SHEET NO.

Lipid 3

METABOLISM

DOCTOR 2019 | MEDICINE | JU

DONE BY : Doctor 2018

SCIENTIFIC CORRECTION :

GRAMMATICAL CORRECTION :

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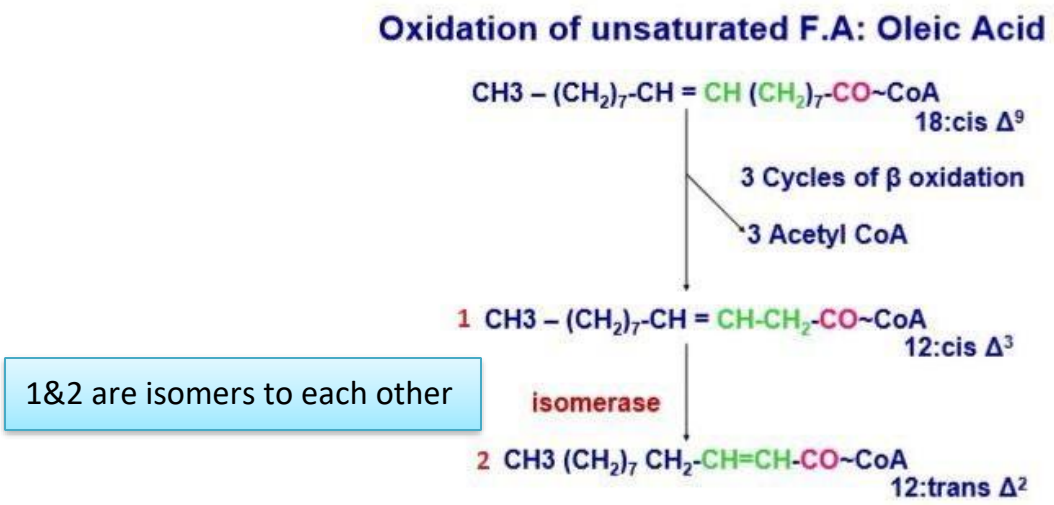
This sheet is written according to video 22

- A brief introduction about the last lecture
  - ✓ Fatty acids are main body storage reserve and the main constituent of your body fat.
  - ✓ The **first step** of fats (TAG) metabolism is the **hydrolysis** of TAG to fatty acids by the enzyme **lipase**.
  - ✓ Lipases are **activated** by **glucagon** (secreted when blood sugar is low and by NE, EPI, ACTH when there is increased demand for energy "Remember FIGHT OR FLIGHT STATE"). And **inhibited** by **insulin**.
  - ✓ Fatty acids then undergo β-oxidation pathway, in mitochondria of eukaryotes, to produce energy.
  - ✓ Each cycle of β-oxidation produces: NADH, FADH2, Acyl-CoA and Acetyl-CoA.

Oxidation of unsaturated FA

❖ **Monounsaturated FAs:** Oleic acid (18:cis Δ_9)

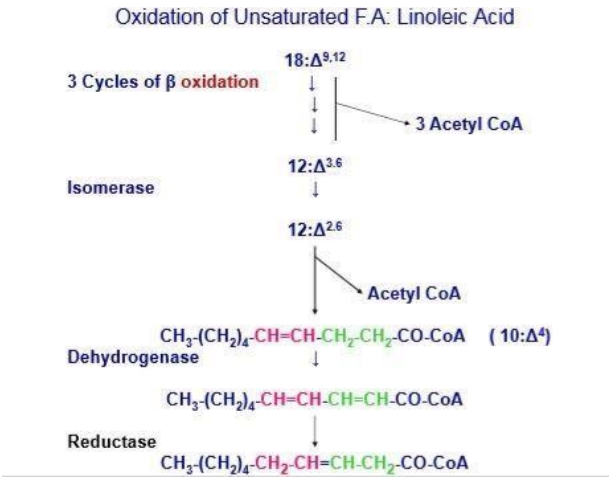
- Oleic acid is 18 carbon FA with a double bond at C9 (Cis configuration).
- After **3 cycles of β-oxidation** (6 carbons are removed and 3 Acetyl CoA).
- The no.of carbon atoms in the remaining FA are **12 carbon atoms**
- There will be a double bond between C3 and C4.



