthesised exclusively by the **liver mitochondria**.



Step 1. Condensation

Two molecules of acetyl CoA are condensed to form acetoacetyl CoA.

Step 2. Production of HMG CoA

One more acetyl CoA is added to acetoacetyl CoA to form HMG CoA (beta hydroxy beta methyl glutaryl CoA). The enzyme is HMG CoA synthase. **Mitochondrial HMG CoA is used for ketogenesis**, while cytosolic fraction is used for cholesterol synthesis.

Step 3. Lysis

Then HMG CoA is lysed to form acetoacetate. Acetoacetate may also be formed by the degradation of carbon skeleton of ketogenic amino acids like leucine, lysine, phenylalanine and tyrosine. HMG CoA lyase is present **only in liver**.

Step 4. Reduction

Beta-hydroxy butyrate is formed by reduction of acetoacetate. Ratio between acetoacetate and beta hydroxy butyrate is decided by the cellular NAD:NADH ratio.

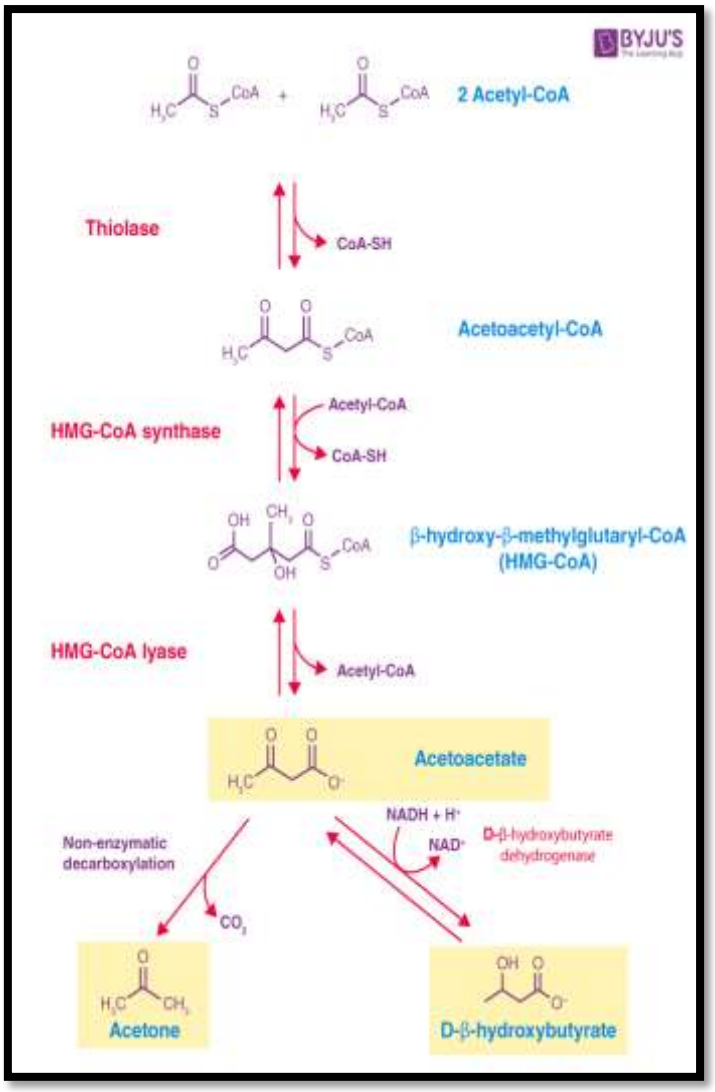
Step 5. Spontaneous decarboxylation

Acetone is formed

β hydroxy butyrate is quantitatively the predominant ketone bodies found in the blood and urine of uncontrolled diabetes (diabetes with ketosis).

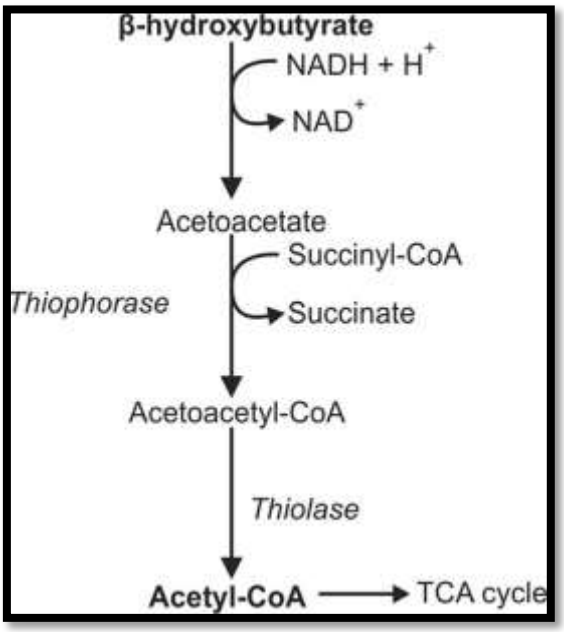
Q. Why the β hydroxy butyrate is quantitatively the predominant ketone bodies found in the blood and urine ?

