DOCTOR 2020 | JU

METABOLISM

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Part 2 of lecture 4, good luck 🍀

We will talk about Ketone bodies ;)

The resources:

- This lecture
- Lippincott's Biochemistry, Ch. 16
- Diabetic, alcoholic and starvation ~~ketoacidosis~~
    - https://derangedphysiology.com/main/cicm-primary-exam/required-reading/acid-base-physiology/acid-base-disturbances/Chapter%20617/diabetic-alcoholic-and-starvation-ketoacidosis

The link is optional, not mandatory

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what do we mean by **ketone bodies**?!

They are molecules that are are formed from conjugating 2 Acetyl CoA, these reactions that result in formation of ketone bodies take place in the liver specifically in the mitochondria, the ketone bodies are the molecules that you see in the white box in the photo, you have Acetone, Acetoacetate and hydroxybutyrate, if you look at the acetone it has a ketone group, and if you look the acetoacetate it has a ketone group and it has a carboxyl group as well, but if you look to hydroxybutyrate it doesn't have a ketone group, it just has a carboxyl and hydroxyl group but still it is known as ketone body.

Acetone although it is ketone body, it is volatile (means that once it is formed in the body it leaves the body by exhaling it) so the body doesn't use the acetone a much as a source of energy, but the other two molecules of ketone bodies are used as a source of energy, what is important that in liver you have the production of ketone bodies, then they leave the liver and they go to the peripheral tissues, so tissues like muscles, heart and brain can utilize these ketone bodies, specifically muscles and heart tissues, but RBCs don't, why????

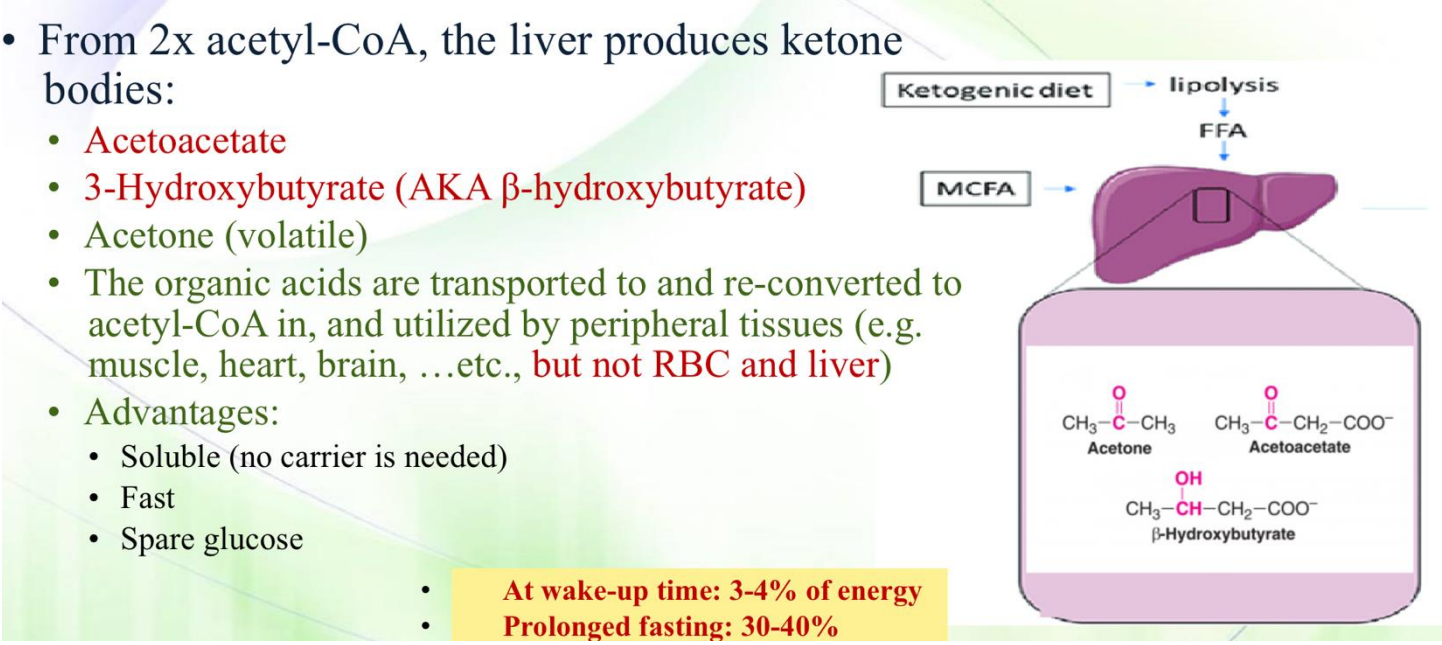
Because they don't have mitochondria, so that they don't relay on ketone bodies as a source of energy.

