Incomplete Oxidation Of Fatty Acids And There Products

Ketone Body Metabolism

Ketogenesis And Ketolysis
OR
Formation And Breakdown Of Ketone Bodies

Formation And Fates Of Ketone Bodies In Human Body

What are Ketone Bodies ?

When ? Where? Why? and How?

Ketone Bodies are Formed In Human Body???

- **Ketone body Metabolism Includes:**

–**Ketogenesis** : Formation of Ketone bodies

–**Ketolysis**: Breakdown and Utilization of Ketone bodies

–**Ketosis:** Imbalance in Ketogenesis and Ketolysis.

REVIEW!

–Main role **of Glucose to body cells is to serve** as **primary source of energy.**

–Glucose is **completely oxidized to CO2,H2O and generate ATPs**.

–When body **has very excess Glucose available it is utilized as below:**

– **Required amount** of **Glucose is fully oxidized**

–**Further Stored as Glycogen**

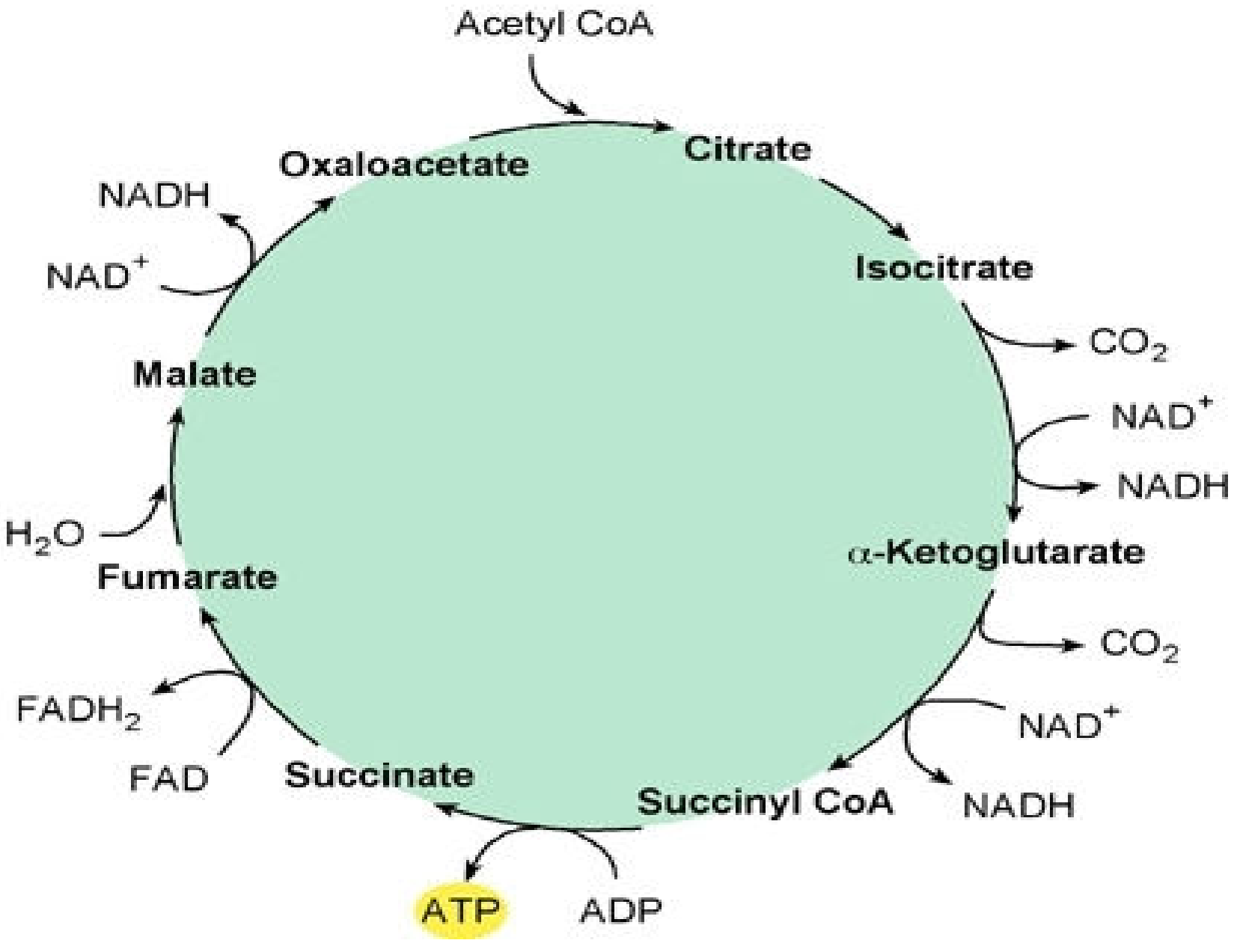
– **Still further transformed to fatty acids and stored as TAG.**

In Emergency Condition

- When **cellular Glucose uptake go below sub normal**

- Fatty acids secondary source of energy undergo **β-oxidation** to **form Acetyl-CoA.**

- Normally, **Acetyl-CoA obtained from beta oxidation of Fatty acids is further oxidized via TCA cycle**.



In Emergency
How Acetyl-CoA Gets Accumulated And Diverted For Ketogenesis ?

- In Emergency Condition
- When **Cellular Glucose is low**

- In response to hormones **Glucagon and Epinephrine**

- There is **increased Lipolysis and beta oxidation Fatty acids.**

- In emergency conditions
- Cellular Glucose levels **decreases**
- **This decreases cellular Oxalo acetate (OAA).**
  - Since **source of OAA is Glucose**
    (By Pyruvate Carboxylase Rxn).
  - **OAA is diverted for Gluconeogenesis which lowers cellular OAA.**

- **OAA is the starting material required to initiate and operate TCA .**

- Due to **low levels** of **cellular OAA**, end product of Fatty acid oxidation- **Acetyl-CoA** is **not utilized via TCA cycle**.

- **The underutilized Acetyl-CoA in the Mitochondrial matrix of Liver gets accumulated and diverted for Ketogenesis.**

Ketogenesis

What Is Ketogenesis?

- **Ketogenesis is biosynthesis of Ketone bodies**

- **In emergency conditions at Mitochondrial matrix of Hepatocytes.**

Condition In Which Ketogenesis Occurs

- Ketogenesis efficiently occur **in Emergency conditions**

  - **Fasting/Starvation Phase**
  - **Low Cellular Glucose Metabolism**

Site For Ketogenesis

OR

Where Does Ketogenesis Occurs ?

- **Ketone bodies are biosynthesized in** the **Liver/Hepatocytes at the Mitochondrial Matrix**

- **Ketone bodies formed in Mitochondria of Hepatocyte come out in cytosol**
- **Later they are diffused** into blood
- **Transported to reach extrahepatic /peripheral tissues**

Who is Precursor For Ketogenesis ?

- **Acetyl CoA is precursor/starting material for Ketogenesis.**

Source Of Acetyl-CoA For Ketogenesis

- Ketone bodies are formed from **Acetyl CoA ,obtained through beta oxidation of Fatty acids.**

- **Acetyl-CoA accumulated in Mitochondrial matrix due to underutilization via TCA cycle is diverted for Ketogenesis.**

Biochemical Basis for Ketogenesis
OR
What Favors Ketogenesis ?
OR
Why Ketogenesis Occurs In Emergency Condition ?

What Factors

Promotes/Triggers Ketogenesis ?

- **Normal Insulin** activity **do not promote Ketogenesis.**
- **Low Insulin** activity **promotes Ketogenesis.**
- **High Glucagon Promotes Ketogenesis.**

- **Availability of Glucose in cells, do not promote Ketogenesis** and form Ketone bodies.
- **Unavailabity of Glucose in cells promote Ketogenesis** and **form Ketone bodies**
- **Increased Lipolysis and Beta Oxidation of Fatty acids promotes Ketogenesis**
- **Under utilization of Acetyl-CoA via TCA and its accumulation in Mitochondrial matrix triggers ketogenesis.**

Biochemical Causes for Ketogenesis

- **In Emergency Condition**

–**Due to Cellular Glucose deprivation**

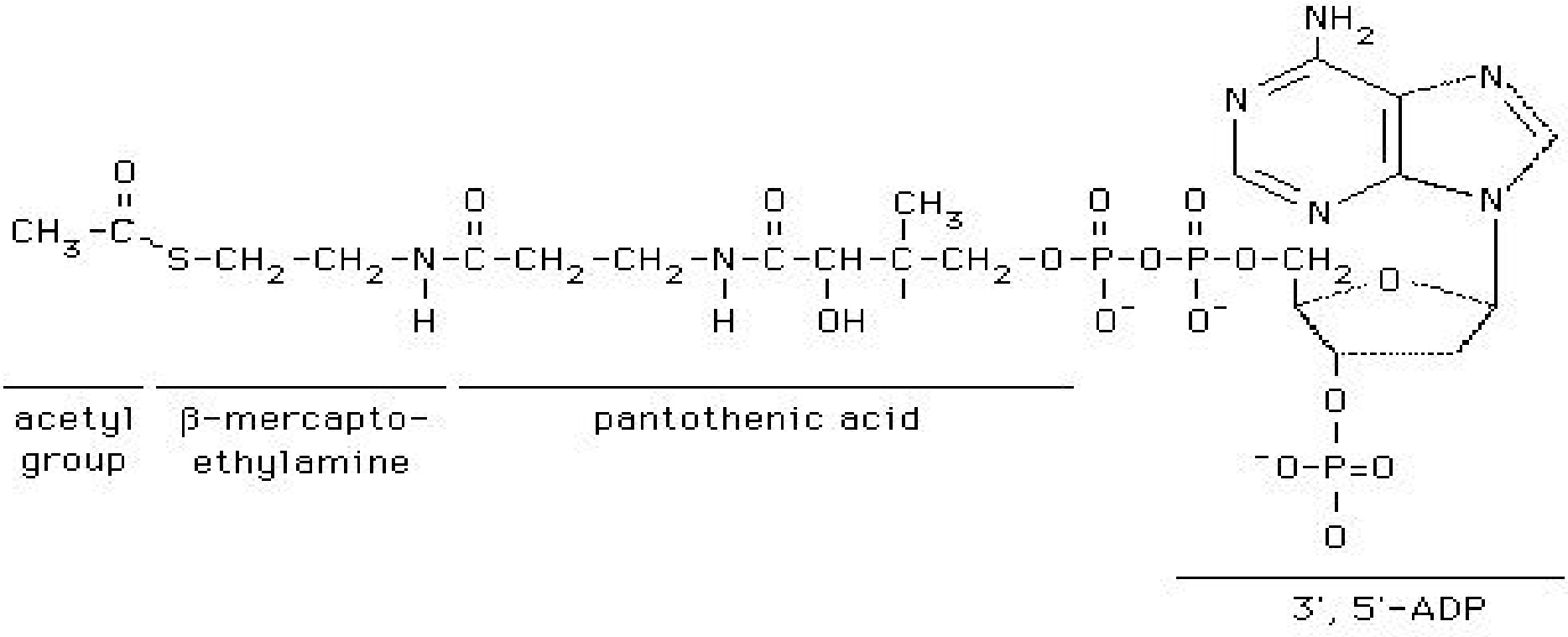
–**Low Glucose metabolism**

–**Low Cellular Oxaloacetate**

–**Oxaloacetate diverted for Gluconeogenesis**

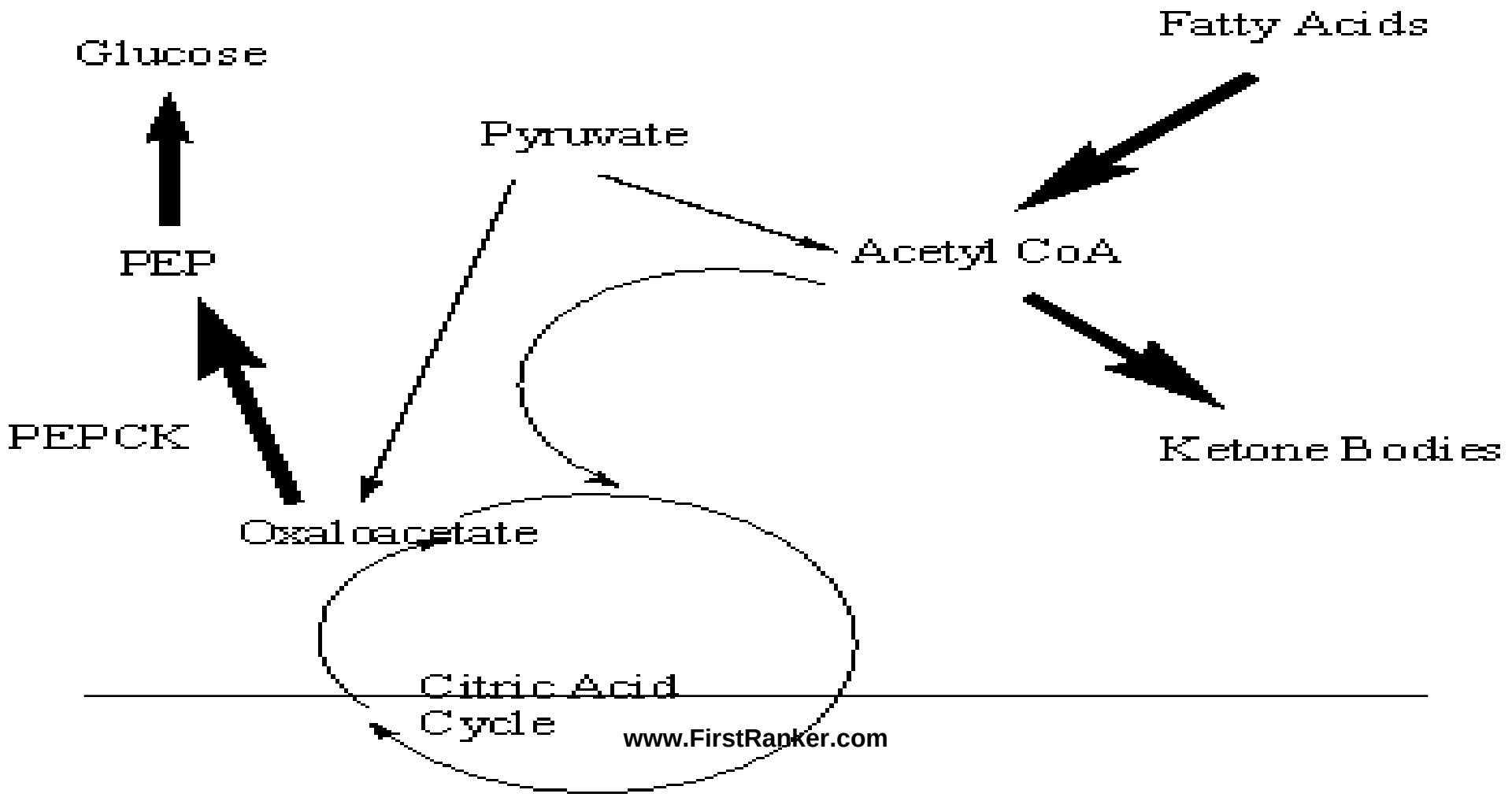
–**Low Operation of TCA cycle**

Complex Str Of Acetyl-CoA Is Impermeable through Mitochondrial Membrane



Acetyl coenzyme A, showing its constituents

Way For KETOGENESIS Is To Remove Accumulated Acetyl-CoA Out Of Mitochondrial Matrix



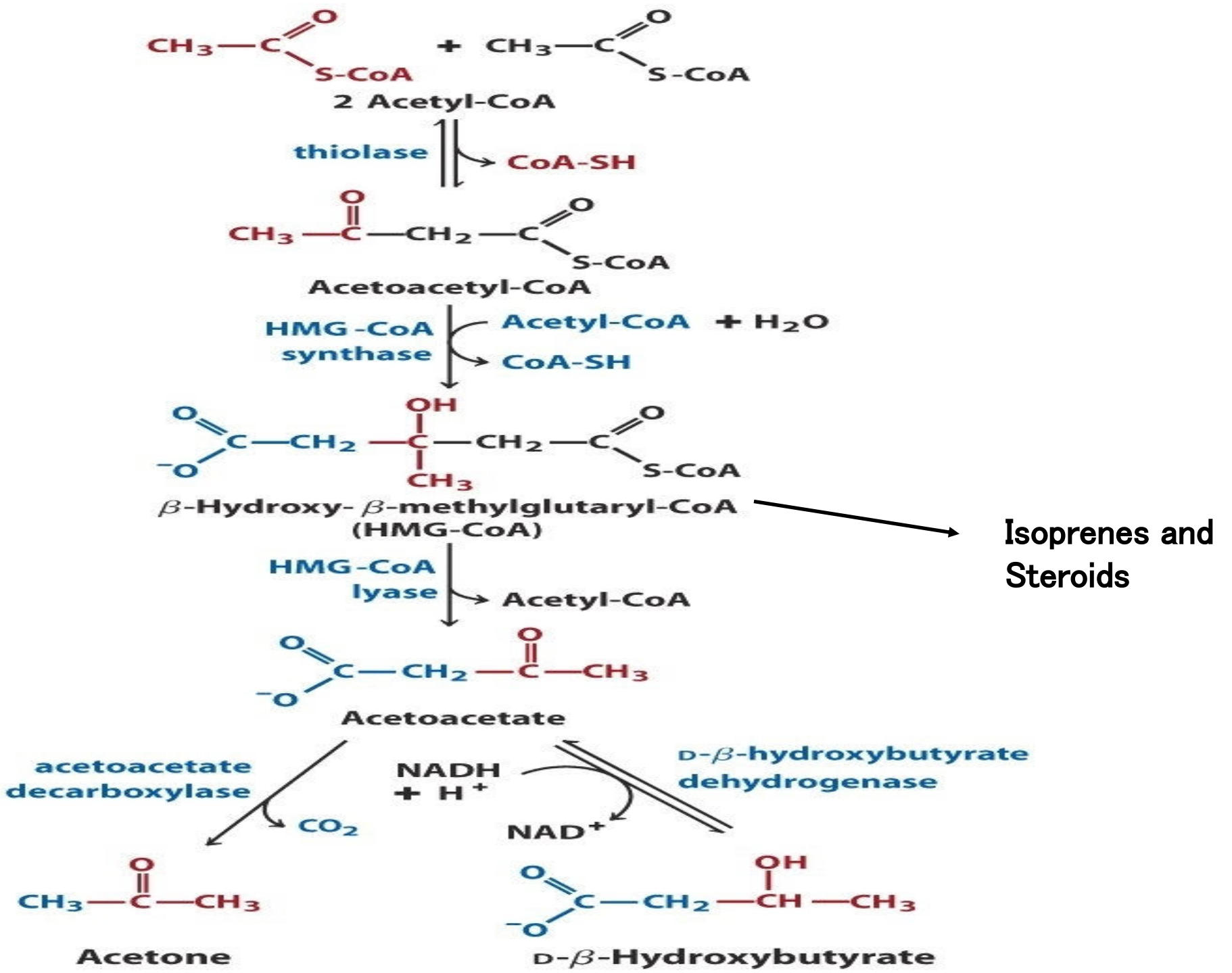
What Are Steps Of Ketogenesis?