- If it was saturated FA, the next step will be formation of a double bond between **C2** and **C3** by the enzyme **Acyl-CoA Dehydrogenase** not **C3 and C4**
- But $CH_3-(CH_2)_7-CH=CH\,CH_2-CO\sim CoA$ (12:cis Δ^3) is not a substrate for **Acyl-CoA Dehydrogenase** (C3 already has a double bond and it cannot except another one)
- So, an enzyme Isomerase solve this problem by shifting the double bond to C2,C3.
- **isomerase** also changes the configuration from **Cis** to **Trans** double bond.
- The next step will be **addition of water** and complete the β-oxidation pathway as usual.

❖ **polyunsaturated FAs**: Linoleic Acid (18:$\Delta_{9,12}$)

- Such as oleic acid, after 3 cycles of β-oxidation there will be a double bond (C3 & C4). As we know, isomerase solves this conflict (12:$\Delta_{3,6}$ to 1:$\Delta_{2,6}$).
- But **at the 4th cycle** the structure is (10:Δ_4) with C4=C5 double bond and this is a substrate for **Acyl-CoA Dehydrogenase** .
- Dehydrogenase works as usual (formation of C2=C3).

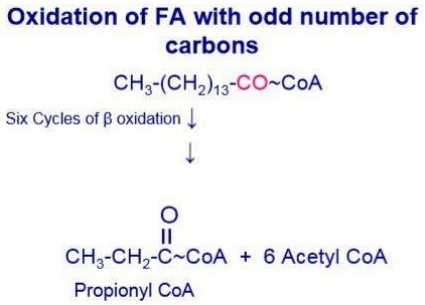


- The produced compound with **conjugated doubled bonds** at C2 and C4.
- Then **reductase** functions by reducing the two double bonds into one between C3=C4 by adding hydrogen at C2 and C5.
- The next step will need **isomerase** (formation of C2=C3) as we mentioned before.

➢ In general, **monounsaturated** FAs need additional **isomerase** and **polyunsaturated** FAs need additional **isomerase and reductase**.

➢ Oxidation of **unsaturated** FAs provide **less amount of energy** than saturated ones, as saturated are more reduced.

Oxidation of FA with odd number of carbons

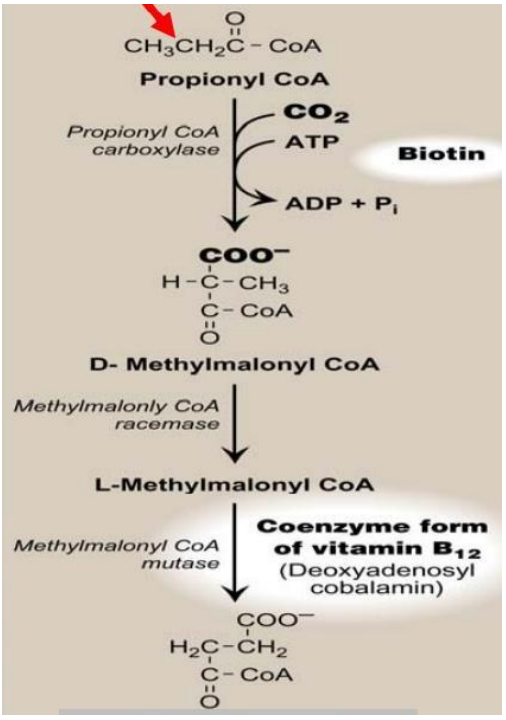


➢ Most of FAs we have are even number carbon atoms (Oleic and Linoleic) but some FAs are odd number like animal fat contain about 10% of FAs as odd number