Because the formation of the ketone bodies is the result of increase the rate of β oxidtion that result in increase the production of NADH (more than the NAD) this NADH catalyze the conversion of acetoacetae to β hydroxy butyrate.



Ketolysis

The ketone bodies are formed in the liver; but they are utilised by **extrahepatic tissues**. The heart muscle and renal cortex prefer the ketone bodies to glucose as fuel. Tissues like skeletal muscle and brain can also utilise the ketone bodies as alternate sources of energy, if glucose is not available. Acetoacetate is activated to acetoacetyl CoA by **thiophorase** enzyme.

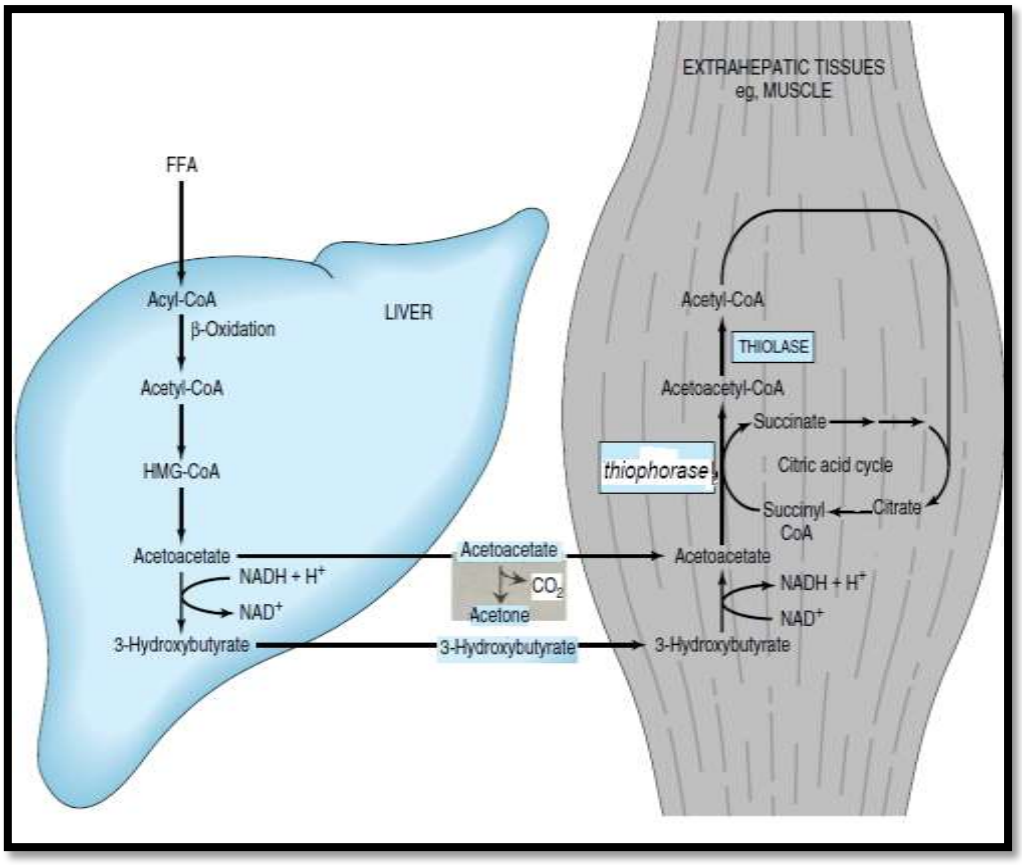


KETOSIS

i. Normally the rate of synthesis of ketone bodies by the liver is such that they can be easily metabolised by the extrahepatic tissues. Hence the blood level of ketone bodies is less than 1 mg/dl and only traces are excreted in urine (not detectable by usual tests).