Precursor For Ketogenesis

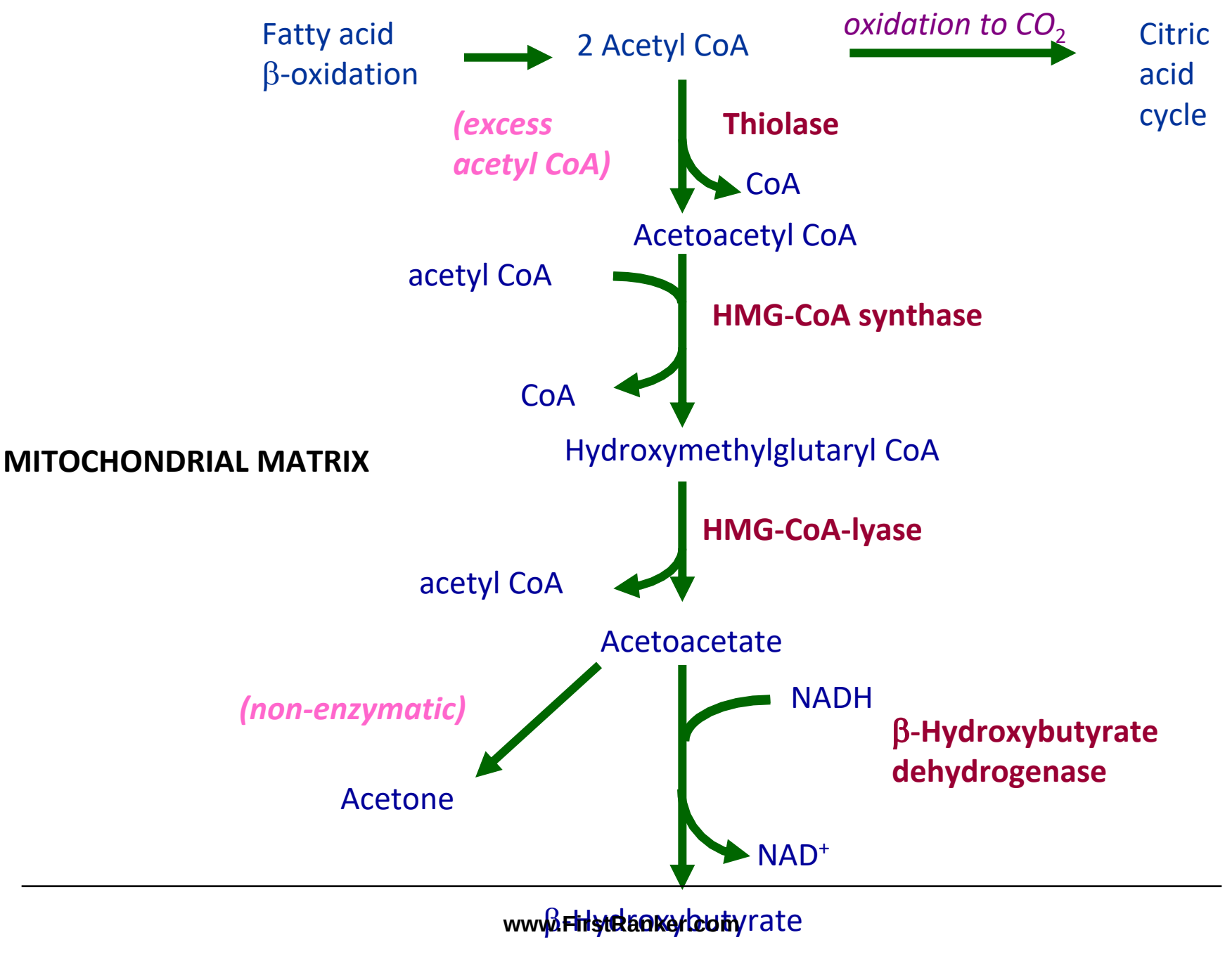
- **Accumulated Acetyl-CoA in Mitochondrial matrix obtained from Beta oxidation of Fatty acids in emergency condition.**

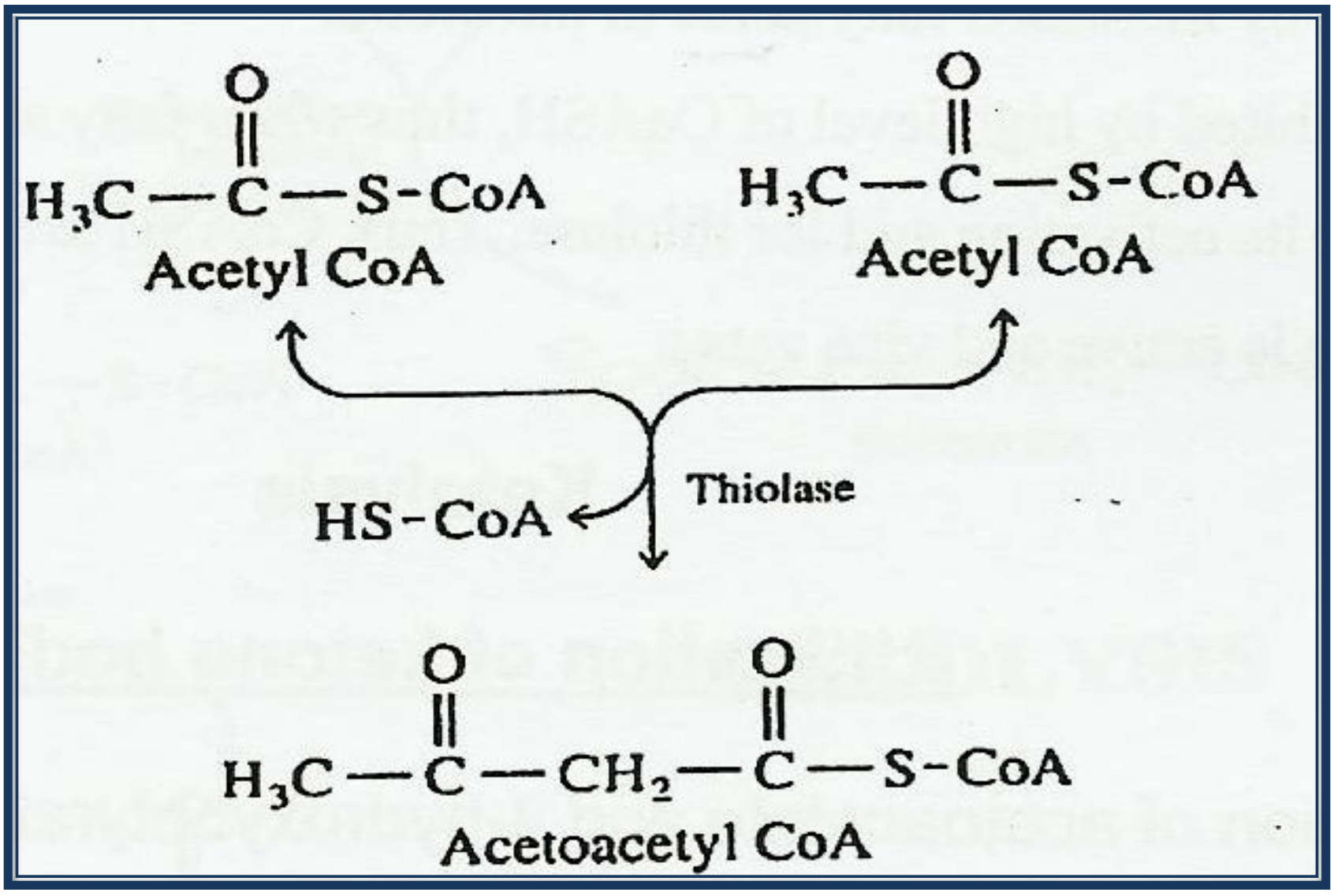
- **Accumulated Acetyl-CoA is** diverted for **Ketogenesis since**.
  - **Acetyl-CoA is complex and impermeable cannot cross mitochondrial membrane.**
  - **Acetyl-CoA is transformed to form Ketone bodies during steps of Ketogenesis.**
  - **Ketone bodies formed from Acetyl-CoA are simple, permeable and cross mitochondrial membrane to come out of Hepatocytes.**