The liver also can't use ketone bodies as a source of energy, we will say why in following pages, remember that when you see the three stars ***

They are advantages to use ketone bodies as a source of energy:

1. They are soluble (they don't use carriers or transporters) they swim in the blood and they get into the peripheral tissues.
2. Their metabolism is really fast (producing it and it's really fast breaking them down to Acetyl CoA (can enter krebs cycle), they are fast source of energy)
3. They spare glucose (brain really does not depend on fatty acid oxidation as a source of energy it relays more on glucose and very little in ketone bodies and what tissues do is that they leave the glucose for the brain, so they use other sources of energy (like ketone bodies) sparing the glucose).

once you wake up time 3-5% of energy comes from ketone bodies, but in prolonged fasting that is (several days of not eating) a lot of energy comes from ketone bodies (30-40%).



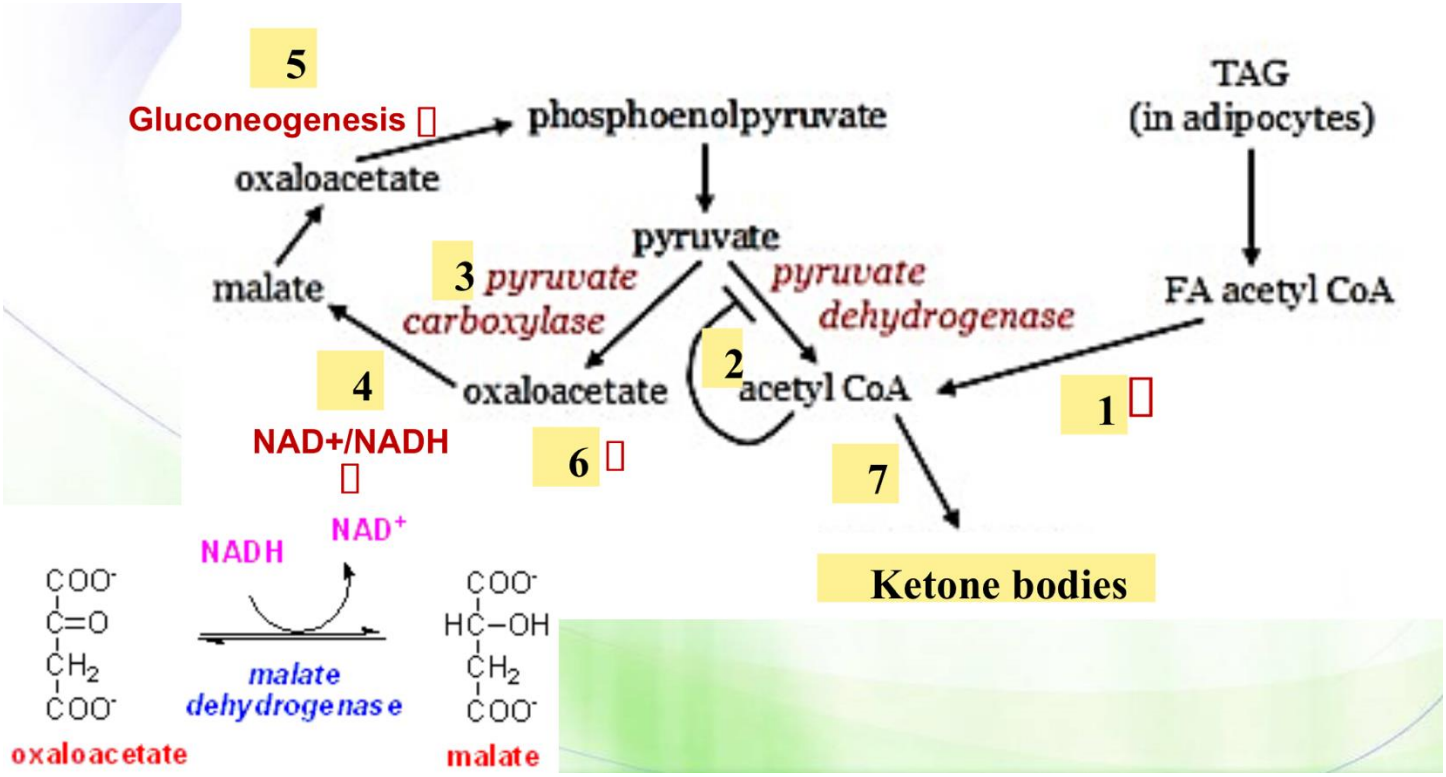
How are they formed? What is the reason biochemically that ketone bodies are formed?