➢ The last product of Odd number FAs is not **Acetyl-CoA**

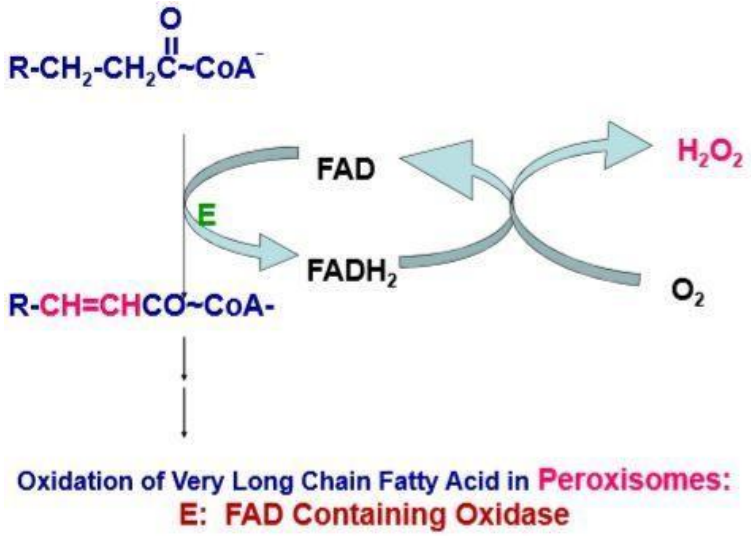
➢ How they are oxidized? We convert it to a product of TCA.

- After 6 cycles of β-oxidation, 15 Carbons FA yields **6 Acetyl-CoA** and **propionyl CoA** (3 carbon atoms)



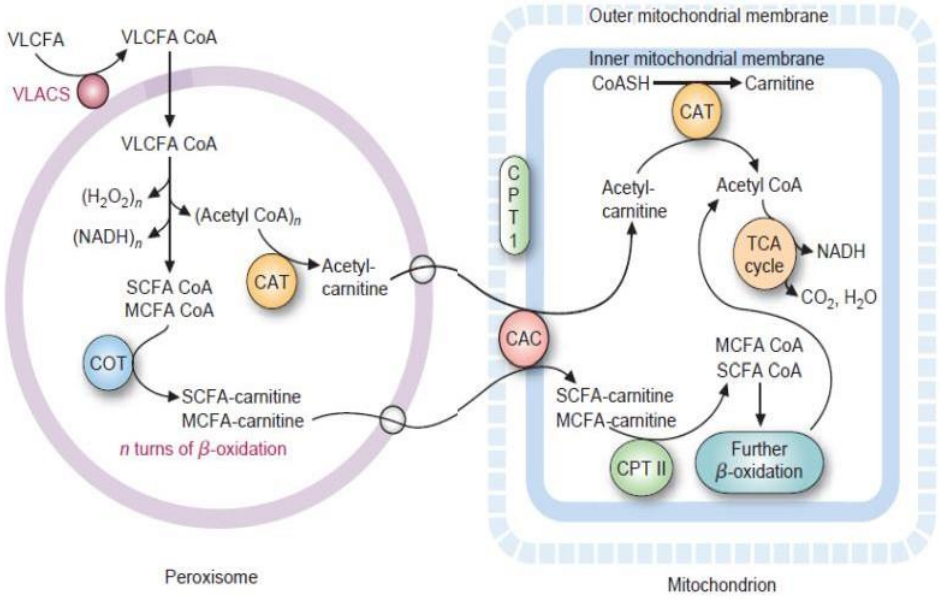
1) Propionyl CoA is monocarboxylic acid with 3 carbons which is carboxylated by **propionyl CoA carboxylase** to produce **D-methylmalonyl CoA**.
   - This enzyme needs the cofactor biotin, vitamin B7, which is a carrier of activated carboxyl group.
   - Methylmalonyl CoA (3 carbons) is similar in structure to succinyl CoA (4 carbons) **both are dicarboxylic acids** with carbons. The difference is the branching of methyl group on C2 in methylmalonyl CoA.
   - Methylmalonyl CoA is derivative of malonic acid.
   - Malonic acid is dicarboxylic acid with 3 carbons.
   - Propionyl CoA carboxylase needs **ATP** and **Biotin**
2) The next step is conversion of **D methylmalonyl CoA** to **L-methylmalonyl CoA** by the enzyme **methylmalonyl CoA racemase**. (Remember the racemic mixture is 50% L and 50% D.)
3) **L-methylmalonyl CoA** is converted to **SUCCINYL COA**, which is intermediate of TCA that can be further converted to Oxaloacetate and by this pathway we can produce acetyl CoA and glucose.
   - Remember when we said that FAs can't be converted to sugar??? Odd chain FA is one of the exceptions.
   - The enzyme functions by transforming carboxyl group from the middle carbon to the terminal one. Thus, it's called mutase.
   - This reaction also needs a cofactor called **cobalamin**, vitamin B12.
   - Nowadays, measuring levels of Vitamin B12 in the blood require chemical tests (Vitamin B12 deficiency). But before the availability of this test, they used to measure it by **levels of L-methylmalonyl (methylmalonic acid)**. Why not succinyl CoA??
     - ✓ Levels of succinyl CoA are not affected by odd FAs oxidation.
   - **High** levels of L-methylmalonyl "methylmalonic acidemia" means **deficiency** of vitamin B12.