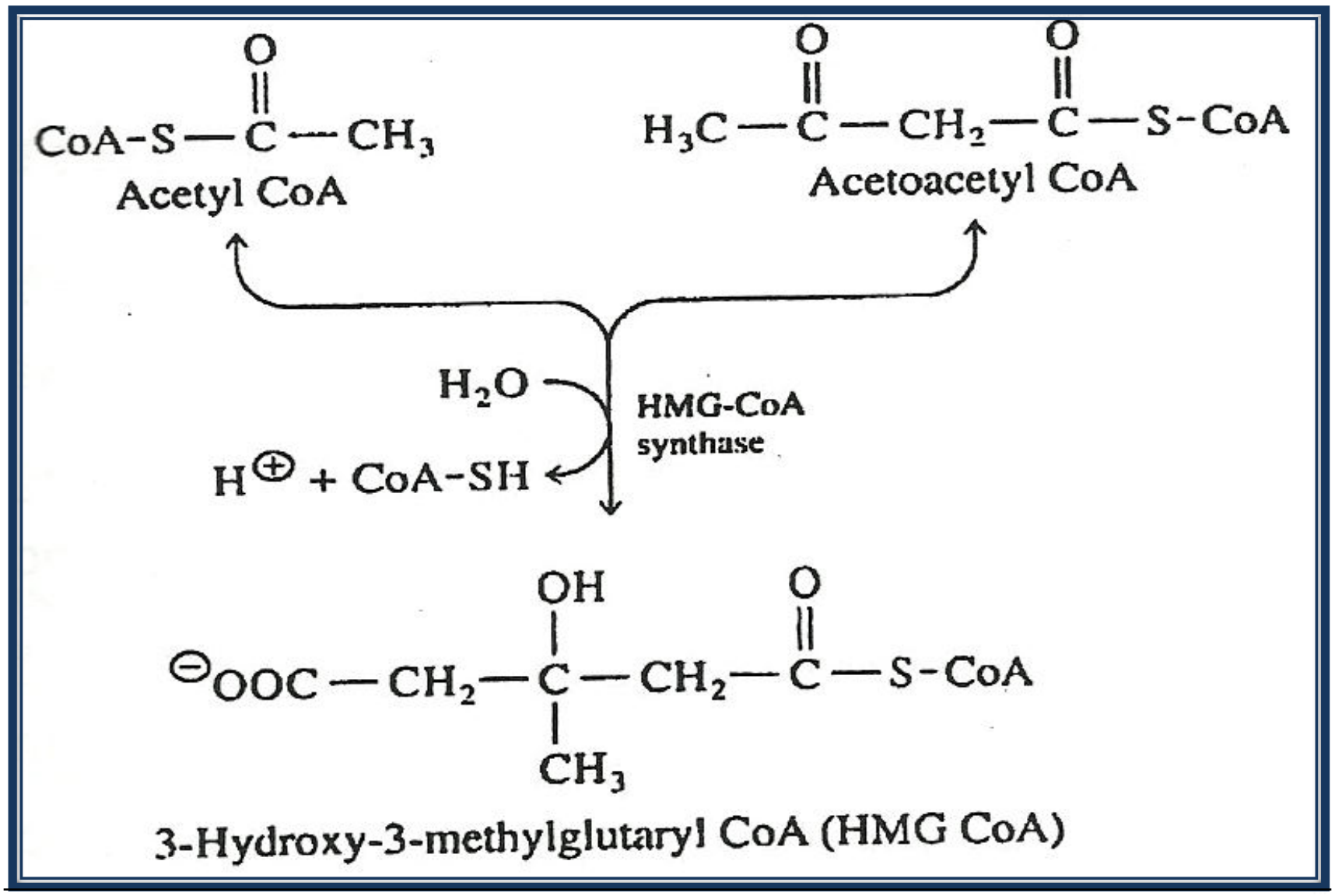
Steps Of Ketogenesis

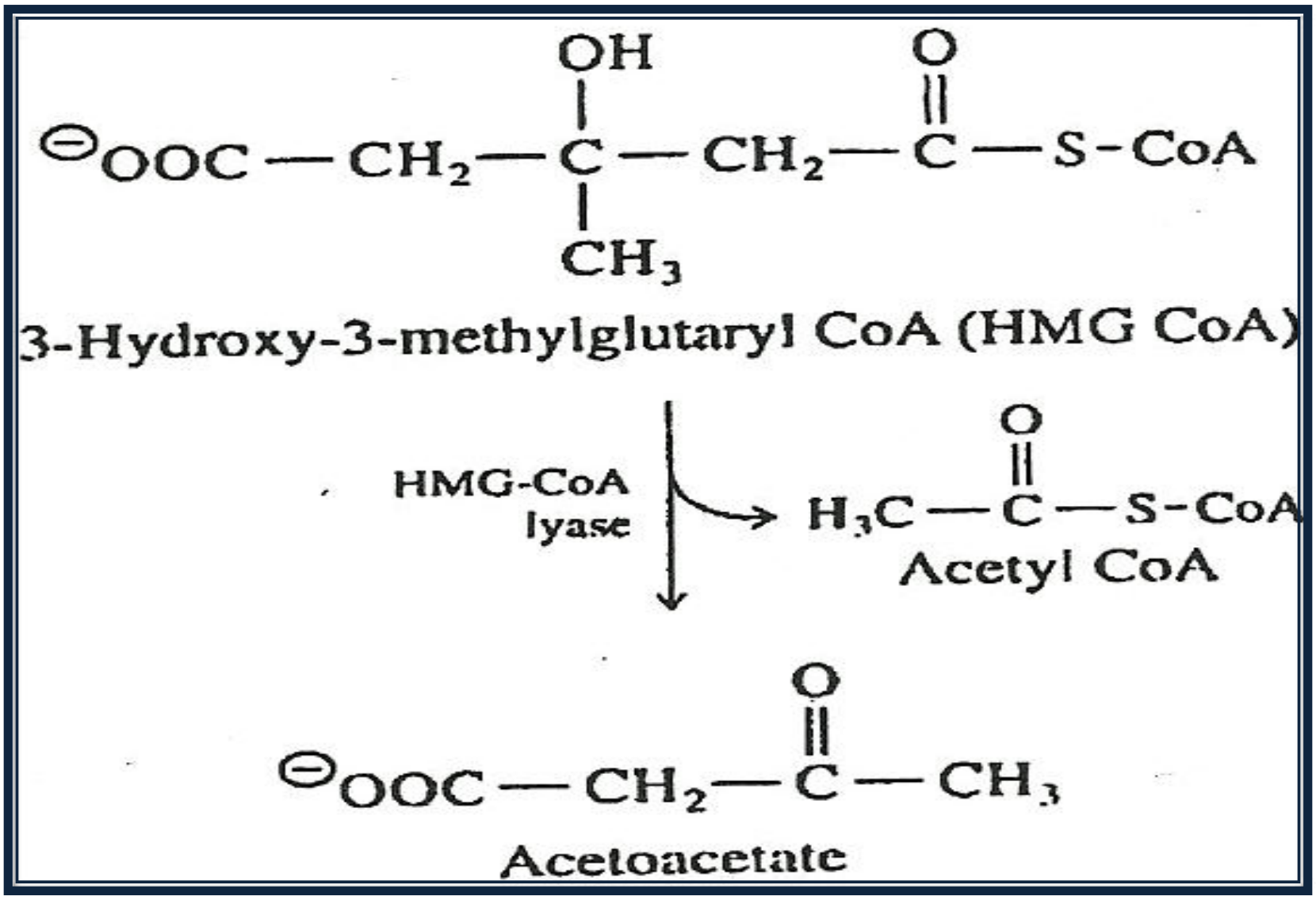


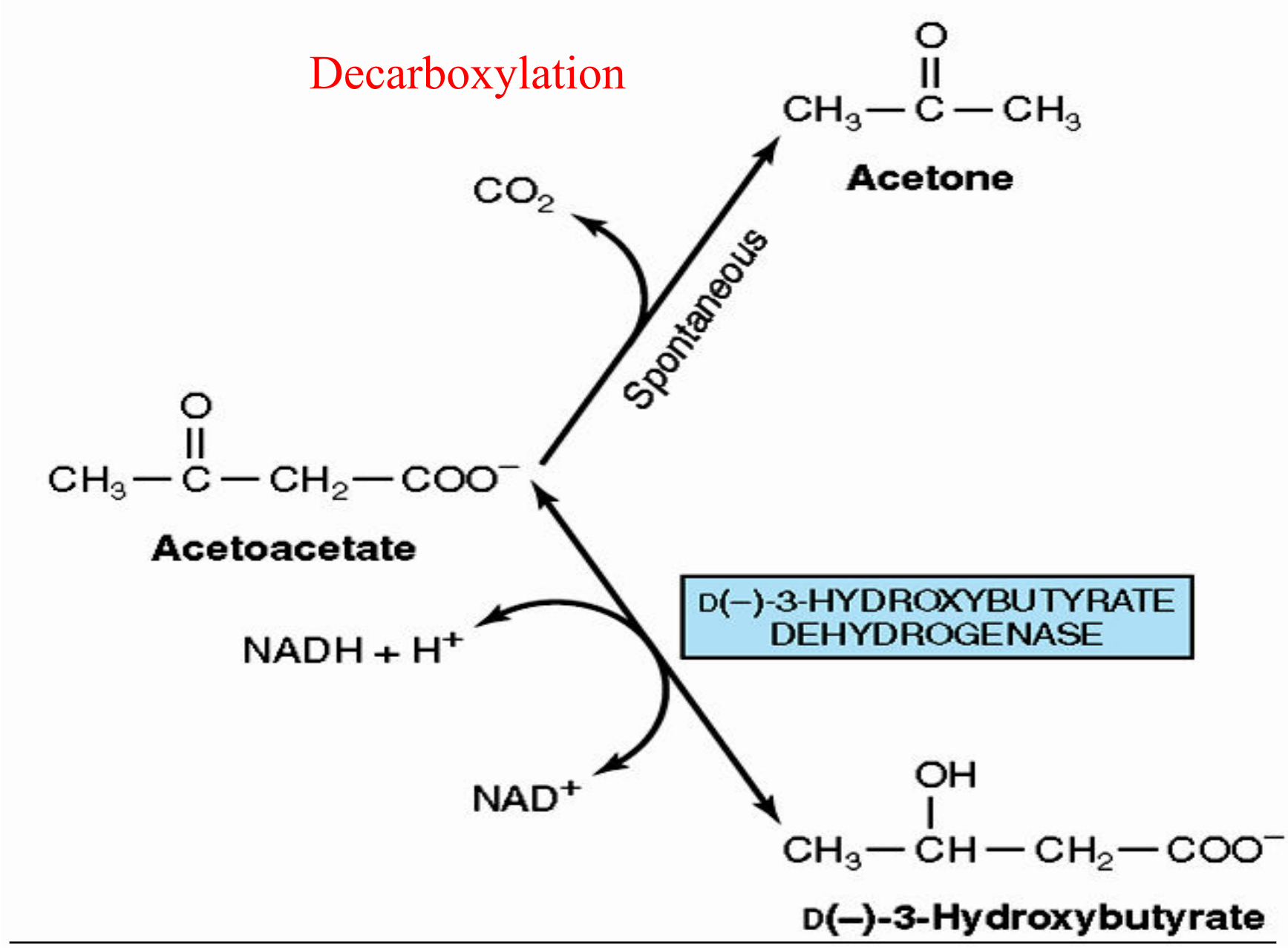
Isoprenes and Steroids



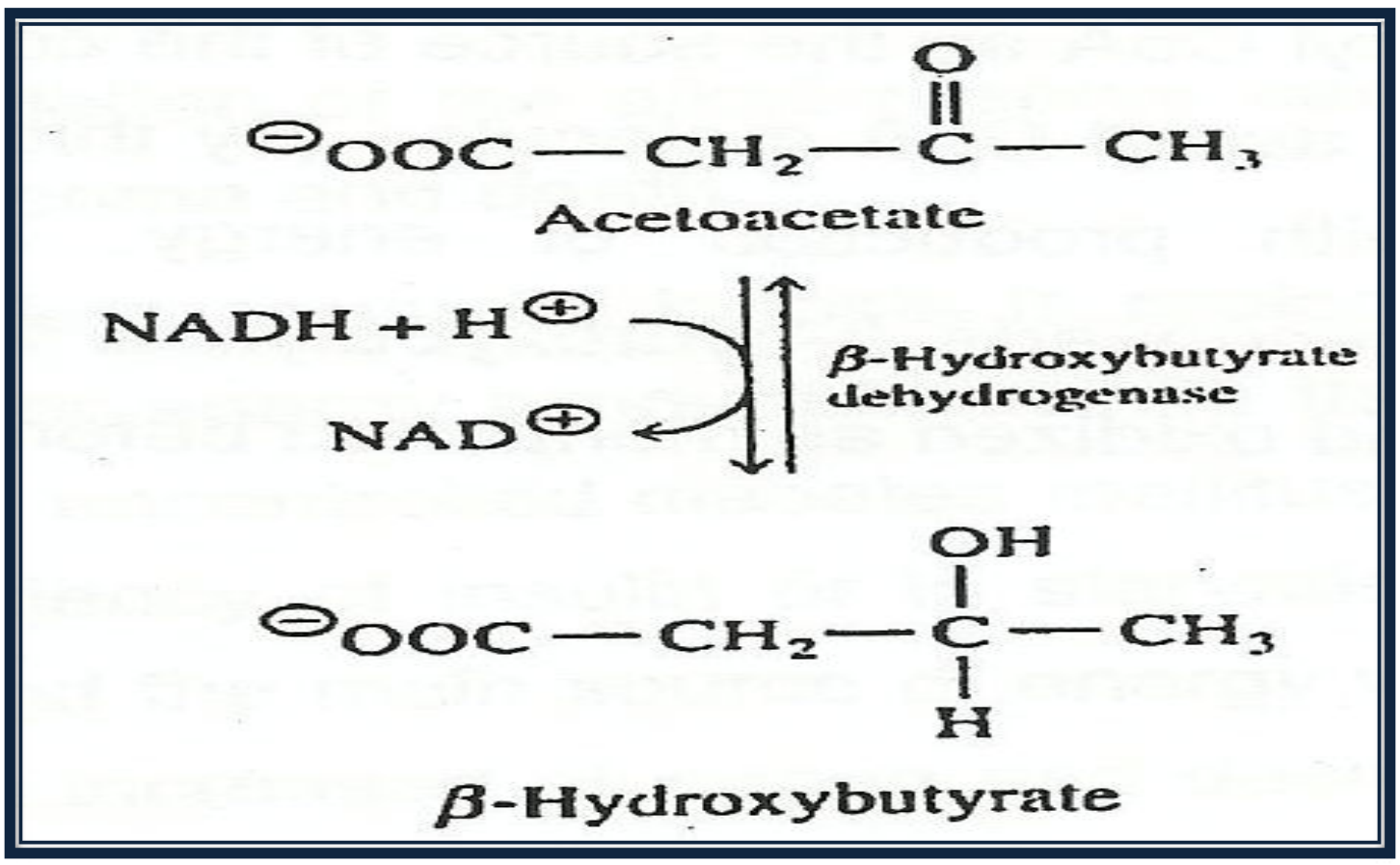


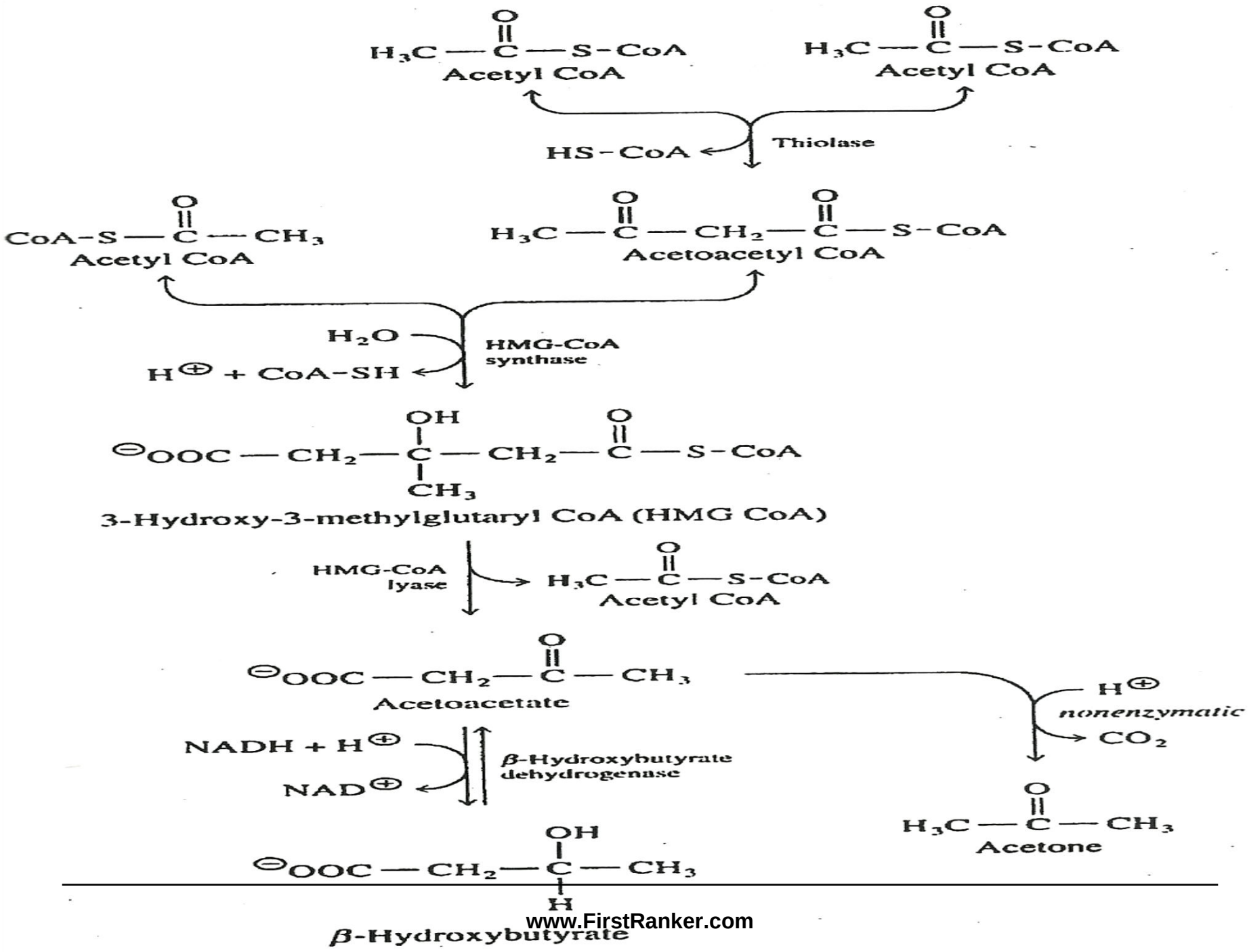


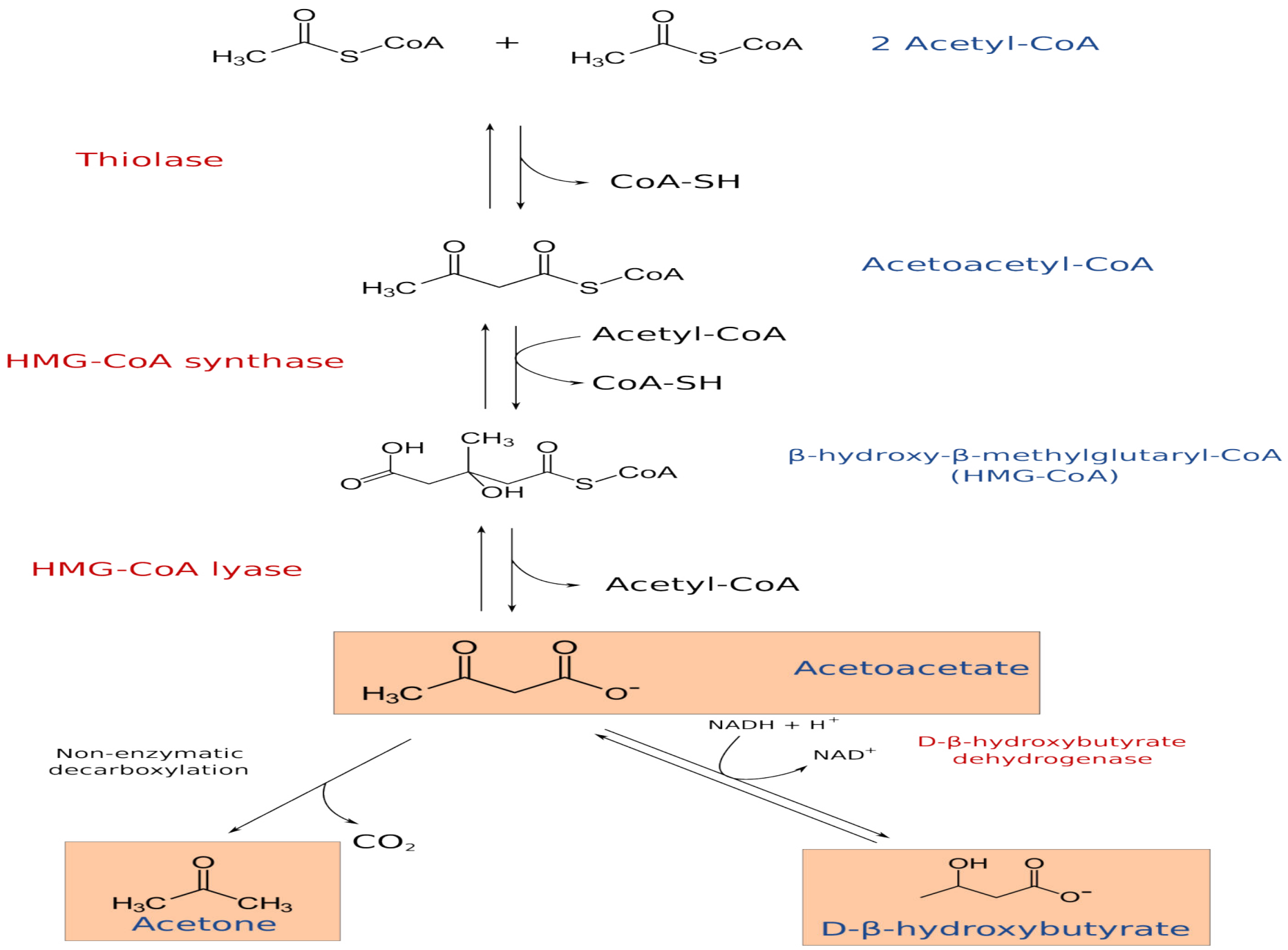


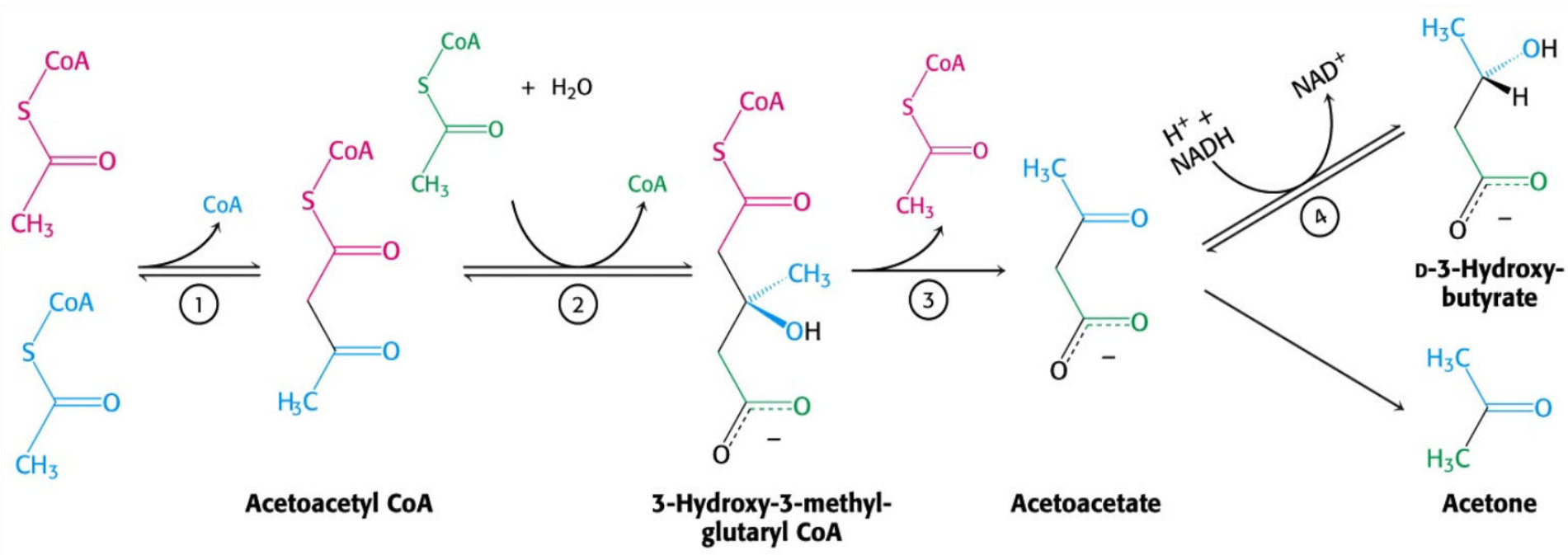


- **Acetoacetate** produces β-Hydroxybutyrate in a reduction reaction catalyzed by **β-Hydroxybutyrate Dehydrogenase i**n the presence **of NADH+H+**

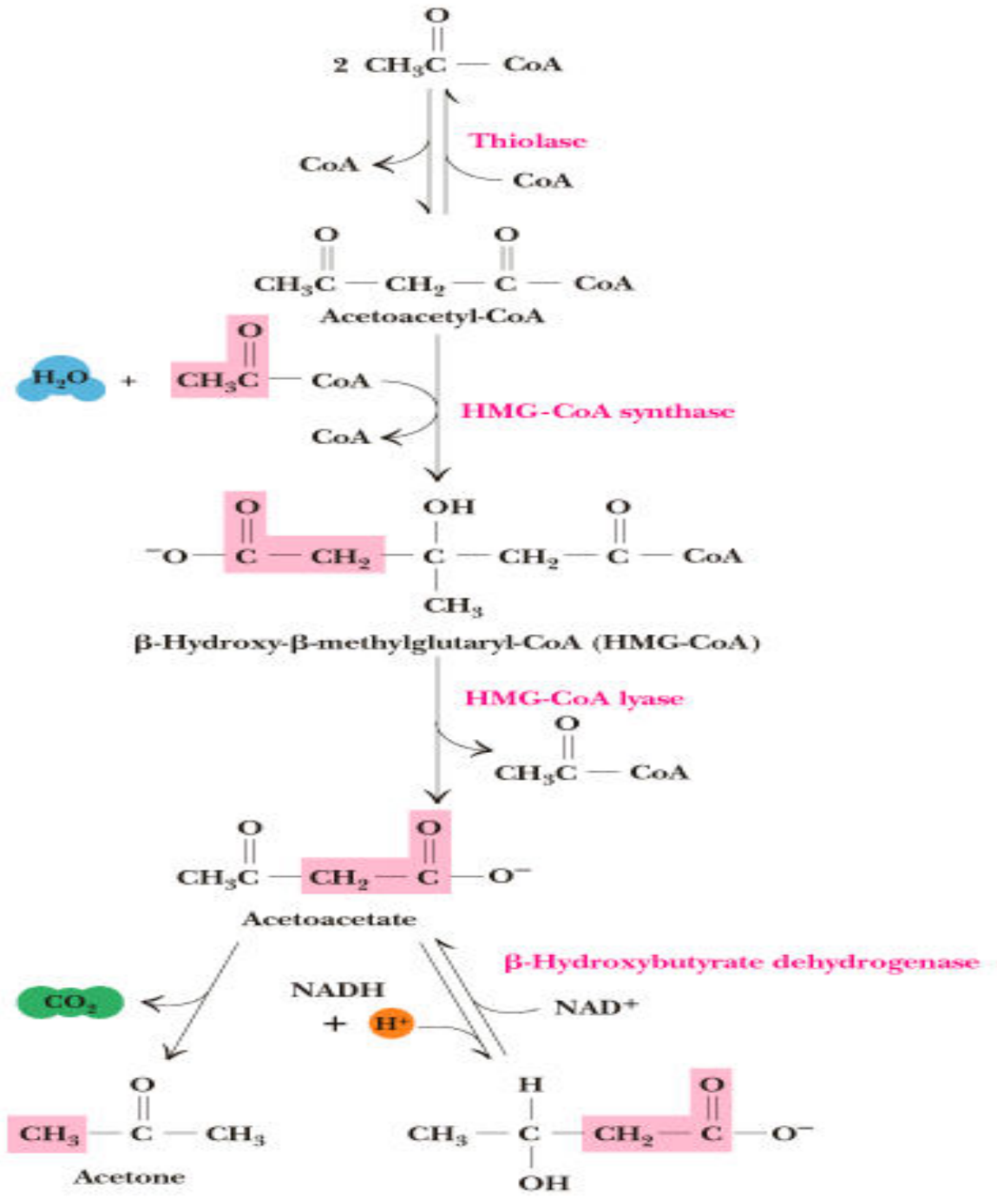


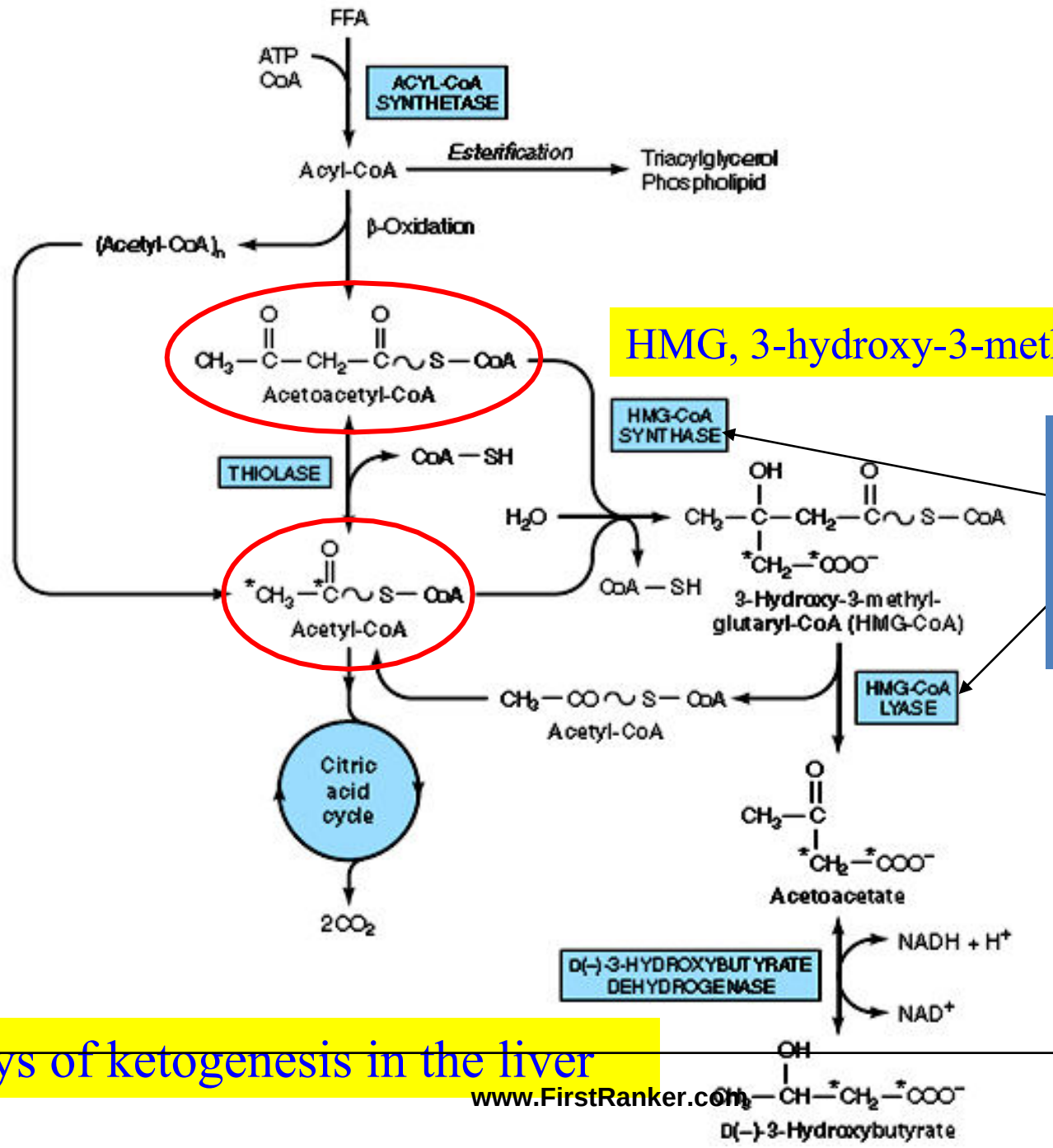






Formation of ketone bodies





HMG, 3-hydroxy-3-methylglutaryl

Both enzymes must be present in mitochondria for Ketogenesis to take place.