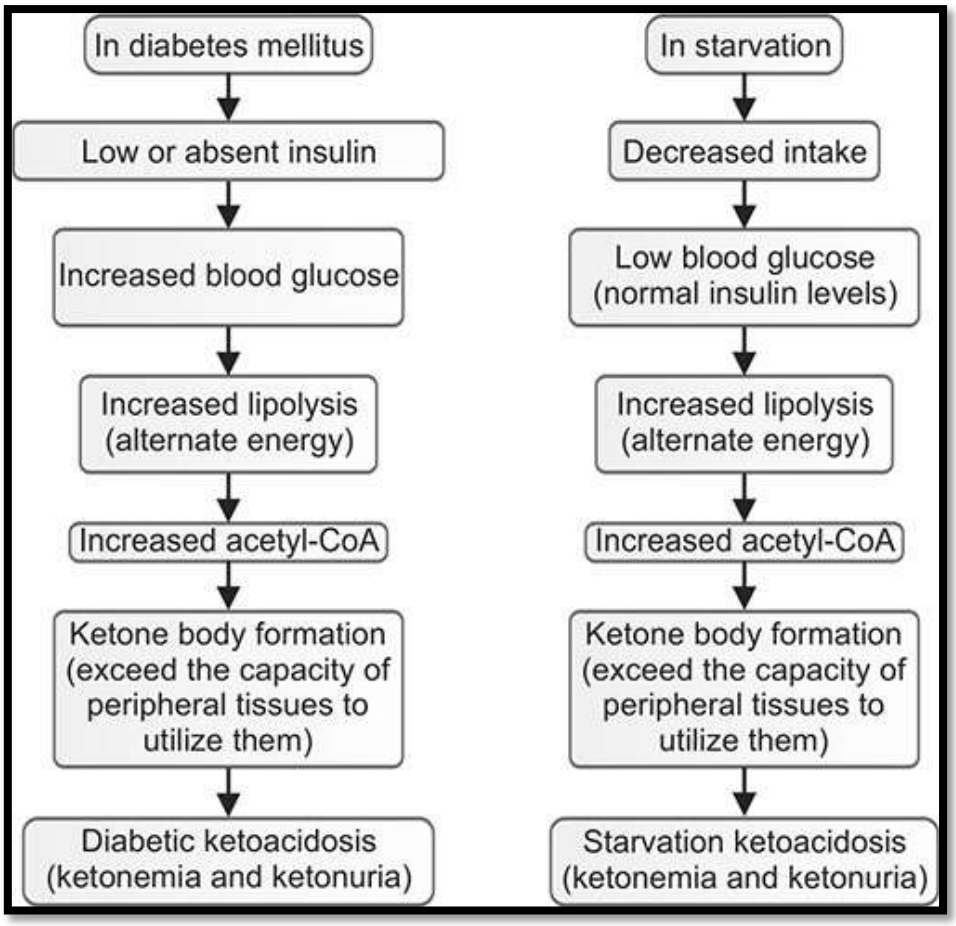
ii. But when the rate of synthesis exceeds the ability of extrahepatic tissues to utilise them, there will be accumulation of ketone bodies in blood.

iii. This leads to **ketonemia**, excretion in urine (**ketonuria**) and smell of **acetone** in breath. All these three together constitute the condition known as **ketosis**.



Causes for Ketosis

1. **Diabetes Mellitus:** Uncontrolled diabetes mellitus is the most common cause for ketosis. Even though glucose is in plenty, the **deficiency of insulin** causes accelerated lipolysis and more fatty acids are released into circulation. Oxidation of these fatty acids increases the acetyl CoA pool.
2. **Starvation:**
   a. the dietary supply of glucose is decreased.
   b. Available oxaloacetate is channelled to gluconeogenesis. The increased rate of lipolysis is to provide alternate source of fuel. The excess acetyl CoA is converted to ketone bodies.
   c. The high **glucagon** level favors ketogenesis. The brain derives 60-75% of energy from ketone bodies under conditions of prolonged starvation.
   d. **Hyperemesis** (vomiting) in early pregnancy may also lead to starvation like condition and may lead to ketosis.



Salient Features of Ketosis

1. Metabolic acidosis. Acetoacetate and betahydroxy butyrate are acids. When they accumulate, metabolic acidosis results .

2. Reduced buffers. The plasma bicarbonate is used up for buffering of these acids.

3. Kussmaul's respiration. Patients will have typical acidotic breathing due to compensatory hyperventilation.

4. Smell of acetone in patient's breath.

5. Osmotic diuresis induced by ketonuria may lead to dehydration.

6. Sodium loss. The ketone bodies are excreted in urine as their sodium salt, leading to loss of cations from the body.

7. Dehydration. The sodium loss further aggravates the dehydration.

8. Coma. Dehydration and acidosis contribute to the lethal effect of ketosis.

Diagnosis of Ketosis

The presence of ketosis can be established by the detection of ketone bodies in urine by usual strip**.** Supportive evidence may be derived from estimation of serum electrolytes, acid-base parameters, glucose and urea estimation.