Oxidation of very long chain FAs in Peroxisomes (22C or more)



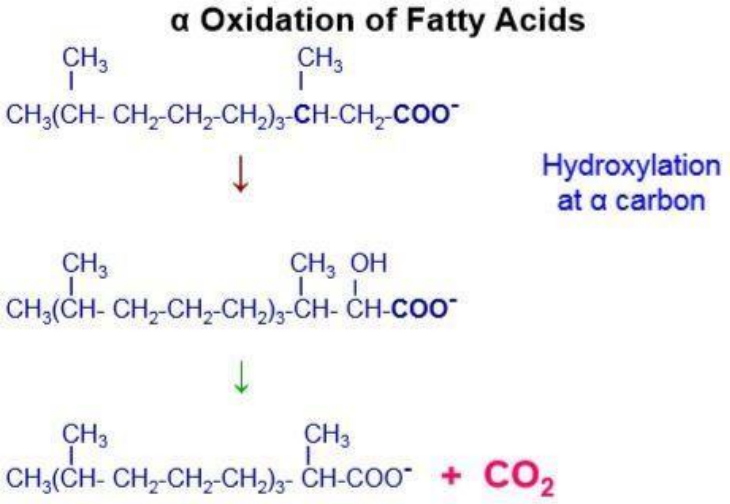
- Very Long FAs are **not oxidized** directly in mitochondria. Rather, In peroxisomes.
- The oxidation is accompanied with reduction of FAD into FADH2.
- As we know, there is no electron transport chain in peroxisomes. FADH2 must be oxidized into FAD in order to oxidize more FAs.
- Oxidation of **FADH2** is accomplished by the **presence of O2** by the enzyme **oxidase** producing **H2O2** and **FAD**.
- The enzyme is **oxidase** not **dehydrogenase** as it **reduces** O2.
- This process continuous until we reach the level of **middle or short FA**. Then, transported into the **mitochondria** via **carnitine**.

VLCFA: very long chain fatty acid.