Pathways of ketogenesis in the liver

- **Three molecules of Acetyl-CoA** are involved during steps of Ketogenesis.

Description Of Reaction Of Ketogenesis

- **Two molecules of Acetyl-CoA formed as an end product of β-oxidation condenses with one another to form Acetoacetyl – CoA**
- **This reaction is by a reversal of the Thiolase reaction by an enzyme Acetoacetyl-CoA Thiolase.**

- **Acetoacetyl-CoA, which is the starting material for Ketogenesis,**
- **May also arises directly from the terminal four carbons of a fatty acid during β-oxidation.**

- **The further steps of Ketogenesis involves:**
- **Synthesis and breakdown of β Hydroxy β Methyl Glutaryl-CoA/ 3-Hydroxy-3-Methylglutaryl-CoA (HMG CoA) from Acetoacetyl-CoA.**
- **By two key Enzymes:**
- **HMG-CoA Synthase**
- **HMG-CoA Lyase**

– **Subsequently in the second step a third molecule of Acetyl CoA is added to Acetoacetyl CoA.**

- Condensation of Acetoacetyl-CoA with another molecule of Acetyl-CoA to form 3-Hydroxy-3-Methylglutaryl CoA (HMG CoA)
- Catalyzed by **HMG-CoA Synthase.**

- **These two steps are identical to the first two steps in the Cholesterol biosynthesis pathway.**

- **In the third step 3-Hydroxy-3-Methylglutaryl-CoA Lyase (HMG-CoA Lyase) split off HMG-CoA**

- **To release Acetyl-CoA and Acetoacetate.**

- Both Acetoacetate and β-Hydroxybutyrate are permeable through mitochondrial membrane.
- Can be transported across the mitochondrial membrane and plasma membrane of Liver cells,

↓

Ketone bodies enter into blood stream to be used as a fuel by extra hepatocytes /other cells of body.

6. **In blood stream**, small amounts of Acetoacetate are spontaneously (non-enzymatically) **Decarboxylated to Acetone.**
7. **Acetone is a secondary ,volatile, Ketone body expired out by Lungs.**

What are Ketone Bodies?

Ketone bodies are

Ketone group containing compounds

Obtained from Acetyl-CoA

By Steps of Ketogenesis

Permeable, Soluble

Intermediate Products, of Incomplete

Oxidation of Fatty Acids

Produced in Emergency Conditions

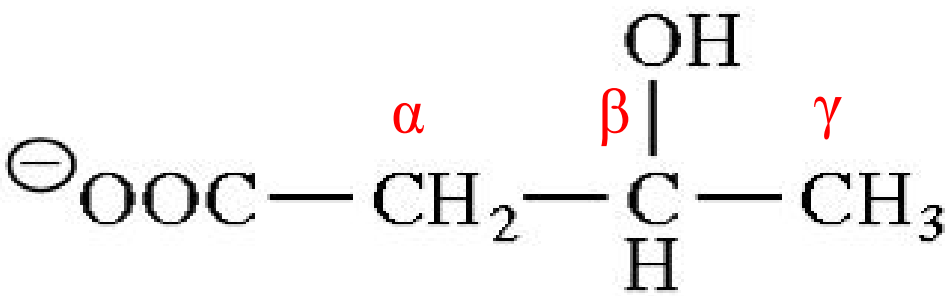
At Mitochondrial Matrix Of Hepatocytes

Due to Cellular Glucose Deprivation

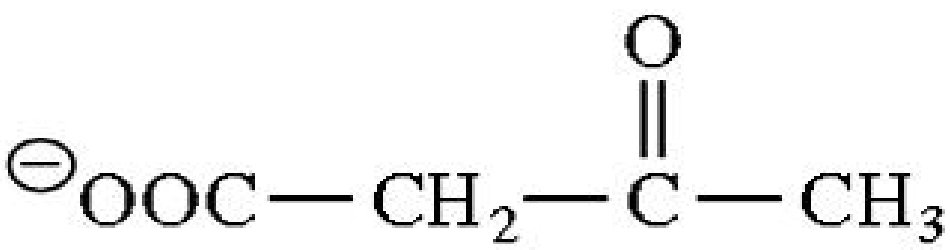
Names of Three Ketone Bodies

- **Three Ketone bodies present in human body are:**
  - **–Acetoacetate**
  - **–Acetone**
  - **–β- Hydroxybutyrate**

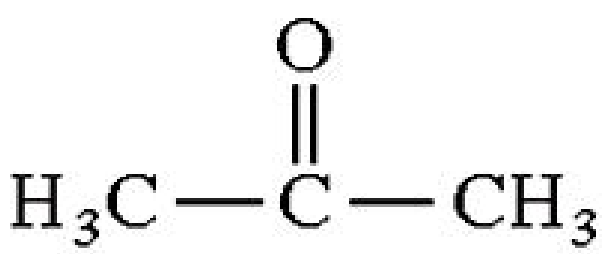
Structures Of Ketone Bodies



β-Hydroxybutyrate



Acetoacetate



Acetone

Acetoacetate
Is the First Ketone body
To Be Formed
Hence Termed As
Primary Ketone Body

1)Primary Ketone Body:(First Formed Ketone Body)

CH_3-CO-CH_2-COOH **Acetoacetic Acid**

(Unstable Product)

2)Secondary Ketone bodies:(Derived From Primary Ketone Body)

CH_3-CHOH-CH_2-COOH **β-Hydroxybutyric Acid**

CH_3-CO-CH_3 **Acetone**

(Non-metabolized product)

- **True Ketone Bodies:**

(Possess Ketone group in their structure)

- **Acetoacetate (Unstable)**
- **Acetone (Volatile)**

Features Of 3 Ketone Bodies

- **Acetoacetate (Primary Ketone body)**
- **Acetone (Secondary Ketone body)**
- **Beta Hydroxy Butyrate (Secondary KB)**

- Ketone bodies formed by Liver are **mobilized out**
- Circulated in blood and they may **enter extra hepatic tissues** for its use.
- **If not utilized remained in blood circulation**(**Ketonemia**) and **excreted through urine**(**Ketonuria**).

- **Acetone is soluble and volatile** and **cannot be detected** in the **blood** and **expired out by Lungs**.

- Odor of Acetone may be **detected in breath(Fruity Odor)**

- Also urine of a person has high level of ketone bodies in the blood **(Ketonuria)**

- Condition where more **Acetone** is produced and expired out gives fruity odor also termed as **Acetone Breath/ Kussmauls Breathing.**

- Acetone Breath is noted in persons with **Prolonged Starvation and Diabetic Ketoacidosis.**

- **β Hydroxy Butyrate** is an **acidic compound.**
- **High levels** of β Hydroxy Butyrate in blood
- May **lower blood pH** and leads to a condition of **Metabolic Acidosis**.
- Acidosis due to increased Ketone bodies is termed as **Ketoacidosis.**

Significance Of Ketogenesis

- **Ketogenesis** becomes of **great significant during starvation.**
- It **improves survival phase of vital organs.**

- **Ketone bodies formed by Ketogenesis** serve as an
- **Alternative source of energy for extra Hepatocytes.**

Ketone Bodies Serves As alternative Fuel In Prolonged Starvation

- **Brain adapts utilizing Ketone bodies** in **starvation conditions** where there is **poor availability of Glucose.**

- **After 3 days of starvation**
  Brain gets **25% of its energy from Ketone bodies**

- **After about 40 days of starvation**, this goes up to **70% energy source to Brain.**

- Thus **Ketogenesis provides energy** for **vital organs and**

- **Maintain there minimal functions during prolonged starvation**

Aim Of Steps Of Ketogenesis
OR
What Happens During Steps Of Ketogenesis?

- **Ketone bodies** can be **simply referred as**
- **Condensed** and **modified forms of Acetyl-CoA**

- **Ketone Bodies** are **partially oxidized products of Fatty Acids (Half broken products of Fatty acids)**
- Obtained **through steps of Ketogenesis.**

- Ketogenesis takes place to **transform impermeable Acetyl CoA** molecules (which are impermeable through mitochondrial membranes) t**o permeable Ketone bodies.**
  - **This is By:**
- **Condensation of Acetyl-CoA** molecules
- **Removal of complex impermeable CoA** from **Acetyl-CoA** moieties.
- ~~Forming **permeable Acetoacetate** (Ketone body)~~

- Main aim to operate Ketogenesis in Mitochondria of Hepatocytes is:
  - **To remove complex impermeable CoA** from carbon units of Acetyl–CoA
  - **Form permeable Acetoacetate(4C)** to mobilize out of Liver.

- **Ketogenesis removes impermeable and accumulated Acetyl-CoA** out of **Liver Mitochondria** .

- Thus steps of **Ketogenesis prevent accumulation of Acetyl-CoA** in matrix of mitochondria.

- **Ketogenesis retains and recycle CoA pool of Mitochondrial matrix .**

- **Carbon units of Acetyl-CoA are removed as Acetoacetate.**

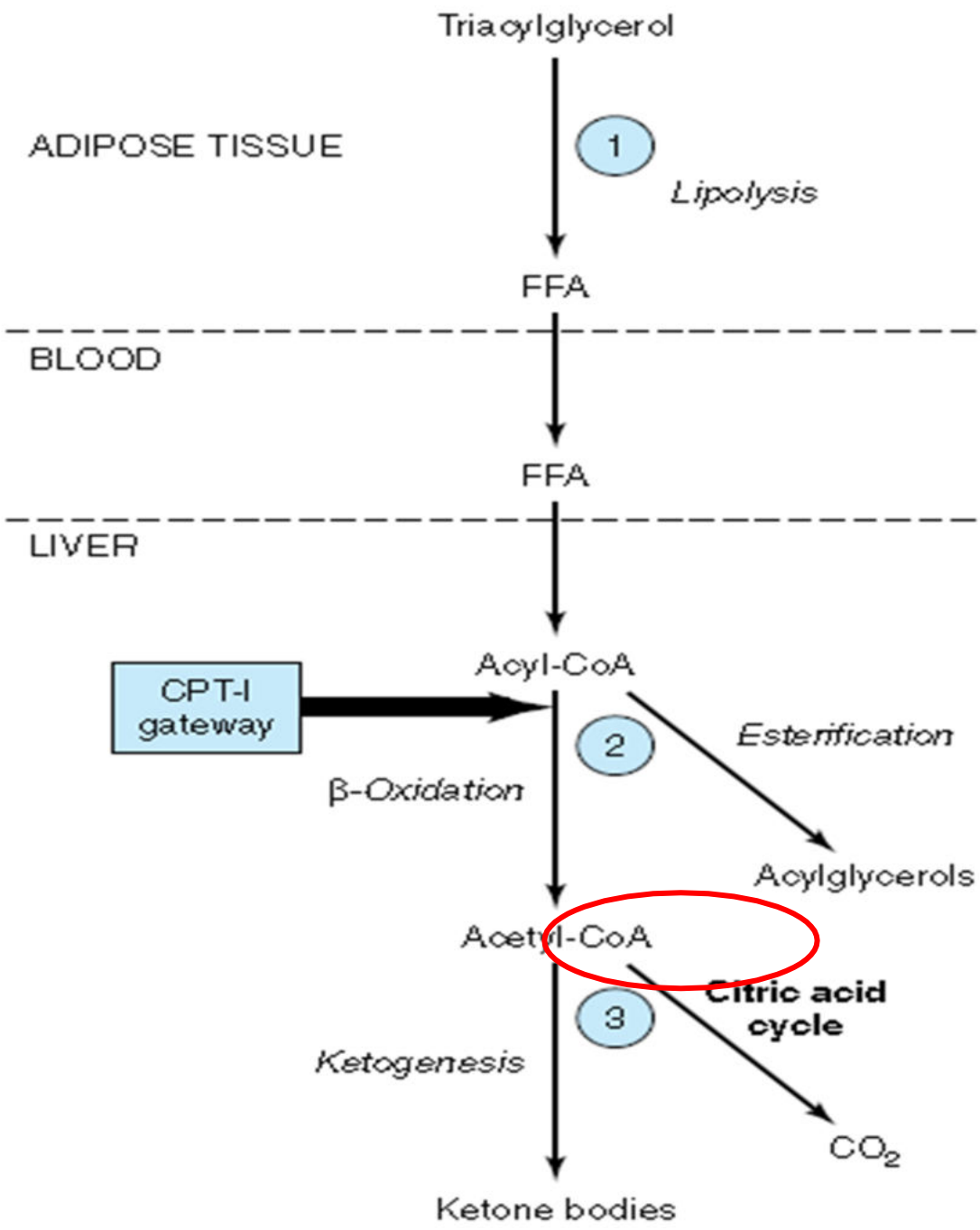
- Formation of **permeable Ketone body Acetoacetate**

- **Significantly removes accumulated carbon units** of **Acetyl-CoA**

- In form of Acetoacetate (Ketone body) from Liver **Mitochondrial matrix.**

Regulation of Ketogenesis

- **Ketogenesis is regulated at three crucial steps:**
  - **Control of Free Fatty acid mobilization from Adipose tissue (Lipolysis)**
  - **Activity of CAT I / Carnitine Palmitoyltransferase-I in Liver.**
  - **Partition of Acetyl-CoA between the pathway of Ketogenesis and the Citric acid cycle by OAA levels.**



Regulation of Ketogenesis

HMG COA Synthase

Is

Regulatory Enzyme of Ketogenesis

- HMG-CoA Synthase activity is **induced by increased fatty acids** in blood.

- **CoA-SH levels regulate Ketogenesis to retain CoA pool in Mitochondrial matrix.**

  - **Reduced CoA-SH** levels stimulates HMG CoA Synthase
  - **Increased CoA-SH** levels inhibits HMG CoA Synthase

Factors Responsible For Increased Ketogenesis

- **Normally Ketogenesis takes place** to **small extent when lowering of cellular Glucose metabolism initiates**.
- Ketone bodies are generated **moderate levels in our bodies,**
  - **During sleep**
  - **Between long duration between two meals**

- Rate of Ketogenesis and its **efficiency directly depends upon:**
  - **Insulin activity**
  - **Levels of Cellular Glucose**
  - **Levels of cellular OAA**

- **Increased and incomplete oxidation of Fatty acids increases Ketogenesis.**

- Condition where there is **more cellular Glucose deprivation**
- **More is efficiency of Ketogenesis.**

- Thus **conditions which accumulates excess of Acetyl –CoA in Mitochondrial matrix**.
- Divert this Acetyl-CoA for Ketogenesis.

Which Conditions Deprives Cellular Glucose And OAA And Increases Rate Of Ketogenesis ?

- **Prolonged Starvation**
- Uncontrolled Condition of Diabetes mellitus: **Diabetic Ketoacidosis**
- **Severe Vomiting**
- **Toxemia of Pregnancy**

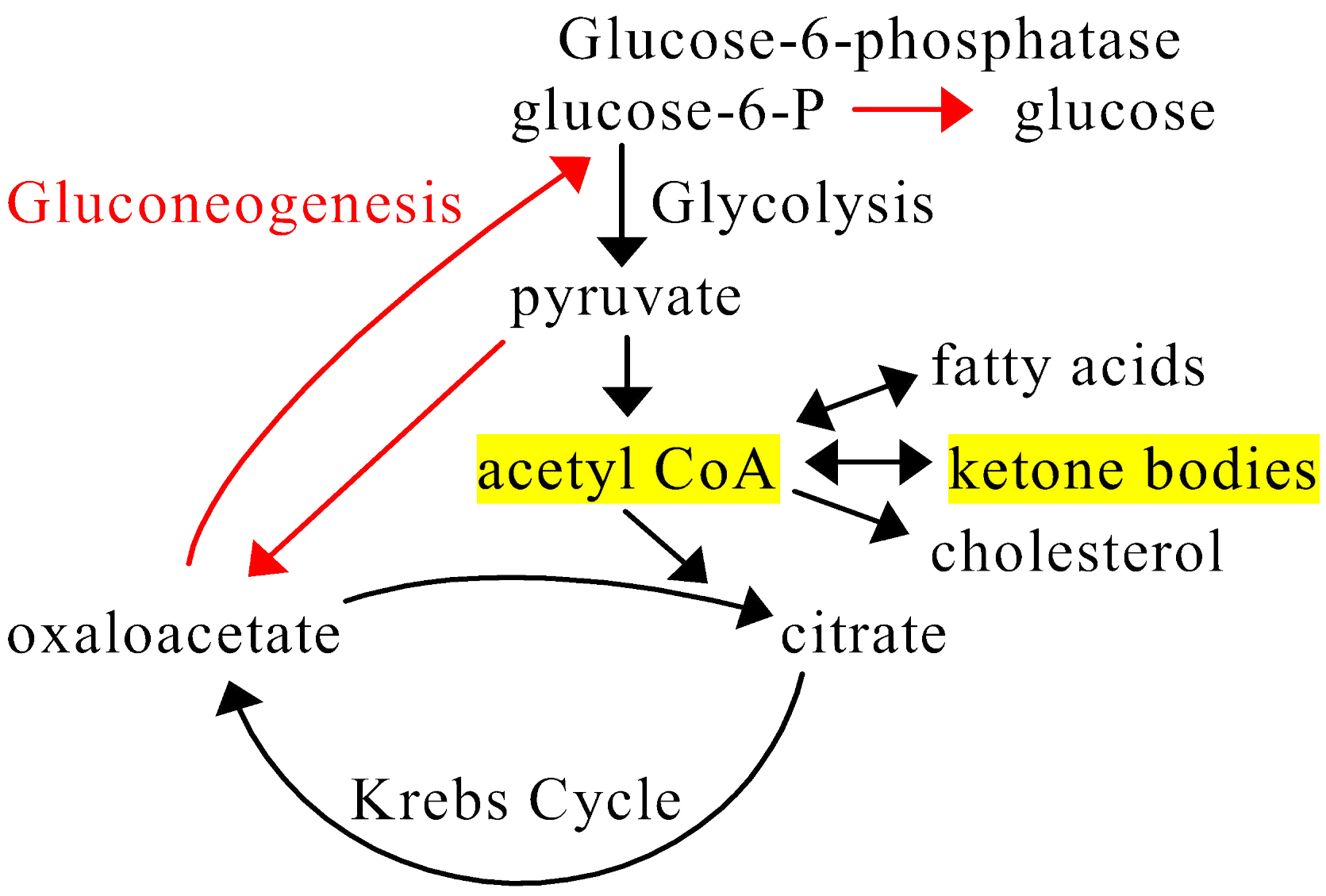
- Deprivation of Cellular Glucose
- High rates of Lipolysis and Fatty acid Oxidation
- Low levels of cellular Oxaloacetate
- Under utilization of Acetyl CoA in TCA cycle
- Large accumulated amounts of impermeable Acetyl-CoA in mitochondrial matrix.
- Accumulated Acetyl-CoA diverted for Ketogenesis and
- Formation of soluble and permeable Ketone bodies which can be easily mobilized out of the Mitochondrial matrix.