During a fast what happens that you have a releasing of epinephrine and glucagon specifically glucagon which acts on adipocytes and you have the activation of enzymes that release fatty acids from TAGs in adipocytes, these fatty acids leave adipocytes to the blood they bind to the albumin and the go to the liver, so you have an increase in fatty acids in the blood and the liver.

In the liver you have activation of beta oxidation and production of Acetyl CoA now there would be a huge amount of Acetyl CoA in the liver more than what it can handle in the Krebs cycle (some of Acetyl CoA will enter Kreb's cycle but a lot of them will still a lot of Acetyl CoA in the liver, this higher concentration of Acetyl CoA results in inactivation (inhibition) of pyruvate dehydrogenase and you have activation of pyruvate carboxylase which converts pyruvate to Oxaloacetate OA which can get into krebs cycle or get into the gluconeogenesis by converting to malate. What happens here is that OA is converted into malate and this reaction is favored, why?! Because there is a change in the ratio between NAD+ and NADH, why? There will be a huge amount of NADH that is produced because of beta oxidation (look at the photo… the conversion between OA and malate) we have NADH being oxidized to NAD+

If you have a large amount of NADH as a result of beta oxidation the reaction will be driven toward the formation of malate and that results in reducing the amount of OA in mitochondrial matrix so you don't have a much OA for being combined with Acetyl CoA to form citrate, so malate leaves the mitochondrial matrix to the cytosol and then it gets converted to OA and it enters gluconeogenesis forming glucose so there isn't much

oxaloacetate in the mitochondrial matrix that results in having a large amount of Acetyl CoA in the mitochondrial matrix, so it will be converted to ketone bodies.



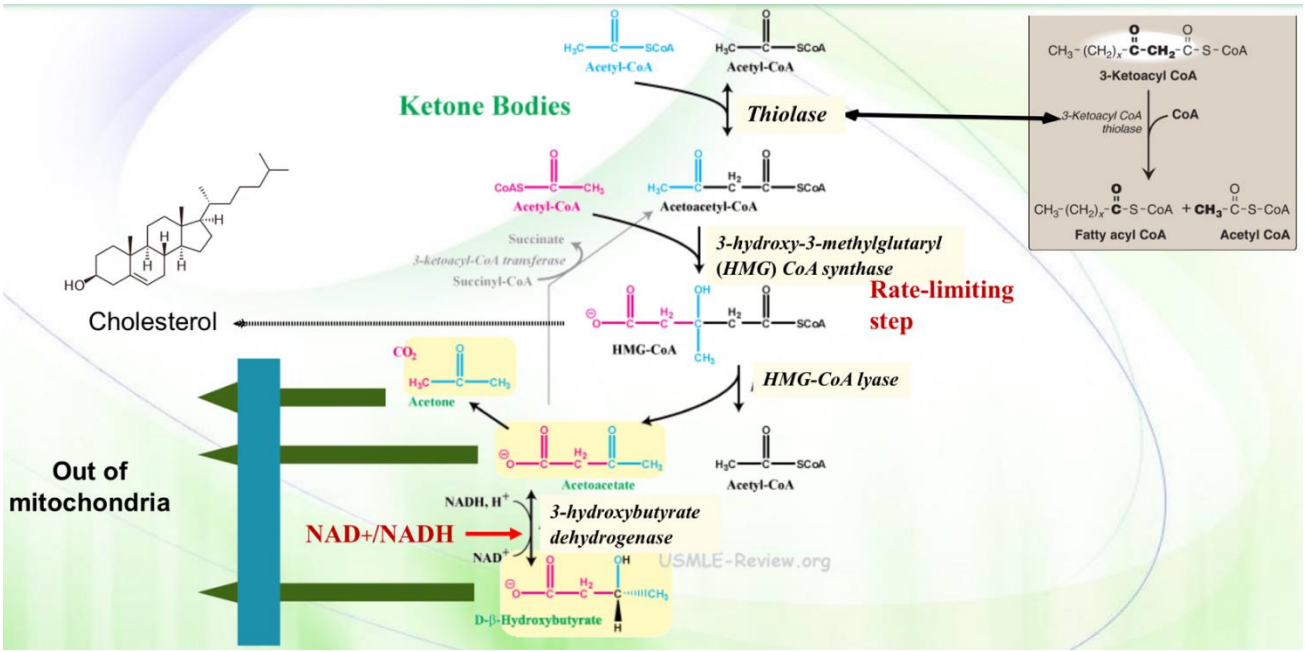
So what are the reactions:

1. Condensation of 2 Acetyl CoA molecules by an enzyme that is called thiolase, this is the exact same enzyme as the one that breaks up fatty acids into Acetyl CoA and a fatty acyl that is shorter by 2 carbons, this enzyme catalyzes the reverse reaction (instead of breaking up the molecules, it condenses 2 Acetyl CoA molecules forming Acetoacetyl CoA)
2. This molecule (acetoacetyl CoA) is conjugated with another Acetyl CoA, the result is six carbon molecule (the rate limiting reaction) it is catalyzed by an enzyme called 3-hydroxy-3-methylglutaryl (HMG) CoA synthase (hint: whenever you hear glutaryl or glutamate … know that we talk about a chain with 5 carbon molecule) so we have a 5 carbon molecule with a methyl group, what's important about the resultant molecule is that it is the precursor of cholesterol synthesis.
3. You end with the formation of HMG CoA molecule, this is followed by a reaction catalyzed by a lyase which removes Acetyl CoA from HMG CoA and formation of acetoacetate this is a very first ketone body that is produced , acetoacetate undergoes a spontaneous decarboxylation (it is not an enzymatic reaction) so we have the removal of carbon in a form of CO2 so it is decarboxylated and converted into acetone the second ketone body to be formed.

4. Acetoacetate is also converted into hydroxybutyrate (beta hydroxybutyrate or 3 hydroxybutyrate) by a dehydrogenase enzyme called 3 hydroxybutyrate dehydrogenase and this reaction is controlled by the ratio between NAD+ and NADH.

So, if there is high NADH to NAD+, the reaction goes towards producing hydroxybutyrate

5. So here we have the formation of ketone bodies (acetone, Acetoacetate and hydroxybutyrate) these molecules leave the mitochondria, they leave the liver to peripheral tissues.



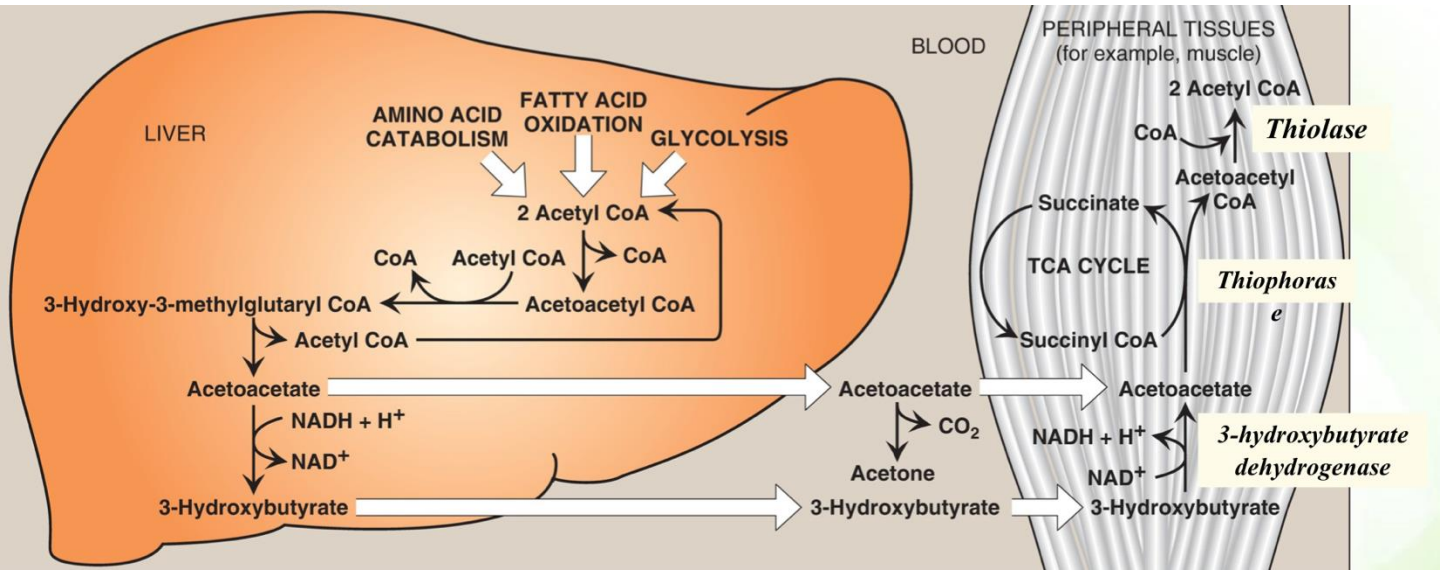
How do the peripheral tissues utilize these ketone bodies?