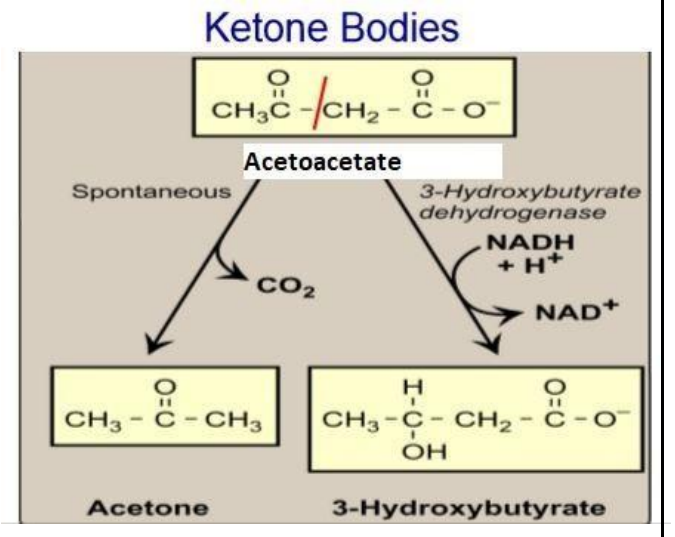
α-Oxidation of FAs

- What about branching FAs? How they are oxidized?
- This is branched FA, all what we have to do is to remove branching. Then keep degradation by β-oxidation.



- This FA is unusual because it has a methyl groups (4 groups) and it's not a substrate for **Acyl-CoA Dehydrogenase**
- So, it has to **hydroxylate at α-carbon** (adding hydroxyl group at α-carbon).
- then it undergoes **oxidative decarboxylation**. (removal of carboxyl group and oxidizing hydroxyl group) and then it can continue as usual.
- This is called α-oxidation and occurs in **peroxisomes.**
- These branching FAs are found in **chlorophyll** in plant cells.
- A deficiency of enzymes catalyzes α-oxidation leads to accumulation of branching FAs and leading to brain damage mental retardations.
- We deal with this case by avoiding food that contain chlorophyll.

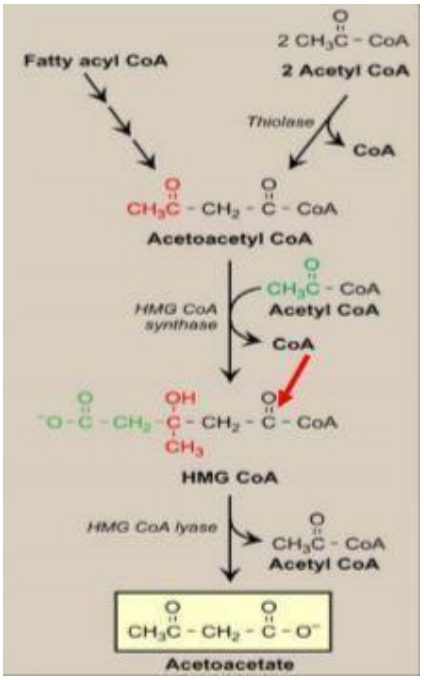
Ketone bodies



- Are **3 water soluble molecules** produced in mitochondria of liver cells from **acetyl CoA.**
- They are **secreted** during **fasting** and uncontrolled diabetes mellitus.
- **Acetoacetate**, if we have a look at its structure, it's **two** acetic acids joined together.
- As the **β-carbon** is a ketone group, it is easy for it to lose the carboxyl group **spontaneously** to produce **acetone**.

- And reduction of **ketone group into hydroxyl group** to produced **3-hydroxybutyrate** " β-hydroxybutyrate". This reaction (reversible) is accompanied by oxidation of **NADH** and the enzyme is called **3-hydroxybutyrate DH**
- **Acetoacetate**, **acetone** and **3-hydroxybutyrate** are all called **ketone bodies**.
- Although 3-hydroxyacetate is not ketone, we consider it ketone body as it's reversibly converted to acetoacetate.
- **The Liver's mitochondria** has the capacity to convert **acetyl CoA** (precursor) derived from fatty acid oxidation into **ketone bodies**, producing them at **high rates** during **fasting** or **uncontrolled diabetes mellitus.**