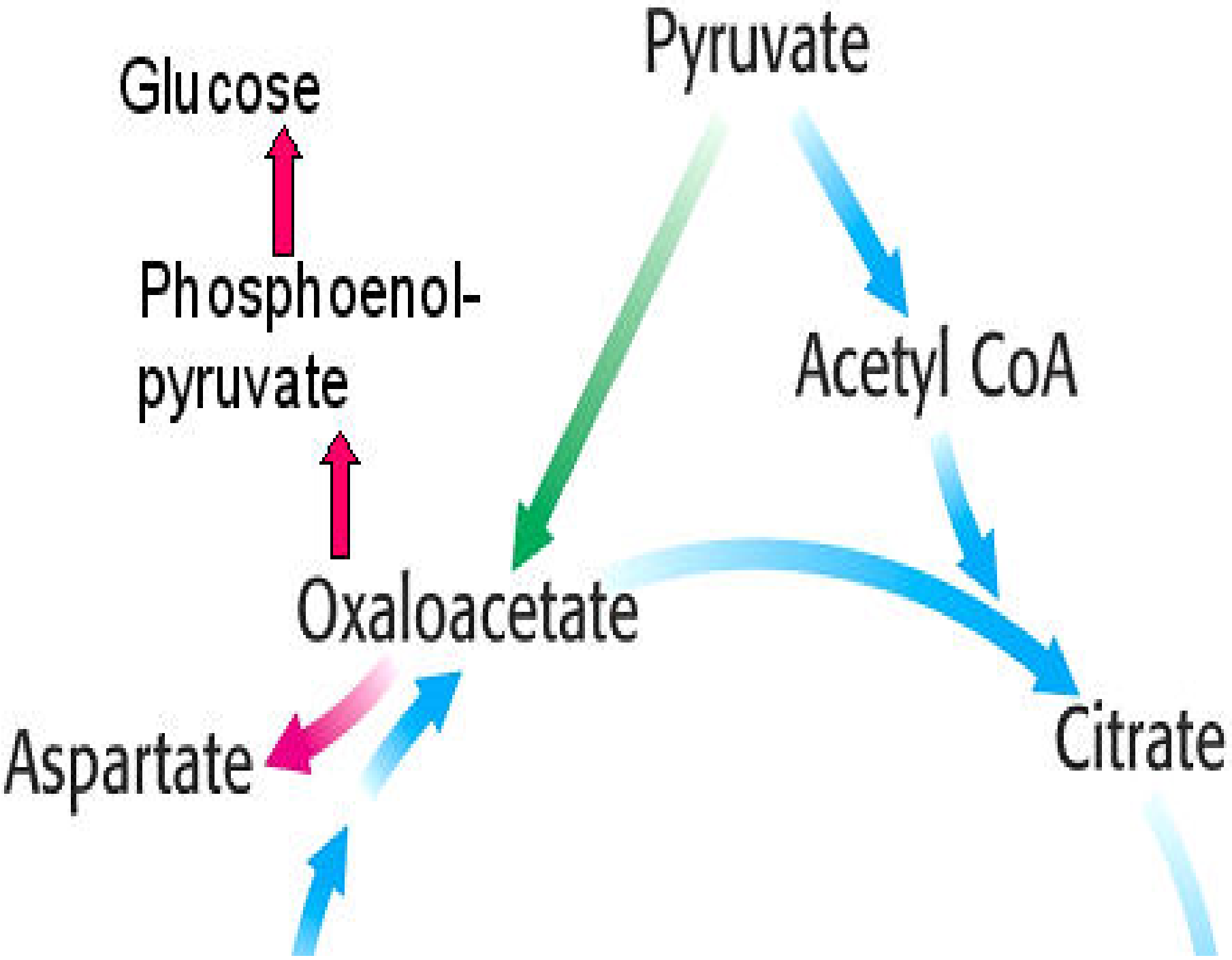
Inter Relationship Of Carbohydrates And Lipid Metabolism

Fats Burns
In The Flame Of Carbohydrates

MEANS

For Complete Oxidation
Of Fatty Acids
There Needs Presence of
Sufficient Glucose In The Cells





–Thus **low/non availability** of **Oxaloacetate** in cells in **emergency condition**

–Does not oxidize **Fatty acid Acetyl-CoA completely via TCA cycle.**

–This **results in accumulation of Acetyl-CoA** in **Mitochondrial matrix**

–Which then **activates and diverts Acetyl-CoA for Ketogenesis.**

- **Fat burns under the flame of Carbohydrates.**

- Complete oxidation of Acetyl-CoA obtained through Fatty acid oxidation via TCA cycle
- **Requires sufficient Oxaloacetate** which is a **source from normal Glucose metabolism**.

- Sufficient cellular **Glucose (Flame)** keeps the **availability** of **OAA**

- To **initiate and operate TCA cycle** and **completely oxidize** the end product of beta oxidation of Fatty acid **Acetyl CoA** to **CO2 ,H2O and ATP**.

- **Entry of Acetyl CoA and its oxidation** through TCA/Citric acid cycle depends on **availability of Oxaloacetate.**
- Low concentration of Oxaloacetate is noted :
  - If Glucose is unavailable (Starvation) or improperly utilized (Diabetes mellitus).
  - Oxaloacetate is normally formed from Pyruvate by *Pyruvate Carboxylase* (Anaplerotic reaction).

- In Starvation or Diabetes mellitus **Liver** Gluconeogenesis is activated and Oxaloacetate is consumed in this pathway.
- Fatty acids are oxidized **producing excess of Acetyl CoA** which is converted to **Ketone bodies**:

- **In deprivation of Glucose**
- **Acetyl CoA is under utilized** and incomplete oxidized via TCA cycle.

Why Ketogenesis Occur?

Main aim for steps of Ketogenesis to occur is:

- To remove **complex, impermeable ,accumulated Acetyl CoA** in **Mitochondrial Matrix**
- **By transforming Acetyl-CoA into permeable Ketone bodies by removing CoA moiety.**
- **Maintain the levels of free CoA pool of Mitochondrial matrix**

- During emergency conditions due to low cellular Glucose.
- There is alternatively increased beta oxidation of Fatty acids, producing Acetyl-CoA.
- Deprivation of cellular Glucose also depletes the levels of Oxalo Acetate which is an initiator of TCA cycle.

- Low levels of cellular OAA under utilizes the Acetyl-CoA via TCA cycle.
- Acetyl-CoA which is obtained by Fatty acid oxidation is less utilized via TCA cycle .

- This accumulates impermeable Acetyl-CoA in the Mitochondrial matrix.
- To remove the accumulated, impermeable Acetyl-CoA out from the Mitochondrial matrix, there occurs Ketogenesis .

Why Fatty Acids Are Not Completely Oxidized In Emergency Conditions?

- Fatty acids in emergency conditions are not completely oxidized to CO2,H2O and ATP.
- Fatty acids in emergency undergo Beta oxidation and produce Acetyl-CoA
- But the produced Acetyl CoA is not further completely oxidized via TCA cycle.

- **Main facts to have incomplete oxidation of Fatty acids in emergency condition are :**
  - **Low levels of cellular Glucose and Oxaloacetate**

What Makes Liver Oxaloacetate To Get Depleted In Emergency Conditions?

Remember

- In emergency conditions where cellular Glucose is low
- Oxaloacetate levels also gets depleted

- **Reasons for depletion of cellular OAA are:**
- Glucose is the main source of OAA
- OAA is, obtained by Pyruvate Carboxylase reaction
- Thus low availability of cellular Glucose brings low production of OAA from Glucose in cells.

- **OAA of Liver in emergency condition** is **diverted for Gluconeogenesis** and transformed **to Glucose**.

- Which reduces actual OAA levels in hepatocytes.

Remember

- OAA is an **initiator of TCA operation** and
- **OAA is required for complete oxidation for Acetyl-CoA.**

Fates Of Ketone Bodies

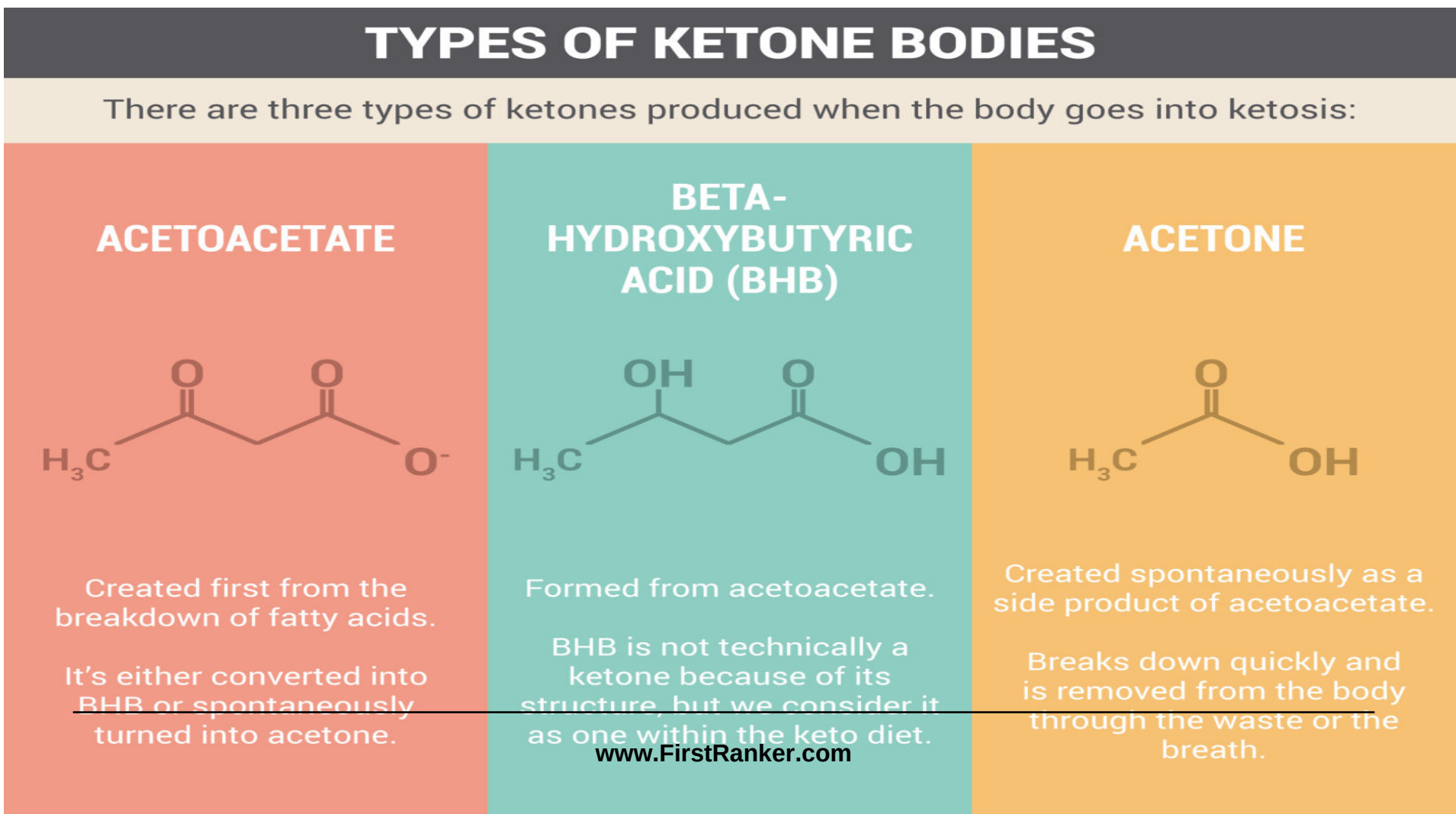
OR

Ketolysis/Breakdown Of Ketone Bodies

OR

Utilization Of Ketone bodies

Types And Fates Of Three Ketone bodies



Uses Of Ketone bodies

- **Ketone bodies serves as a special and major source of fuel/energy**
- For certain tissues **in prolonged starvation phase.**
- In the **starvation condition** where body has **low Glucose**.
- Ketone bodies are used to **generate energy** by **several extra hepatic tissues**

Fate Of Acetoacetate

- Acetoacetate may be oxidized and serve as a **source of energy** to **extrahepatocytes.**
- If not oxidized to form usable energy,

  it is **converted to next two Ketone bodies –Acetone and BHB**
- If it is not utilized Acetoacetate **excreted out through urine.**

Fate of β-Hydroxybutyrate

–It is not technically a Ketone according to IUPAC nomenclature.

–It may be **used up for energy source** or excreted out through urine if not used.

Fate Of Acetone

- **Acetone** is **not used as an energy source**,
- But it is **instead exhaled or excreted as waste through expiration**.

Acetone
Do not Serve as Energy Source

- Acetone being volatile , is not catabolized and oxidized
- To liberate energy in the extra hepatocytes.

Ketolysis

What Is Ketolysis ?
Catabolism of Ketone bodies

- **Ketolysis is breaking and utilization of Ketone bodies as energy source**

- In Mitochondrial matrix of **Extra Hepatocytes.**

- **Ketone bodies have less potential metabolic energy than fatty acids from which they are derived.**

- **They make up for this deficiency by serving as "water-soluble lipid derivatives" that can be more readily transported in blood.**

- **During Starvation and in bodies of uncontrolled Diabetes mellitus, Ketone bodies are produced in large amounts**

- **They become substitutes for Glucose as principal fuel for Brain cells.**

Site Of Ketolysis

- Mitochondrial Matrix of **Extra Hepatic Tissues**.

- **Thus primary tissues using Ketone bodies when available are :**
  - **Brain**
  - **Muscle**
  - **Kidney**
  - **Intestine**
  - **But NOT in the Liver**

- **Ketolysis does not takes place in Liver**

- Due **to absence of enzyme Thiophorase in Liver which is** required for Ketolysis.

- **In early phase of starvation Heart and skeletal muscles primarily use Ketone bodies for energy**

- Thereby **preserving limited Glucose and supply it for use by Brain.**

- **Brain which normally depends on Glucose and do not have capacity to use Fatty acids.**
- **during starvation condition Brain adapts using Ketone bodies as major energy source for its survival**

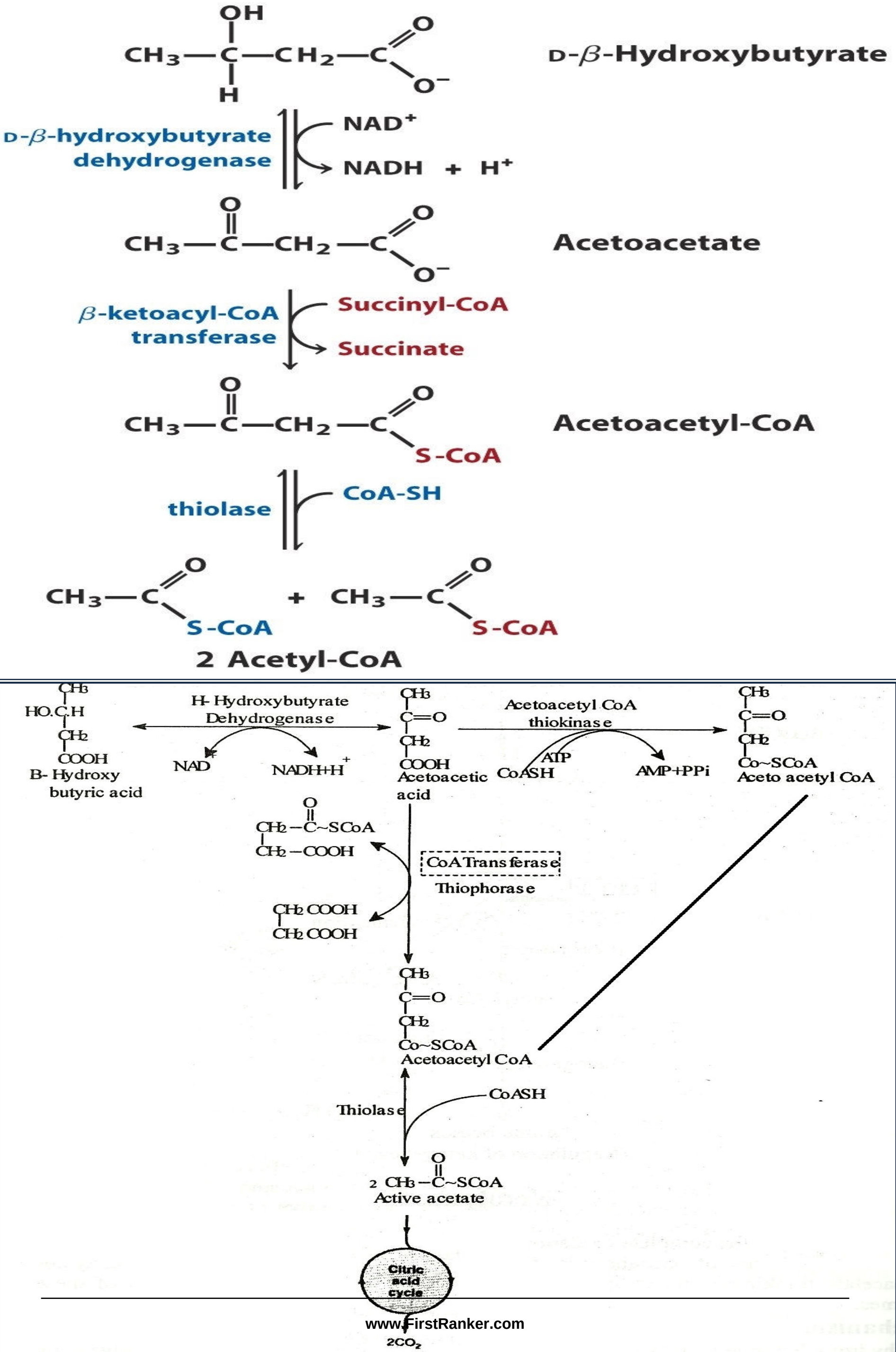
❖ **Heart Muscle** and the **Renal cortex** use **Acetoacetate** in preference to Glucose in **physiological conditions**.