So in liver again you have the formation of these ketone bodies, then they go to the blood

But in the peripheral tissues or in the blood you have these other ketone bodies that travel blood to the peripheral tissues they get into muscles for example and hydroxybutyrate it is converted into acetoacetate again by the same enzyme dehydrogenase enzyme. Acetoacetate is then provided with a CoA molecule taken from succinyl CoA producing succinate and acetoacetyl CoA, this process is catalyzed by Thiophorase. Now acetoacetyl CoA is converted into 2 Acetyl CoA by the same exact enzyme thiolase and Acetyl CoA can get into the Kreb's cycle forming GTP, NADH and FADH2.

There are 2 types of cells that can not utilize ketone bodies:

1. RBCs, they don't have mitochondria.
2. And the other is liver, because liver cells don't have thiophorase enzyme, so they stick in the point where they have just acetoacetate and hydroxybutyrate, and this is good because the main function of liver is to make sure that ketone bodies will go to all cells



Now the process is hormonally regulated,

High level of glucagon will induce lypolysis in adipocytes, freeing fatty acids that will be attached to albumin, and they get into liver tissues where we have the production of ketone bodies, but that results in ketoacidosis (level of ketone bodies is high so we have high level of ketoacidosis) the pH is lower than the normal level so why is the the case?

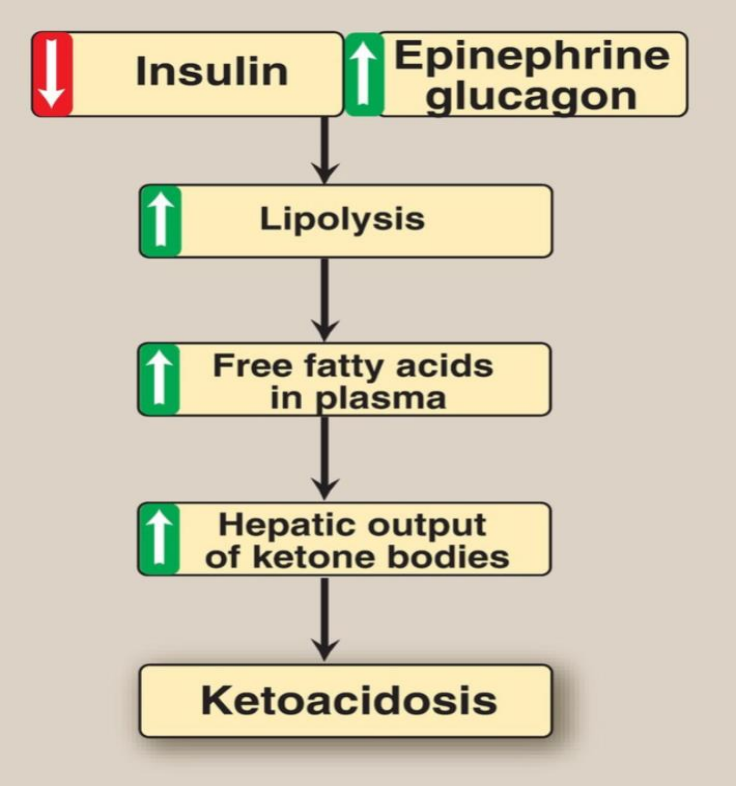
Because of pKa (the pH where 50% of molecules are in the acidic form and the other 50% are in the conjugated base form) the pKa of acetoacetatic acid and hydroxybutyrate is about 4.7 & 3.5 so at physiological pH that is 7.2-7.4 these 2 molecules exist in the conjugated base form releasing their protons and that will result in lower pH and causing what is known as ketoacidosis.