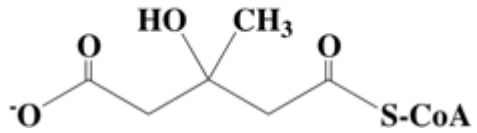
➢ Ketone bodies are synthesized in the **liver** through the following pathway:

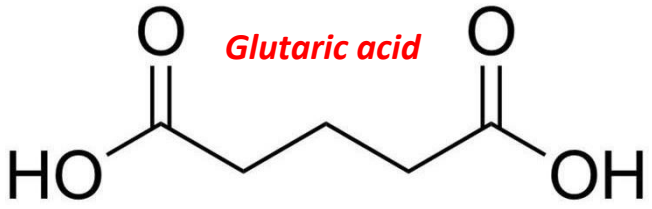


1. The first step, is the **formation of Acetoacetyl CoA** through the condensation of **2 acetyl CoA** catalyzed by the enzyme **Thiolase**, releasing a **CoA** molecule.
   The reverse reaction of thiolase, from acetoacetate to 2 acetyl CoA is the last reaction of β-oxidation. (some amino acid degradation produces **Acetoacetyl CoA**)
2. **Mitochondrial HMG CoA synthase**, combines a third molecule of **Acetyl CoA** with **Acetoacetyl CoA** to produce **HMG CoA,** releasing a **second CoA**.
   Note: HMG CoA synthase is the **rate-limiting step** in the synthesis of ketone bodies, and is present in **significant** quantities **only** in the **liver**
3. **Cleavage of Acetyl CoA** from **HMG CoA** to form **Acetoacetate** by the enzyme **HMG CoA lyase** (the cleavage by lyase produced double bond).
   The Net synthesis of this reaction is *(reactants and intermediates are not counted):*
   2 Acetyl CoA → Acetoacetate + 2 CoA

- HMG is glutaric acid with methylated and Hydroxylated at β carbon.

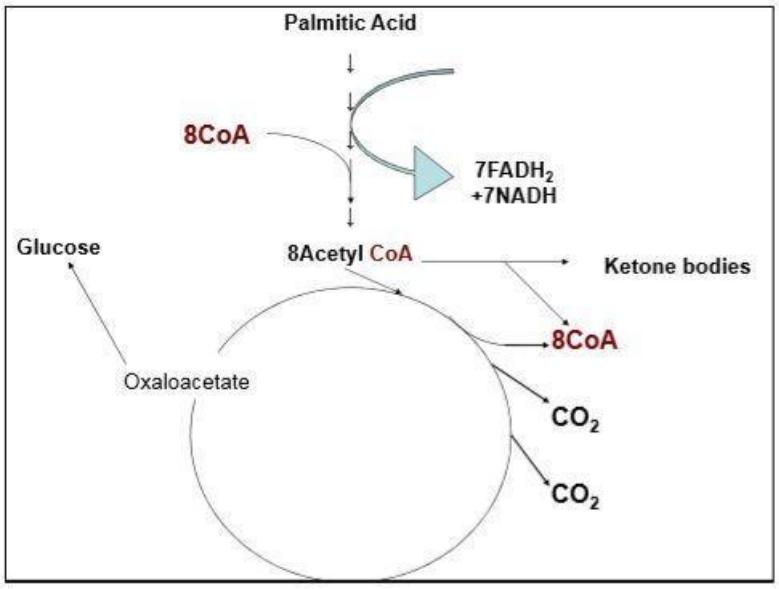
3-hydroxy-3-méthyl-glutaryl-CoA - HMG-CoA





- Note that the 2nd step used acetyl CoA, while the 3rd one yields acetyl CoA.
- So, **the objective of ketone bodies formation (Advantage and Purpose)** is
  - ✓ production of CoA, for the liver
  - ✓ production of acetoacetate for other tissues, as they can use acetoacetate as source of energy.

➢ Why in the **fasting** the rate of ketone bodies is high in liver?