❖ **Brain** adapts to utilization of **Acetoacetate** during **Starvation.**

Steps Of Ketolysis

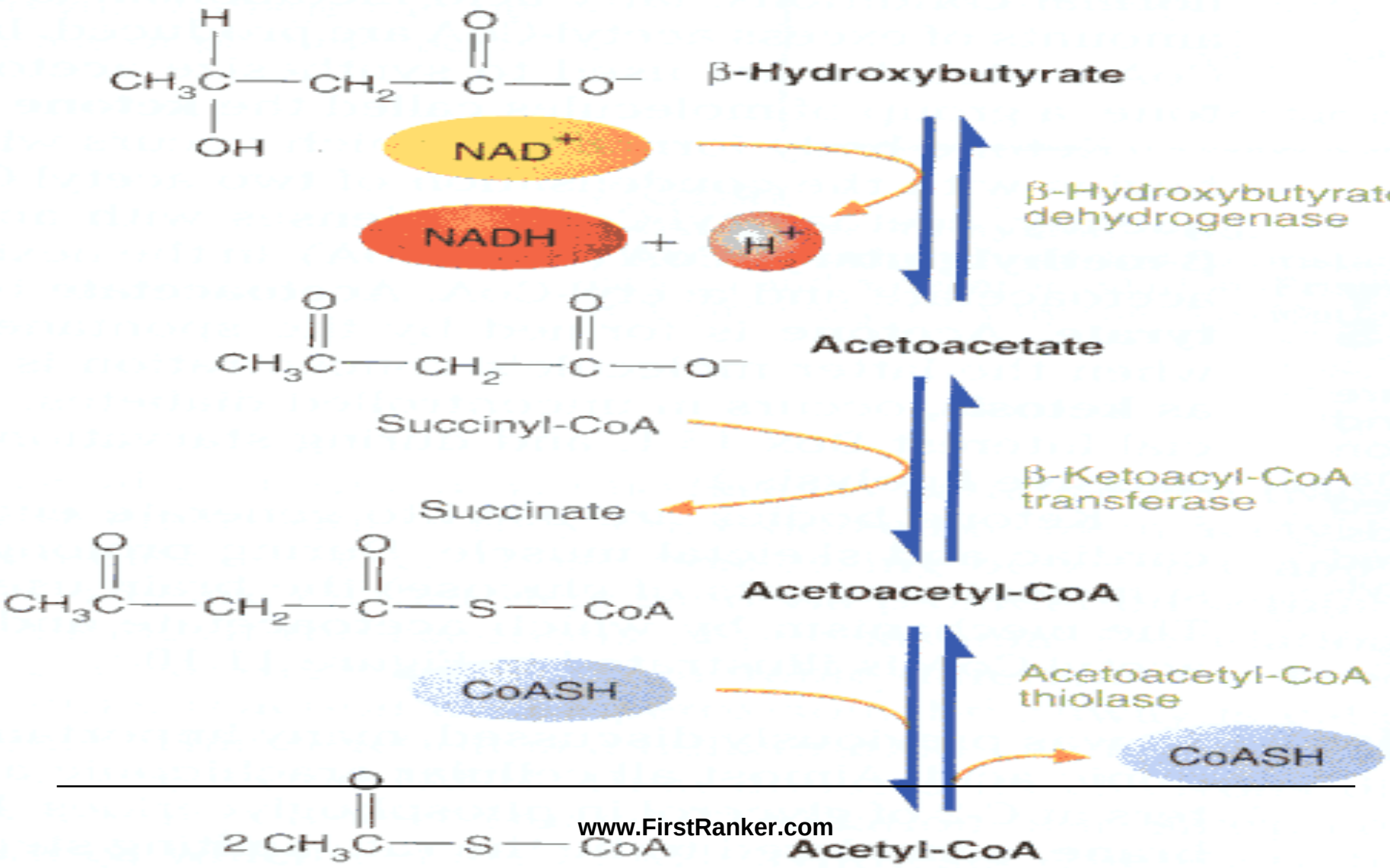
Remember

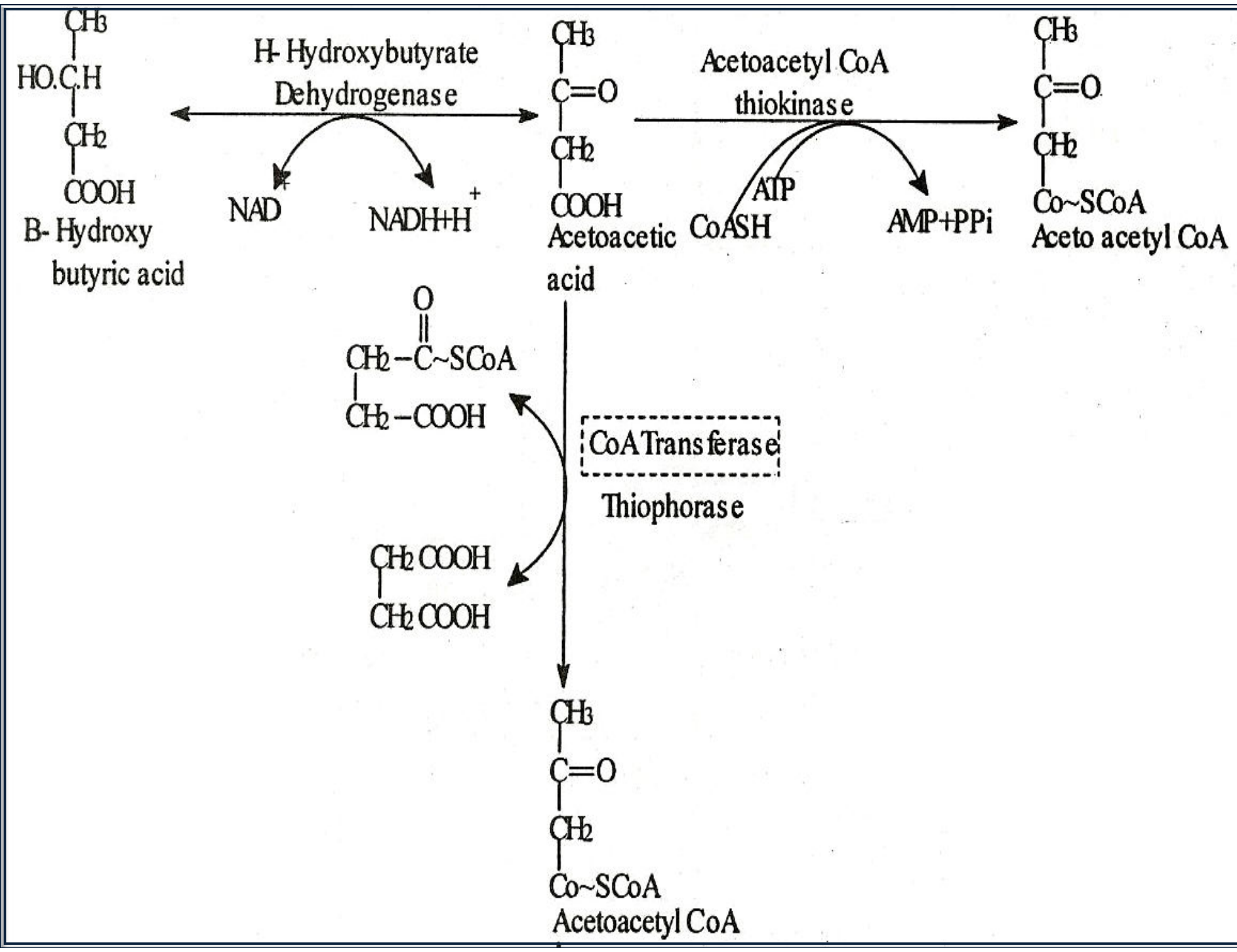
- Ketone bodies will be broken and utilized in only those organs/tissues/ cells
- Which **possess at least some content of Glucose and Oxalo acetate.**



- Ketolysis breaks Ketone bodies and **releases Acetyl – CoA**
- The released Acetyl-CoA is then **finally oxidized via TCA cycle** to **CO2,H2O and ATPs**.

Conversion of Ketone Bodies to Acetyl-CoA





- **Ketone bodies as an energy source, β-Hydroxybutyrate and Acetoacetate**
- **Enter mitochondrial matrix of extra hepatocytes**
- **Where they are converted to Acetyl CoA,**
- **Which is further completely oxidized by the TCA/ Citric acid cycle.**

- **β-Hydroxybutyrate is oxidized to Acetoacetate in a reversible reaction catalyzed by an isozyme of β-Hydroxybutyrate Dehydrogenase of extrahepatocytes.**

- **Remember that this reaction enzyme is distinct from Liver enzyme β-Hydroxybutyrate Dehydrogenase.**

Use Of Succinyl-CoA For Thiophorase Reaction In Ketolysis

- An Enzyme Thiophorase of Ketolysis requires Succinyl-CoA for its reaction.

- **Succinyl-CoA** in this step of Ketolysis is a **donor of Coenzyme A (–CoASH).**

Enzyme Thiophorase Is Naturally Absent In Liver

- **Ketone bodies are broken down only in non hepatic tissues**

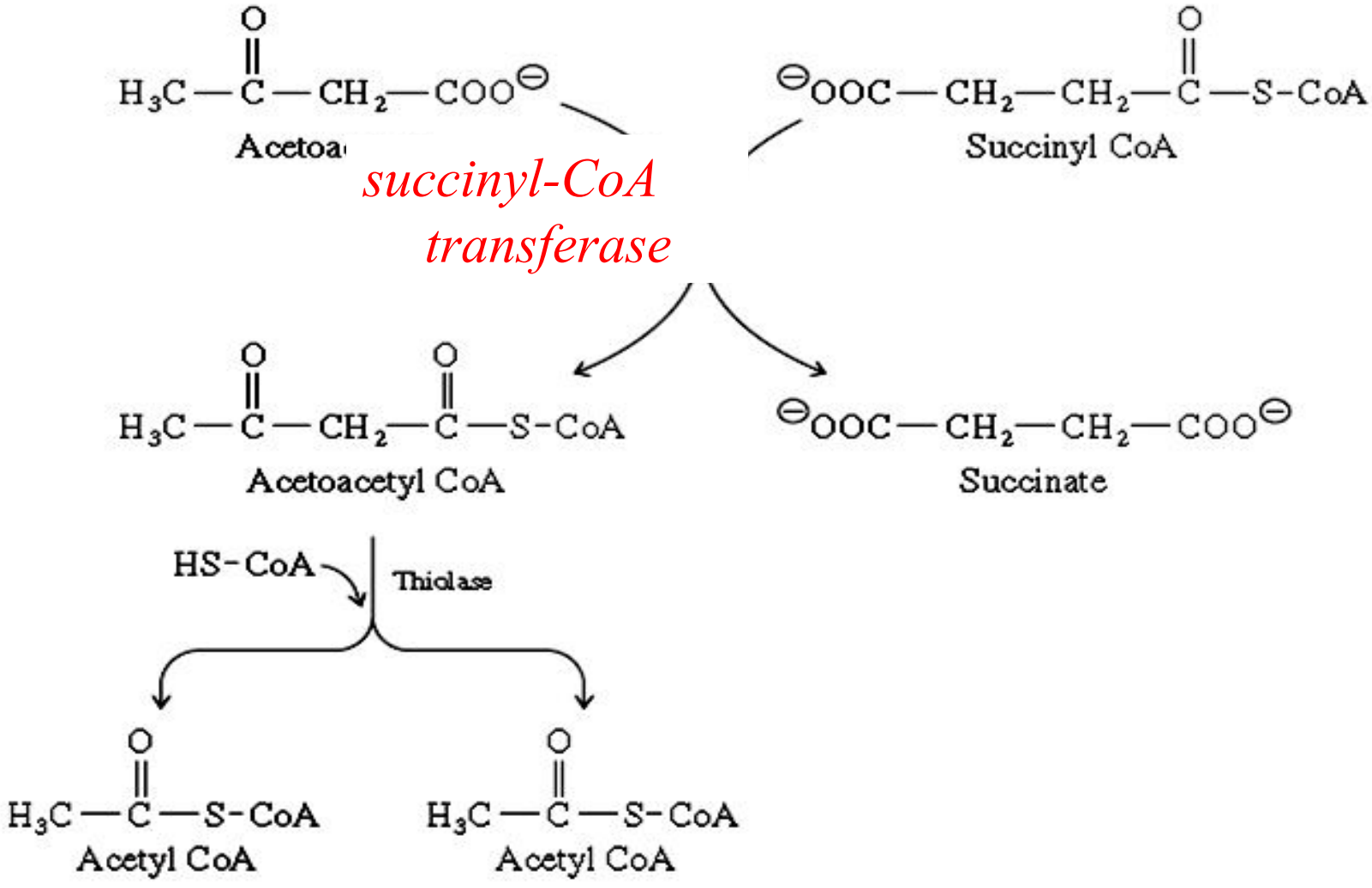
- **Because enzyme Thiophorase is naturally present in all tissues except Liver.**

- **Also some availability of OAA to utilize Acetyl-CoA through TCA cycle.**

- **In extrahepatic tissues, Acetoacetate is activated to Acetoacetyl-CoA by Succinyl-CoA- by catalytic activity of Acetoacetate CoAtransferase/Thiophorase/Succinyl CoA Transferase.**
- **CoA is transferred from Succinyl-CoA to form Acetoacetyl-CoA.**

- **Acetoacetate reacts with Succinyl CoA to form Acetoacetyl CoA in a reaction catalyzed by *Succinyl-CoA Transferase/Thiophorase* .**

- **The Acetoacetyl-CoA is split to Acetyl-CoA by Thiolase and oxidized in the Citric acid cycle.**



Conversion of Acetoacetate to Acetyl CoA.

Significance Of Ketolysis

- **Ketone Bodies Serve as a Fuel for Extrahepatic Tissues on its oxidation in extra hepatocytes in Starvation condition.**

Calorific value of Ketone bodies is 7 Cal/gram

Calculation Of Energetics From Degradation of Ketone bodies in Peripheral tissue

Acetoacetate generates 19 ATPs

- **One molecule of Acetoacetate** in Ketolysis liberates **2 Acetyl CoA,** which enter the Citric acid cycle.
  - Activation of an Acetoacetate **consumes 1 ATP** ,
  - **Total amount of ATP** from metabolism of 2 Acetyl CoA via TCA cycle is **20 – 1 = 19 ATP**

β- Hydroxybutyrate generates 21.5 ATPs

- **Conversion of β- Hydroxybutyrate back into Acetoacetate generates 1 $NADH+H^+$**
- **$NADH+H^+$ produces an additional 2.5 ATP when enters ETC**
- **Net generation is 19 +2.5 = 21.5 ATP**

Balance and Imbalance In Ketone Body Metabolism

- In **normal physiological conditions**.
- There occurs **balance in Ketogenesis and Ketolysis**

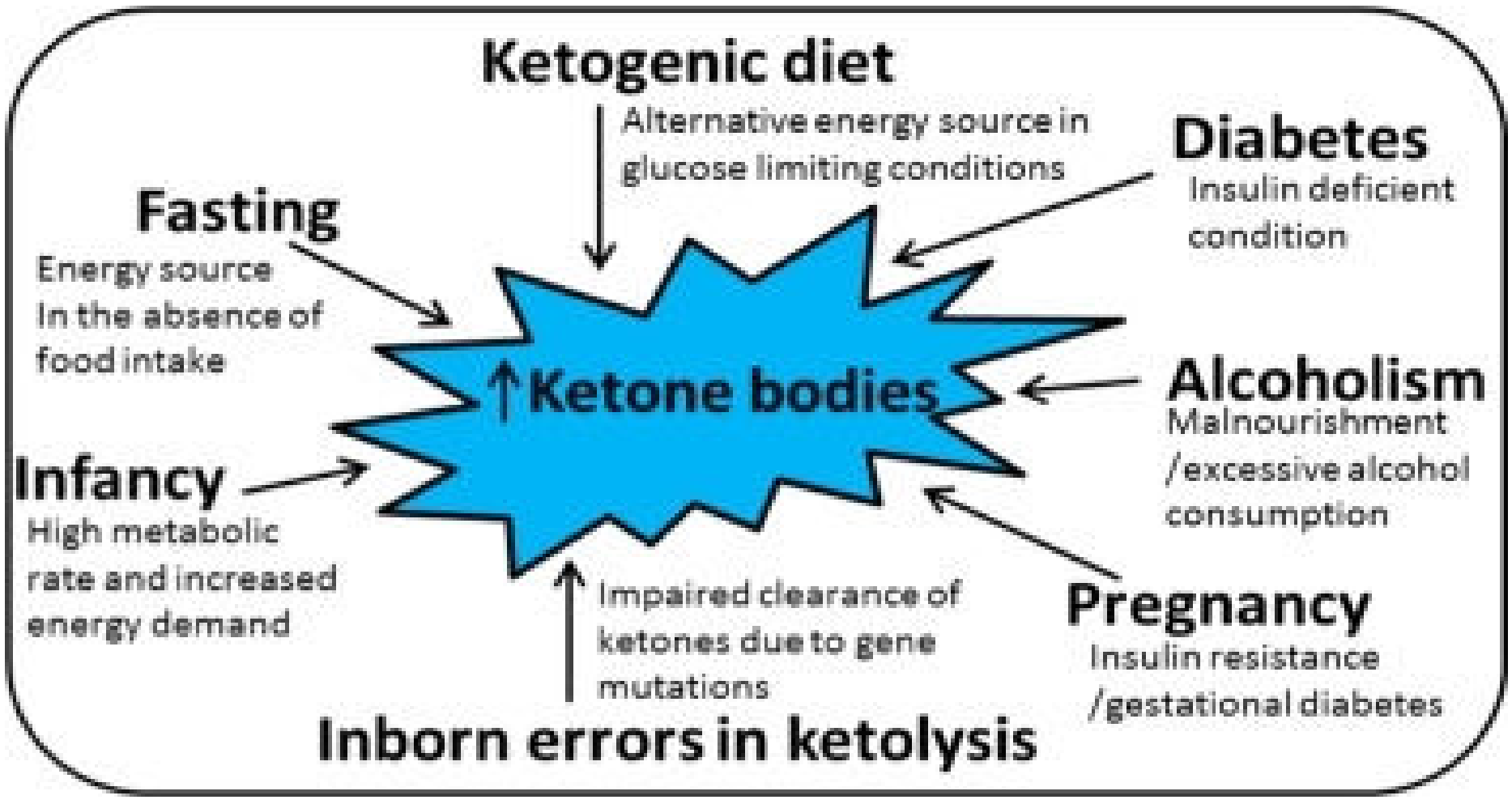
- **When cellular Carbohydrates and Lipids are in proper proportionate.**

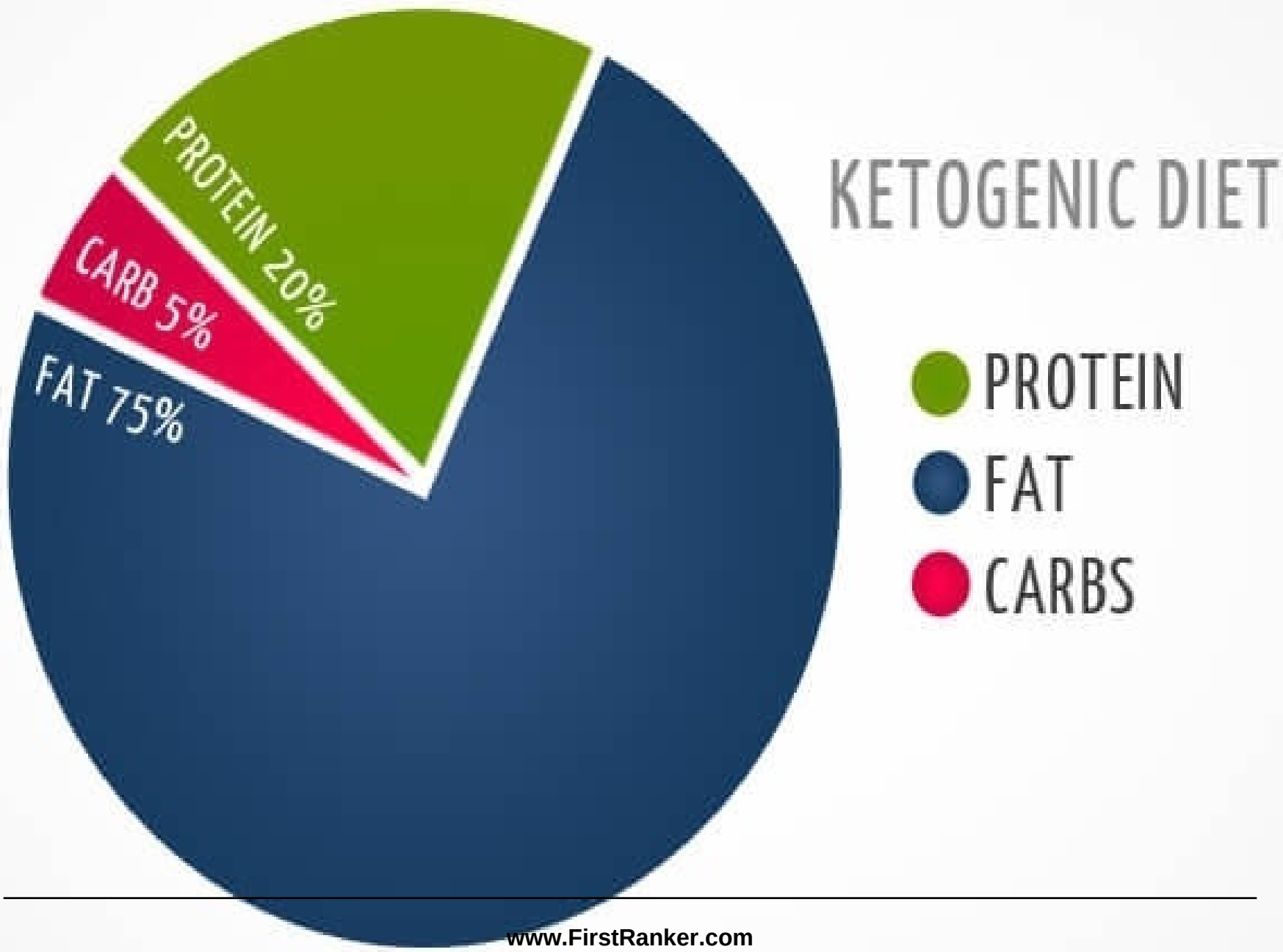
- Then **formation and utilization** of **Ketone bodies** in the body is **balanced and low.**

- There is balance in Ketogenesis and Ketolysis
- A very **low levels of blood Ketone bodies** are present in **normal physiological healthy condition.**

- **Normal blood levels of Ketone bodies** is approx. **less than 1 mg%.**

Causes Of Ketosis





Levels Of Ketone Bodies Increases As Starvation Phase Prolongs

–3 days starvation

[KB]=3mM

–3 weeks starvation

[KB]=7mM

Rate Of Ketolysis

- Rate of Ketolysis in **extra hepatocytes** is **dependent upon** :
  - **Cellular levels** of **Glucose** and **Oxaloacetate** in **extrahepatic tissues .**

- **Rate of Ketolysis decreases**
- In **more deprived conditions** of cellular Glucose and OAA.

Imbalance In Ketone Body Metabolism

- Imbalance in Ketone body metabolism is
- **Increased Ketogenesis and decreased Ketolysis.**

- **No/Low Ketolysis** in body cells
- **Accumulates Ketone bodies** in blood.
- Which leads **to Ketonemia and Ketonuria.**

Ketosis

Ketosis

- Ketosis is a **collective term** used to refer **Ketonemia** and **Ketonuria .**

- **Ketosis** is a **result of imbalance in Ketone body metabolism.**

- **Ketosis** is a condition where there is **increased Ketogenesis and decreased Ketolysis**.