That will result in dehydration as well, why? The body must be able to remove these excess protons, they are removed in the urine this will take away water molecules as well (people who are diabetic they go to the bathroom a lot because the need to get rid of these excess protons (uncontrolled diabetes case) causing dehydration

Normally ketone bodies levels are <3 mg/dl but they can go up to about 90mg/dl and the body get rid from a large amount of them per day about 5 g

So ketoacidosis can result from uncontrolled diabetes, prolonged fast and alcoholism.

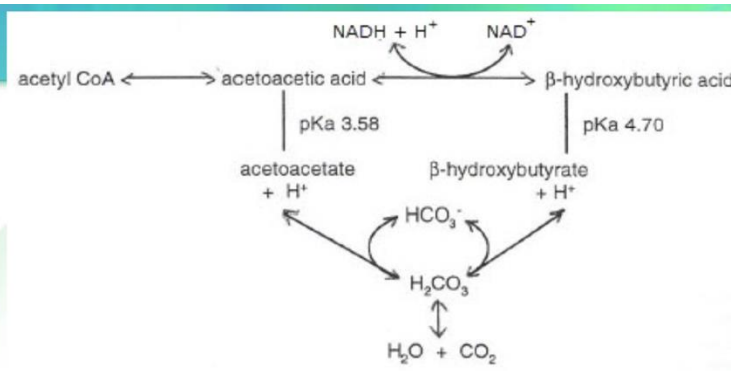
If you we checking an emergency room or diabetic patient and you smell a fruity odor of breath you will know that there is a high level of ketone bodies in the blood, why fruit odor? Because of acetone which is volatile .

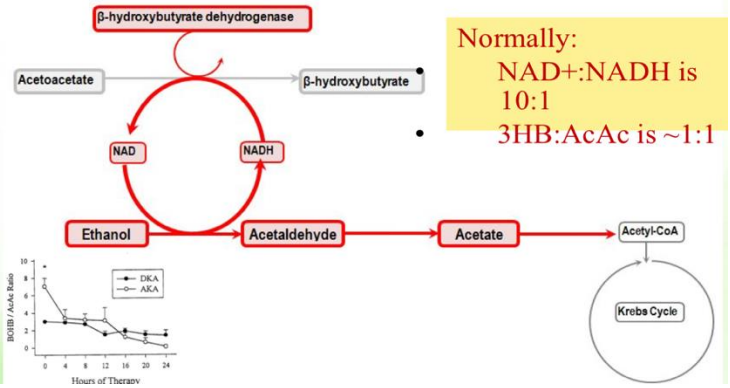


Ketoacidosis

- Remember pKa!!!
- Normally, levels of ketone bodies: <3 mg/dl
- People with excessive production: 90 mg/dl and urinary excretion of ketone bodies may be 5,000 mg/24 hour.
- The end-results:
  - Dehydration
  - Acidemia (ketoacidosis)
    - Diabetic ketoacidosis, prolonged fasting, alcoholism
  - Fruity odor of breath

In alcoholic ketoacidosis: 3HB>AcAc
The ratio gets back to 1:1 after a few hours





Normally:
NAD+:NADH is 10:1
- 3HB:AcAc is ~1:1

Let’s talk a little about alcohol ketoacidosis normally NAD+\NADH is 10:1 and the ratio of beta hydroxybutyrate to acetoacetate is 1:1, in alcoholic ketoacidosis you have high level of hydroxybutyrate in relation to acetoacetate (it could be 10:1 or Something like that) (look to the chart that compare between diabetic ketoacidosis in black and alcoholic ketoacidosis in white) above , if the person drink a lot of alcohol so immediately you have alcoholic ketoacidosis with a ratio that is high hydroxybutyrate to acetoacetate but with time the ratio will go back to the normal.

But in diabetic ketoacidosis the ratio is close to 1:1 but it can be a bit higher.

So why it is very high in case of alcoholic ketoacidosis? What it has to do is with the reaction itself, if there is ethanol in the body it would be converted to acetyldehyde and this reaction requires the reduction of NAD+ to NADH the ratio go higher than 10:1 so we should have a shift in the reaction of acetoacetate to hydroxybutyrate (acetoacetic acid is converted into hydroxybutyrate and this reaction requires the conversion from NADH to NAD+ (that means if you have high level of NADH (results from the oxidation of ethanol …..you will have a conversion from acetoacetate to hydroxybutyrate to back to normal ratio that is 10:1).

Pay attention attention to the directions of arrows in the photo above.