- β-oxidation of **palmitic acid (**16-carbon fatty acid), after 7 cycles yields:
  - ✓ **7 NADH** and **7 FADH2**: They get reoxidized in the ETC to **produce energy**.
  - ✓ **8 Acetyl CoA**: They enter TCA cycle, combine with oxaloacetate **producing citrate** and **free CoA.**
  - ✓ **Oxaloacetate** is required continuously in order to **regenerate CoA.**
- However, **during Fasting (Starvation)** concentration of blood **glucose** is **low**. So, **gluconeogenesis** occurs by consuming **oxaloacetate** to form **glucose**. The level of **oxaloacetate** is highly **decreased**; therefore, the TCA cycle will **stop**. To compensate the lack of energy, liver produces ketone bodies and **CoA**.
- **CoA** leads further breaking of FAs. Thus, producing NADH and FADH2. So, energy is produced by reduction of NADH, FADH2.

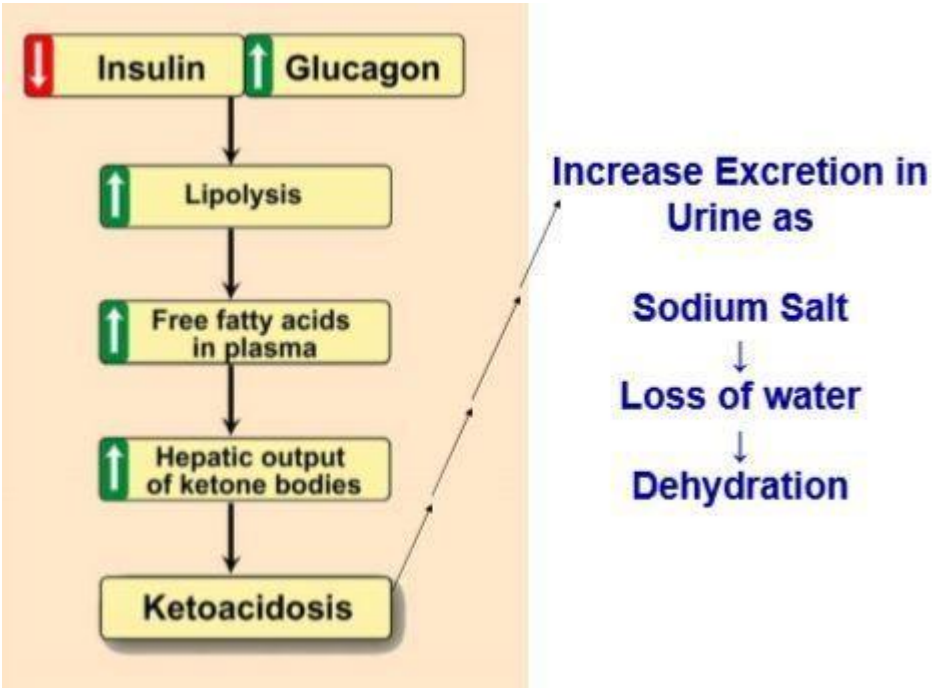
- **Uncontrolled (untreated) Diabetes**
  - When the rate of **formation** of ketone bodies is **greater** than the rate of their **use**, their levels begin to **rise** in the **blood** (ketonemia) and, eventually, in the **urine** (ketonuria). This is seen most often in cases of uncontrolled **Type 1 diabetes.**

  - In the case of diabetes, **insulin** level is **low** while the **glucagon** level is **high** and **blood glucose** is **high**.

  - Therefore, even if the glucose concentration is **high** in the blood, low insulin will **induce gluconeogenesis** and oxaloaceate is converted to glucose.

  - **Lipolysis** is **activated** and continuously **increasing** the free fatty acids in the plasma. These fatty acids will convert into **ketone bodies (are acids)**, **increasing** their **concentrations** in the blood. Thus, the **pH** of the blood will **drop** causing a state called **diabetic ketoacidosis** (DKA).