Ketonemia

- **Ketonemia** is an **abnormal increased levels of circulating Ketone Bodies in Blood more than 1 mg%.**

Ketonuria

- **Ketonuria** is an **abnormal excretion of Ketone bodies in Urine**.

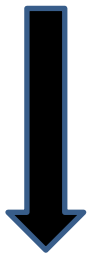
- If blood levels of Ketone bodies **crosses more than the renal threshold levels of KB (3mg%)** it causes-**Ketonuria.**

Ketoacidosis

- Ketoacidosis is Acidosis caused due to increased Ketone bodies.
- Ketoacidosis is a type of Metabolic Acidosis .
- It is caused due to imbalance in Ketone bodies metabolism.

- During KETOACIDOSIS
- Excessive build-up of Ketone bodies results in Ketosis eventually
- Leading to a fall in blood pH due to the acidic Ketone bodies.

Ketosis (Ketoacidosis)



Acetone odor in the breath

Acetoacetate and Acetone in urine

Biochemical Basis Of Ketosis

- **Cellular Deprivation Of Glucose**
- **Low Insulin Activity**

Conditions Of Ketosis

Conditions Of Ketosis

- Prolonged Starvation
- Diabetic Ketoacidosis

(Uncontrolled Diabetes Mellitus)

- **Hyperemesis gravidarum**

  (Severe Vomiting in first trimester)
- **Unbalanced diet i.e. high fat, low carbohydrate diet**
- **Renal Glycosuria**
- **Alcoholics after binge drinking and subsequent starvation**

Biochemical Consequences Of Ketosis

- **Ketone bodies accumulation** in body
- May result to **negative long term effects.**

- **Ketosis create more load on Lungs and Kidneys**

- **To expire and excrete out Ketone Bodies.**

- Ketoacidosis **lowers blood pH affects Enzyme activities**
- **Deranges overall Metabolism**
- **Affects Normal energy metabolism**
- **Affects Water and Electrolytes Balance**

- Increased Ketone bodies in blood is neutralized by alkali reserve (blood buffers HCO3-)
- Very excess of Ketone bodies in blood exhaust $HCO3^-$,this leads to **Metabolic acidosis.**

- **If Ketone bodies are far high than capacity of alkali reserve** to neutralize them they will result in acidemia –
- **Uncompensated acidosis** with a decrease in blood pH **(Acid Base Imbalance)** which is a serious that **results in death if not treated**.

Clinical Features Of Ketosis

Acid Base Imbalance

- **Metabolic Ketoacidosis**
- **Reduced Alkali reserve**(HCO_3^-)
- **Kussamaul's Respiration**
  (**Acetone Breath**)

Water and Electrolytes Imbalance

- **Osmotic Diuresis** (Loss of water and electrolytes along with Ketone bodies)
- **Dehydration**
- **Sodium Loss (Hyponatremia)**
- **Coma**
- **Death**

Diagnosis Of Ketosis

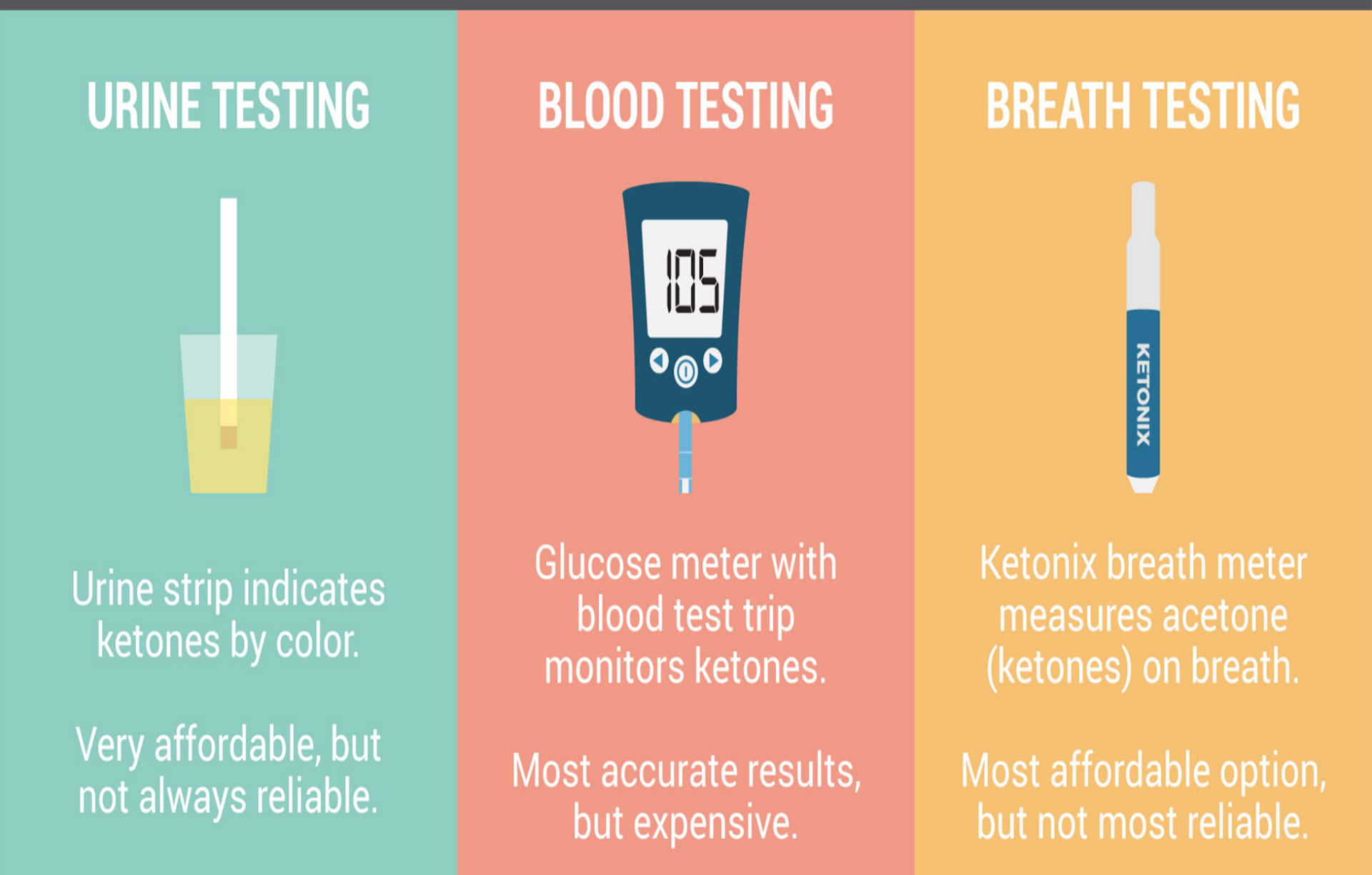
Detection Of Ketone Bodies

Analysis Of
Serum Electrolytes
Arterial Blood Gas

AKA:	DKA:	HHS:
• Acidosis • Ketosis • Hypoglycemia or normal glucose	• Acidosis • Ketosis • Hyperglycemia	• No significant ketosis or acidosis • Hyperglycemia
- **High Ketones[a]** - **Low/Normal Glucose**	- **High Ketones[a]** - **High Glucose[b]**	- **Low/Normal Ketones** - **High Glucose[b]**

[a]**High ketones:** Blood beta-hydroxybutyrate (βHB) concentration greater than 250 µg/ml

[b]**High glucose:** Vitreous humor glucose concentration greater than 6.9 mmol/L



- Volatile Ketone Body ,**Acetone** is **expired** out through Lungs

- It can be smelled in **Ketotic persons as Acetone breath (With Fruity odor)**

- Ketone bodies excreted in Urine can be detected by carrying **Rothera's Test on Urine specimen.**
- **Positive Rothera's Test with Magenta color ring** in the tube **confirms Ketonuria.**

- Ketoacidosis is detected by analyzing :
- The **Blood pH, Bicarbonates**.

- A patient with **Diabetic Ketoacidosis shows:**
  - **–Urine Benedicts Test- Positive**
  - **–Urine Rothera's Test- Positive**
- A patient with **prolonged Starvation shows:**
  - **–Urine Benedicts Test- Negative**
  - **–Urine Rothera's Test- Positive**

Management Of Ketosis

- **Increasing Cellular Glucose**
- **Increase Insulin Activity**
- Manages condition of Ketosis.

- In Starvation **Oral or intravenous Glucose infusion**
- In Diabetic Ketoacidosis **infuse Insulin dosage with Check on Serum Potassium levels.**

Prevention Of Ketosis

- **Avoiding cellular Glucose deprivation prevents Ketosis**.

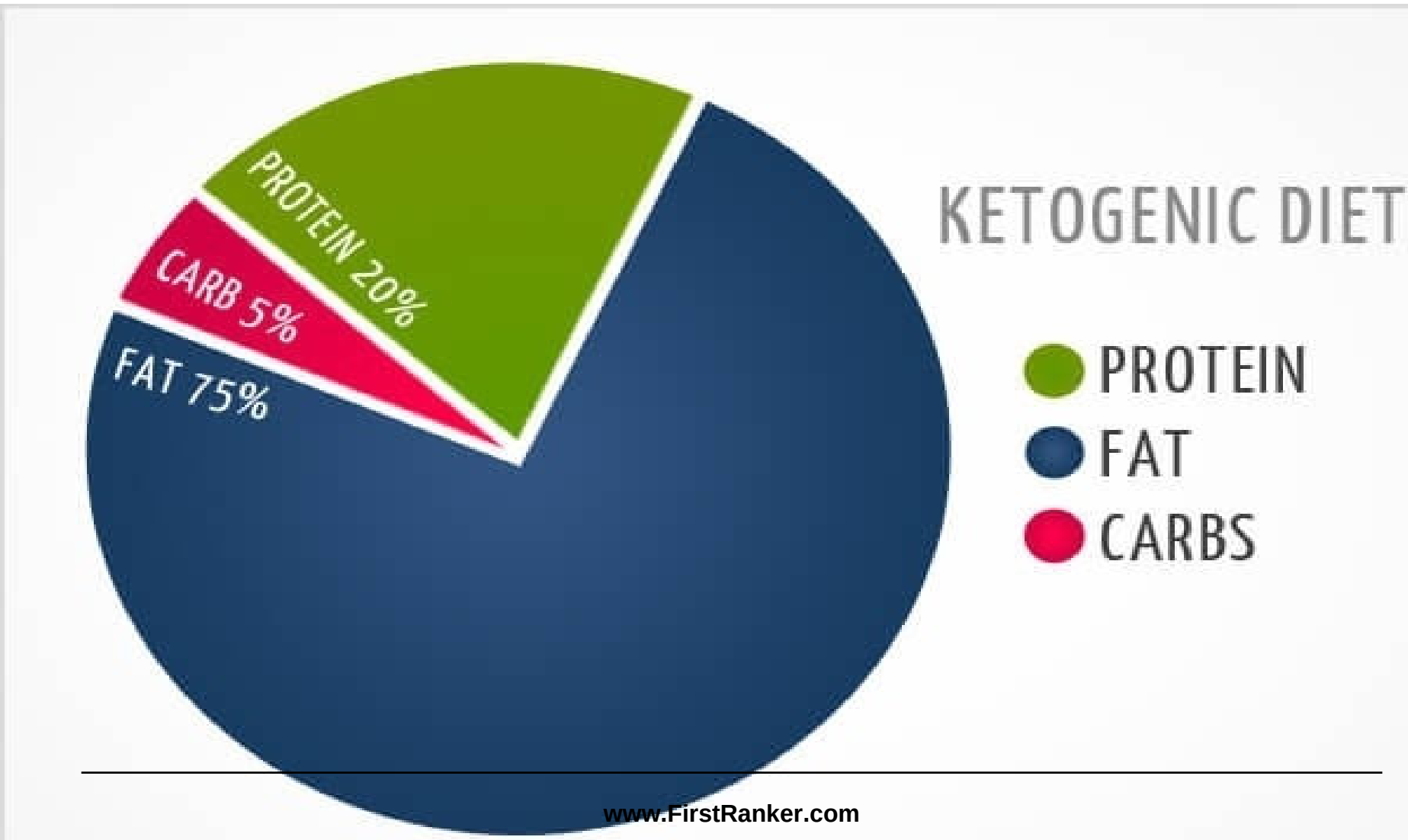
- A Patient of Diabetes mellitus (Type I) to prevent **Ketosis should control his/her blood Glucose.**

- With **proper dosage of Insulin** and maintaining cellular Glucose in cells.

Ketogenic Substances

- Substances **Promoting Ketogenesis** and **increases Ketone bodies are:**
  - **Low Cell Glucose**
  - **Excess Fatty acids**
  - **Ketogenic Amino acids**
  - **High Glucagon**
  - **Low Insulin**

Prevent Ketogenic Diet



Antiketogenic Substances

- Substances **inhibiting Ketogenesis and decreasing Ketone bodies:**
  - **–Sufficient Cellular Glucose**
  - **–Glucogenic Amino acids**
  - **–Glycerol**
  - **–Normal Insulin activity**

Most Common Cause Of Ketoacidosis

Diabetic Ketoacidosis

Type I Diabetes Mellitus Complication

- **Diabetic Ketoacidosis** is an **Immediate complication** of **severe uncontrolled cases** of **Diabetes mellitus(Type I/IDDM)**

KETOSIS In Diabetes Mellitus

The Absence of Insulin in Diabetes mellitus

- Liver Glucose Metabolism Altered
- inhibition of glycolysis
- activation of gluconeogenesis

↓

- Deficit of oxaloacetate

- activation of fatty acid mobilization by adipose tissue

↓

- Large amounts of acetyl CoA which can not be utilized in Krebs cycle

↓

- Large amounts of **ketone bodies** (moderately strong acids)

↓

- Severe Acidosis **(ketosis)**

↓

Impairment of the tissue function, most importantly in the central nervous system

In Diabetic patients events that can lead to ketosis are:

⇧ Relative or absolute deficiency of insulin

↓

⇧ Mobilization of free fatty acids (from adipose Lipolysis)

↓

⇧ Increased delivery of free fatty acids to the liver

↓

⇧ Increased uptake and oxidation of free fatty acids by the liver

↓

⇧ Accelerated production of ketone bodies by the liver

- When there is not enough Insulin in the blood in cases of IDDM
- Cellular Glucose deprivation affects its efficient use to produce energy.
- Thus, the body utilizes the Lipids for its energy.
- Excessive Lipid degradation with low Glucose contents , leads to ketones build up in the blood .

- Ketone bodies then spill over into the urine so that the body can get rid of them.
- Acetone can be exhaled through the lungs. This gives the **breath** a **fruity odor.**
- Ketones that build up in the body for a long time lead to serious illness and coma. (Diabetic Ketoacidosis)

- **Ketone bodies Acetoacetate and Beta Hydroxy Butyrate are acidic**
- **When produced in excess over long periods in Diabetes, causes Diabetic ketoacidosis.**

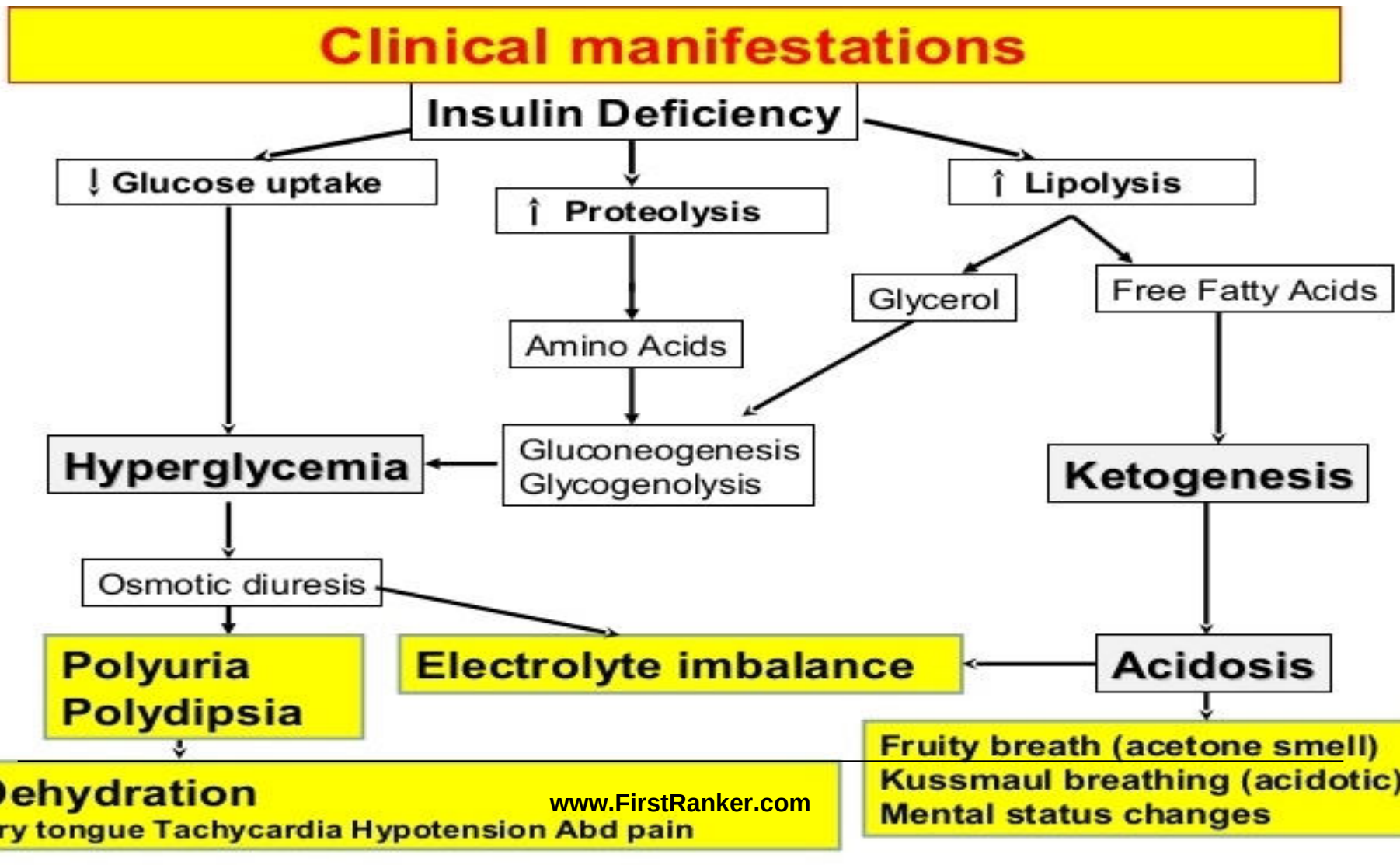
- In a case of **severe Diabetic Ketoacidosis**
- The **Ketone bodies** in the **blood and urine may reach Life threatening concentrations.**

- **Blood Ketone bodies may be up to 100 mg% (Normal1mg%)**
- **Urinary** excretion of **Ketone bodies** may be as high as **5 gm /day**.

(Normal 125 mg/day)

Clinical Features OF DKA Creates Medical Emergency

Biochemical Basis Of Diabetes Ketoacidosis (DKA)



Biochemical Alterations In DKA

Lab values associated with DKA	
Blood glucose	> 250 mg/dL
Arterial pH	≤ 7.30
Anion gap	> 10
Serum bicarbonate	≤18 mEq/L
Urinalysis	Ketones, glucose present
Serum creatinine	Often elevated
Serum sodium	Often elevated or normal
Serum potassium	Often elevated or normal
Serum phosphate	Often elevated or normal
White blood cell count	Mildly elevated

Signs and Symptoms of DKA

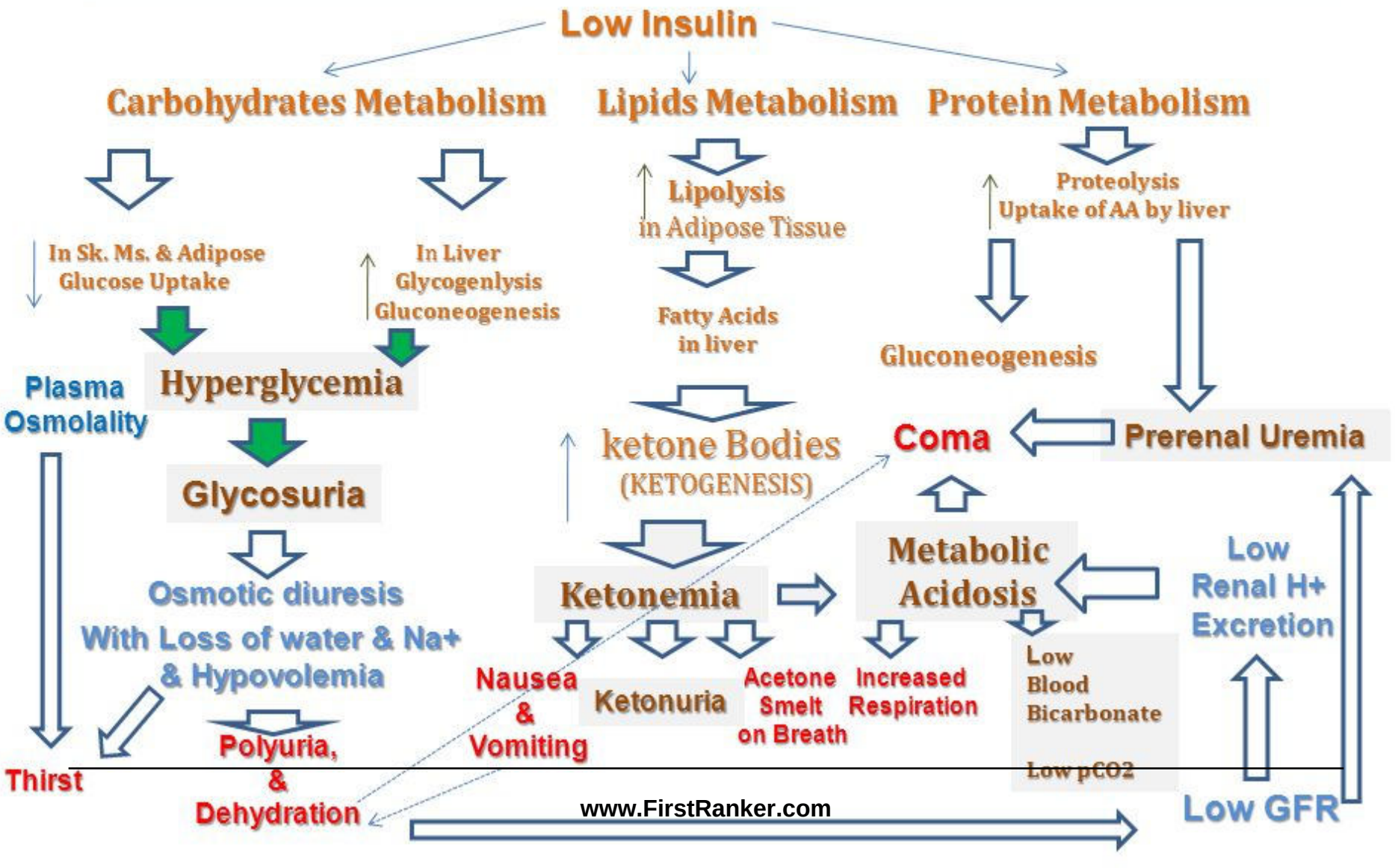
- Polyuria, polydipsia
  - Enuresis
- Dehydration
  - Tachycardia
  - Orthostasis
- Abdominal pain
  - Nausea
  - Vomiting

- Fruity breath
  - Acetone
- Kussmaul breathing
- Mental status changes
  - Combative
  - Drunk
  - Coma

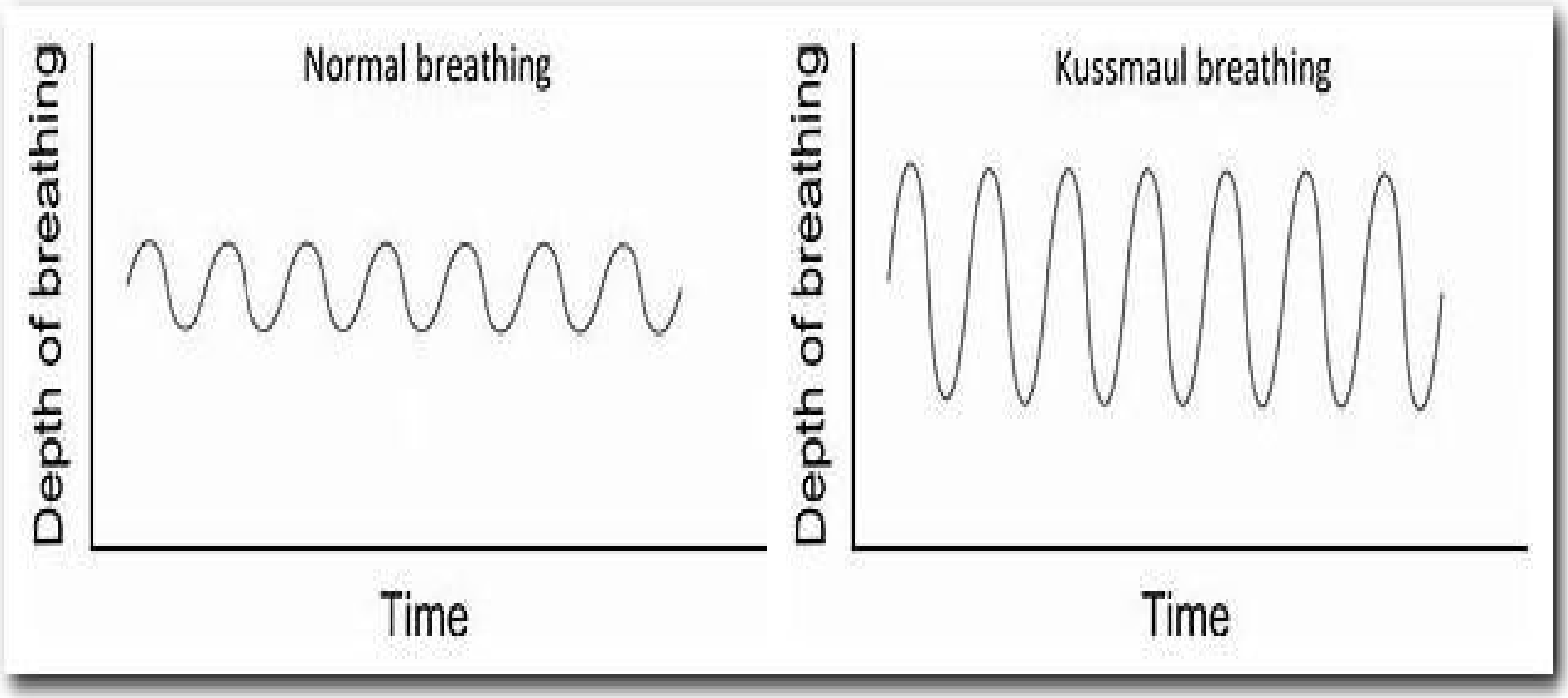
DKA: Clinical Manifestations

- Dehydration- Early signs include:
  - ✓Poor Skin Turgor
  - ✓Dry mucous membranes
  - ✓Tachycardia
  - ✓Orthostatic Hypotension
  - ✓Lethargy, weakness
- Severe Dehydration:
  - ✓Skin dry & loose
  - ✓Eyeballs soft, sunken

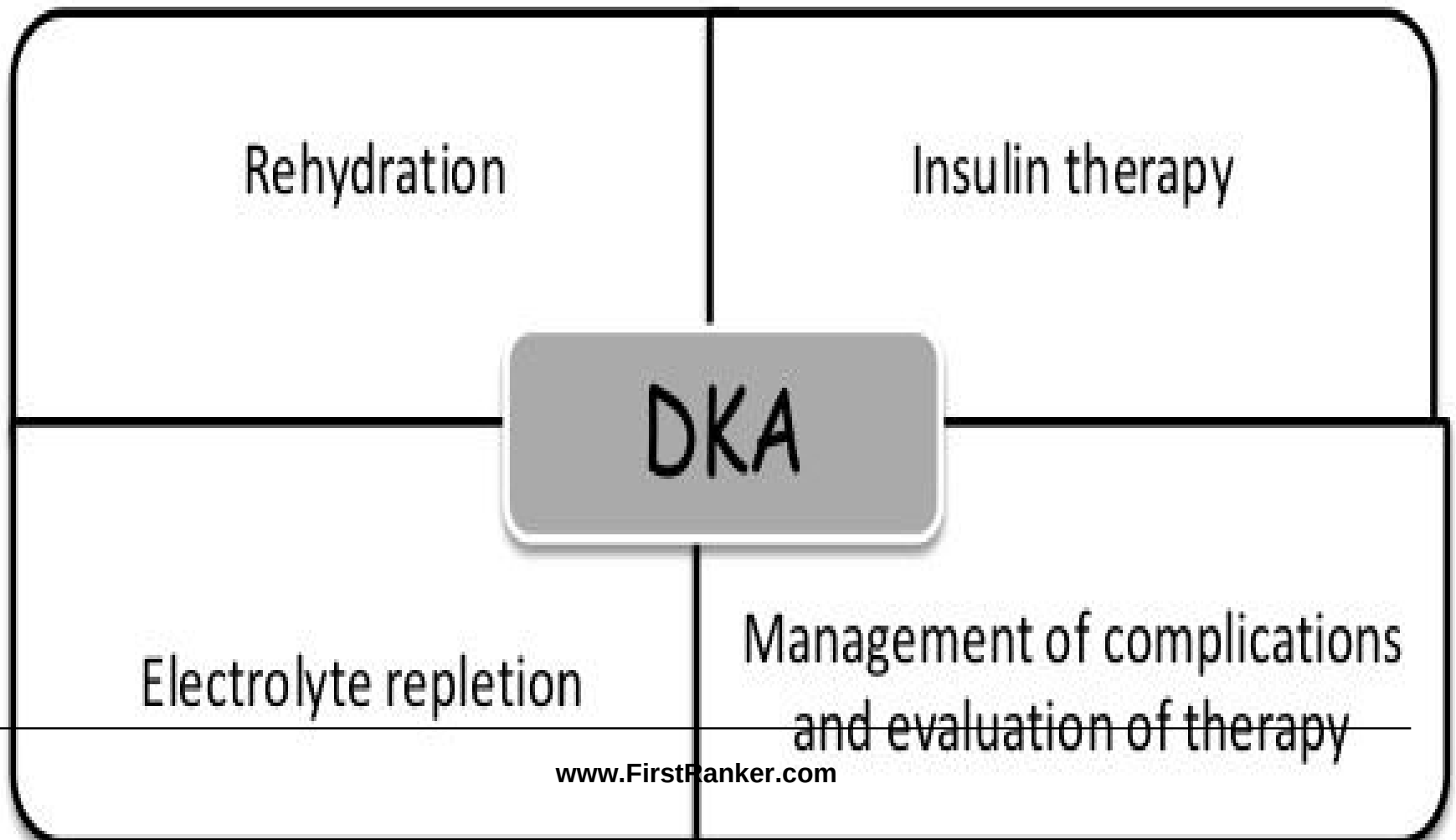
Metabolic Changes & Clinical Manifestations in DKA



- Hyperglycemia
- Metabolic Ketoacidosis
- Hyperventilation
- Kussmaul’s Respiration
- Low Bicarbonate ions
- Severe Dehydration /Water Imbalance
- Electrolyte Imbalance
- Acid Base Imbalance
- Coma
- Death



Management



TREAT DKA WITH DKA

	ADULTS	PEDS
DEHYDRATION	Give 2L IVF over first 2 hrs	2 x Maintenance fluids Decompensated: 5-10 cc/kg boluses (repeat as needed)
K+	K+ < 3.5: Give K+, hold insulin K+ 3.5-5.3: Give K+,give insulin K+ >5.4: Start insulin	K+ <5.5 and the patient has urinated: add 40KCL to IVF
ANION GAP	Regular insulin IV until AG closed: 0.1-0.14 units/kg/hr (Bolus not needed) Subcutaneous insulin in mild DKA (0.2 units/kg)	Insulin 0.05-0.1units/kg/hr infusion (after patient has received IVF) Subcutaneous insulin in mild DKA
ADDRESS TRIGGER	Infection Iatrogenic (not enough insulin) Infraction (forgot insulin) Ischemia Infant (pregnant) Intoxication Initial presentation	

DKA - MANAGEMENT

- **Insulin replacement-**

  0.1U/kg bolus followed by 0.1U/kg/hr and if BG does not ↓ by 10%-repeat the loading dose –if still no response –double the infusion dose in every 2 hr.

- **Fluids:**

  0.9% NS-1-2 ltr in 1st hr

  0.45%NS-2-5 ml/kg/hr

  0.45%NS - when the BG< 250 mg/dl

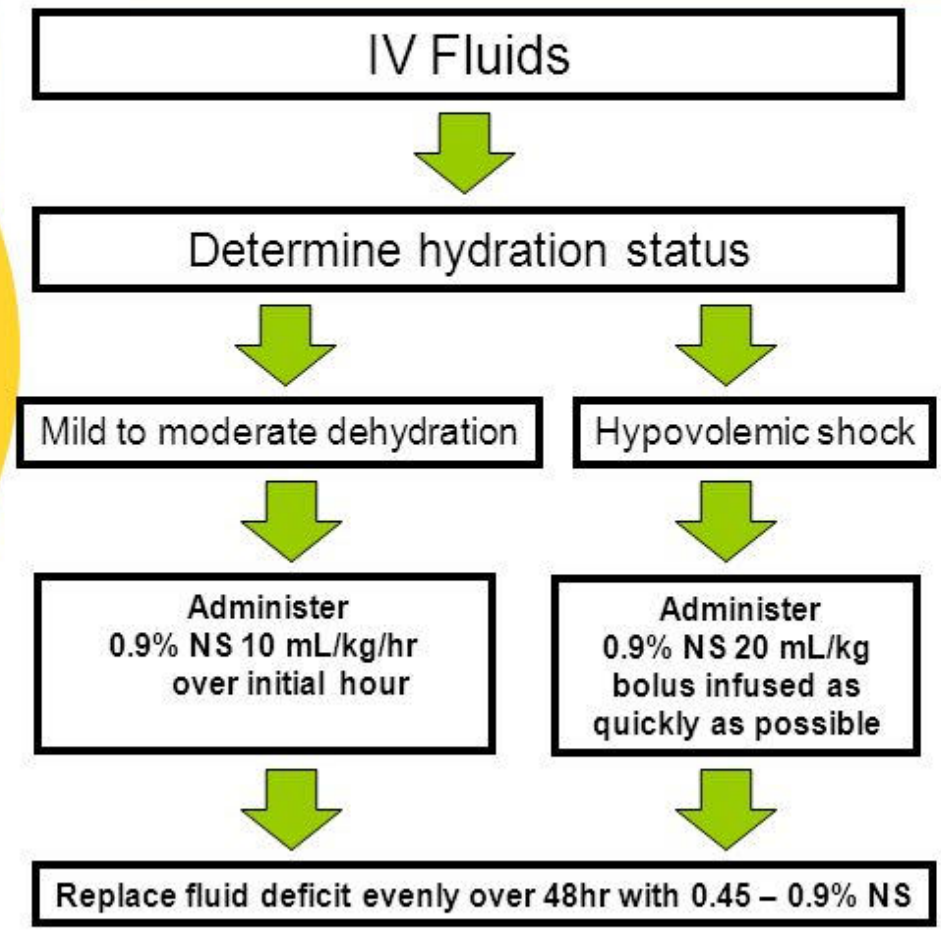
  & 5%DS

- **Electrolyte:**

  20-30meq of K^+/hr after 2 hr of t/t

  Replace phosphate when, <1mg/dl

IV Fluid Administration



The goal of the first hour of treatment

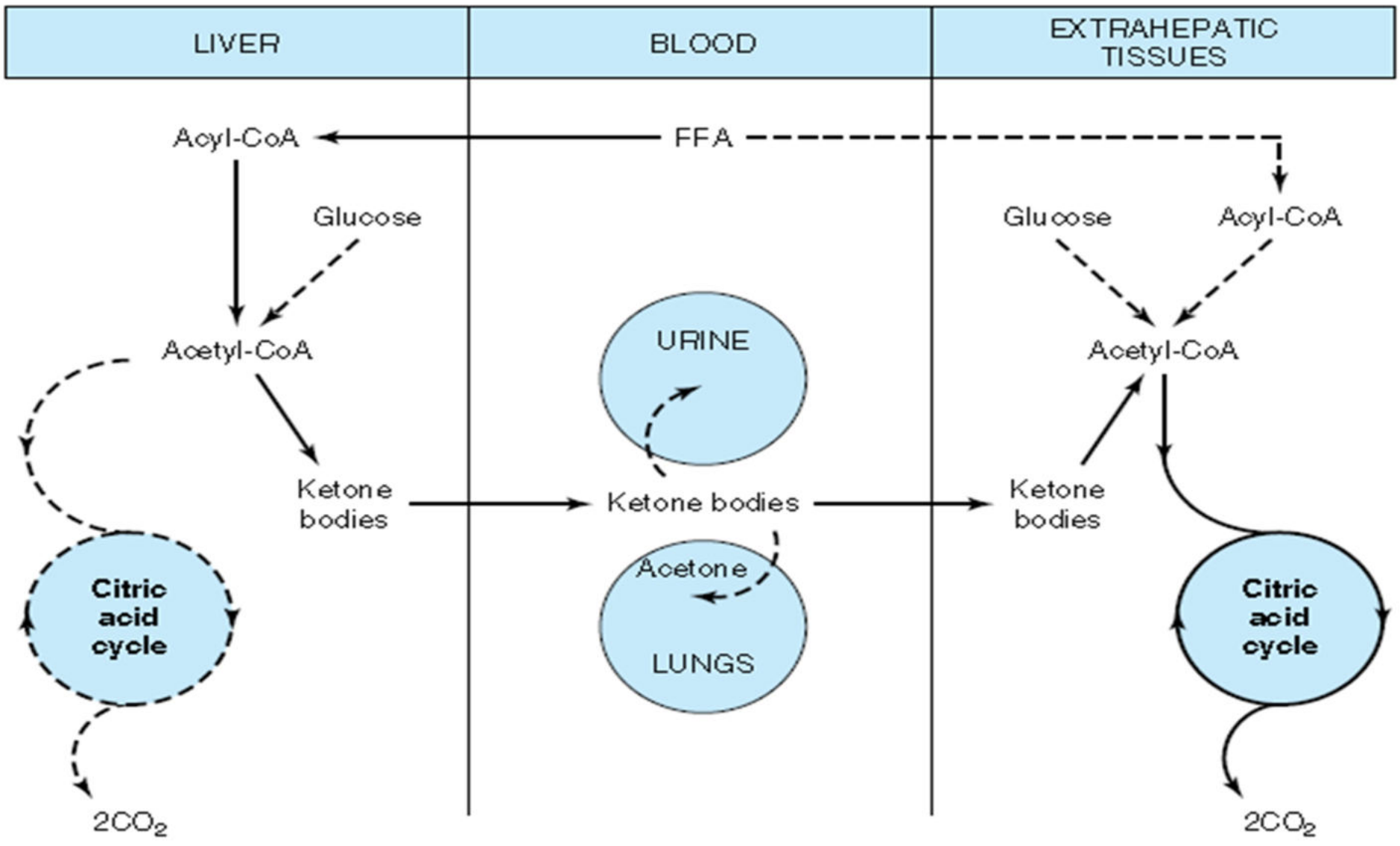
- fluid resuscitation
- confirmation of DKA by laboratory studies

The goals of the second and succeeding hours

- slow correction of hyperglycemia, metabolic acidosis and ketosis
- continued volume replacement

This usually requires several hours and meticulous attention to the patient's response to therapy

Adapted from:
Kitabchi AE, Umpierrez GE, Murphy MB, et al; American Diabetes Association. Hyperglycemic crises in diabetes. *Diabetes Care*. 2004;27(Suppl. 1):S94-S102



Formation, Utilization, and Excretion of Ketone bodies

Endocrine Interaction And Communication With Liver