  - The diabetic ketoacidosis (DKA) is a very common case in uncontrolled diabetes. **excretion** of **glucose** and **ketone bodies (are acids)** in the **urine** as **sodium salts**, results in **dehydration** of the body (Level of sodium decreases: Water level decrease ''dehydration''), which may lead eventually to a **coma** or **death** if not managed . This diabetic ketoacidosis (DKA) is life threatening, we treat it with **insulin**.



- **Use of ketone bodies for the peripheral tissue**
  - Muscles and the brain efficiently **oxidize acetoacetate** and **3-hydroxybutyrate** to provide **energy** during starvation (excluding cells lacking mitochondria like red blood cells).

1. **3-Hydroxybutyrate** is oxidized to **acetoacetate** by 3-hydroxy butyrate **dehydrogenase**, producing NADH.

2. **Thiophorase** transfers CoA from **succinyl CoA** to **Acetoacetate** forming **Acetoacetyl CoA** and **succinate**

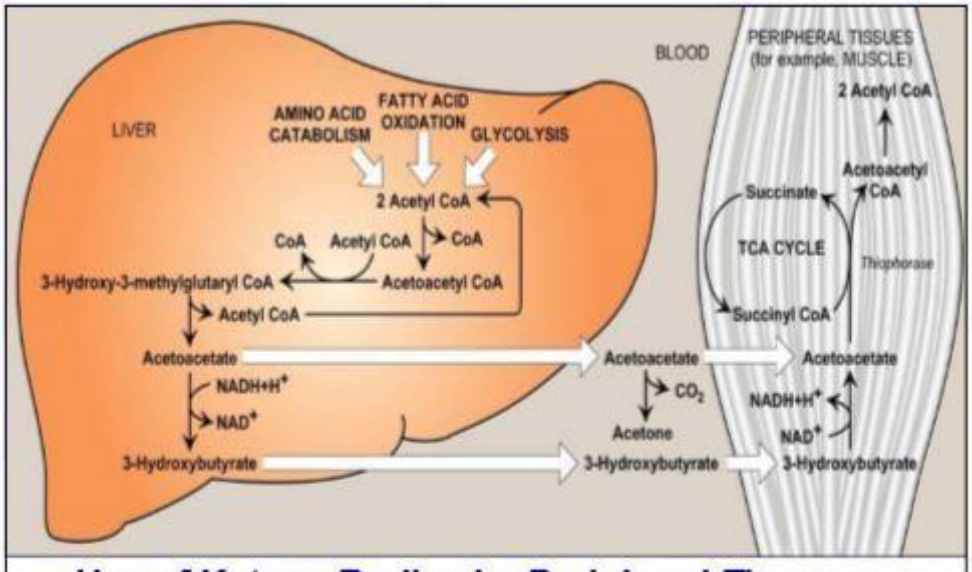
3. **Acetoacetyl CoA** gives **2 Acetyl CoA** (by the reversible reaction) which is used in the **TCA cycle**, providing **energy**.

Note: The **liver**, **lacks** the **Thiophorase** enzyme. That is why it does not use **ketone bodies** as a source of **energy** (Liver can't oxidize acetyl **CoA** in prolonged fasting as a result of unavailability of oxaloacetate).

In summary:

Liver → While **fasting**, **gluconeogenesis** occurs, **highly** consuming **oxaloacetate**. Thus, acetyl CoA is accumulated. Ketone bodies are produced to **consume** the **acetyl CoA**, **regenerating** free CoA used for **beta oxidation** to provide **energy** for tissues. (main purpose is regenerating CoA)

Peripheral Tissue → **Thiophorase**, forms **succinate** from **acetoacetate** which is used in the TCA cycle to provide the **energy needed**. (main purpose is producing Acetyl CoA)



Use of Ketone Bodies by Peripheral Tissues: Skeletal Muscle, Cardiac Muscle and In Brain During Prolonged Fasting (Starvation)