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**Course Title:** Medical Biochemistry IV  
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**Question**

1. Define the following terms
2. Ketogenesis
3. Ketonaemia
4. Ketouria
5. Ketogenesis
6. What are the consequences of ketosis
7. Write concisely on the management of ketoacidosis

**Answers**

1. Ketogenesis

**Ketogenesis** is the [biochemical](https://en.wikipedia.org/wiki/Biochemistry) process through which organisms produce [ketone bodies](https://en.wikipedia.org/wiki/Ketone_bodies) through [breakdown of fatty acids](https://en.wikipedia.org/wiki/Fatty_acid_metabolism) and [ketogenic amino acids](https://en.wikipedia.org/wiki/Ketogenic_amino_acid" \o "Ketogenic amino acid). This process supplies energy under circumstances such as [fasting](https://en.wikipedia.org/wiki/Fasting) or [caloric restriction](https://en.wikipedia.org/wiki/Caloric_restriction) to certain organs, particularly the [brain](https://en.wikipedia.org/wiki/Brain), [heart](https://en.wikipedia.org/wiki/Heart) and [skeletal muscle](https://en.wikipedia.org/wiki/Skeletal_muscle). Insufficient [gluconeogenesis](https://en.wikipedia.org/wiki/Gluconeogenesis) can cause [hypoglycemia](https://en.wikipedia.org/wiki/Hypoglycemia" \o "Hypoglycemia) and excessive production of ketone bodies, ultimately leading to a life-threatening condition known as [ketoacidosis](https://en.wikipedia.org/wiki/Ketoacidosis)

Production

Ketone bodies are produced mainly in the [mitochondria](https://en.wikipedia.org/wiki/Mitochondria) of [liver](https://en.wikipedia.org/wiki/Liver) cells, and synthesis can occur in response to an unavailability of blood glucose, such as during [fasting](https://en.wikipedia.org/wiki/Fasting). Other cells, e.g. human [astrocytes](https://en.wikipedia.org/wiki/Astrocytes), are capable of carrying out ketogenesis, but they are not as effective at doing so. Ketogenesis occurs constantly in a healthy individual. Ketogenesis in healthy individuals is ultimately under the control of the master regulatory protein [AMPK](https://en.wikipedia.org/wiki/AMPK), which is activated during times of metabolic stress, such as carbohydrate insufficiency. Activation in the liver inhibits lipogenesis, promotes fatty acid oxidation, switches off acetyl-CoA carboxylase, turns on malonyl-CoA decarboxylase, and consequently induces ketogenesis. [Ethanol](https://en.wikipedia.org/wiki/Ethanol) is a powerful AMPK inhibitor and therefore can cause profound disruptions in the metabolic state of the liver, including halting of ketogenesis, even in the context of severe glucose shortage.

Ketogenesis takes place in the setting of low glucose levels in the blood, after exhaustion of other cellular carbohydrate stores, such as [glycogen](https://en.wikipedia.org/wiki/Glycogen). It can also take place when there is insufficient [insulin](https://en.wikipedia.org/wiki/Insulin) (e.g. in type 1 (but not 2) [diabetes](https://en.wikipedia.org/wiki/Diabetes_mellitus)), particularly during periods of "ketogenic stress" such as intercurrent illness

The production of ketone bodies is then initiated to make available energy that is stored as [fatty acids](https://en.wikipedia.org/wiki/Fatty_acid). Fatty acids are enzymatically broken down in [β-oxidation](https://en.wikipedia.org/wiki/Beta_oxidation) to form [acetyl-CoA](https://en.wikipedia.org/wiki/Acetyl-CoA). Under normal conditions, acetyl-CoA is further oxidized by the [citric acid cycle](https://en.wikipedia.org/wiki/Citric_acid_cycle) (TCA/Krebs cycle) and then by the mitochondrial [electron transport chain](https://en.wikipedia.org/wiki/Electron_transport_chain) to release energy. However, if the amounts of acetyl-CoA generated in fatty-acid β-oxidation challenge the processing capacity of the TCA cycle; i.e. if activity in TCA cycle is low due to low amounts of intermediates such as [oxaloacetate](https://en.wikipedia.org/wiki/Oxaloacetate), acetyl-CoA is then used instead in biosynthesis of ketone bodies via acetoacetyl-CoA and β-hydroxy-β-methylglutaryl-CoA ([HMG-CoA](https://en.wikipedia.org/wiki/HMG-CoA)). Furthermore, since there is only a limited amount of coenzyme A in the liver, the production of ketogenesis allows some of the coenzyme to be freed to continue fatty-acid β-oxidation. Depletion of glucose and oxaloacetate can be triggered by fasting, vigorous exercise, high-fat diets or other medical conditions, all of which enhance ketone production. Deaminated amino acids that are ketogenic, such as leucine, also feed TCA cycle, forming acetoacetate & ACoA and thereby produce ketones. Besides its role in the synthesis of ketone bodies, HMG-CoA is also an intermediate in the synthesis of [cholesterol](https://en.wikipedia.org/wiki/Cholesterol), but the steps are compartmentalised. Ketogenesis occurs in the mitochondria, whereas cholesterol synthesis occurs in the [cytosol](https://en.wikipedia.org/wiki/Cytosol), hence both processes are independently regulated

**Mechanism**

Ketogenesis occurs primarily in the mitochondria of liver cells. Fatty acids are brought into the mitochondria via carnitine palmitoyltransferase (CPT-1) and then broken down into acetyl CoA via beta-oxidation. Two acetyl-CoA molecules are converted into acetoacetyl-CoA via the enzyme thiolase; this is also known as acetyl coenzyme A acetyltransferase (ACAT). Afterward, acetoacetyl-CoA is converted to HMG-CoA via the enzyme HMG-CoA synthase. HMG-CoA lyase then converts HMG-CoA to acetoacetate. Acetoacetate can be converted to either acetone through non-enzymatic decarboxylation, or to beta-hydroxybutyrate via beta-hydroxybutyrate dehydrogenase.

Acetoacetate and beta-hydroxybutyrate are the two ketone bodies used by the body for energy. Once they reach extrahepatic tissues, beta-hydroxybutyrate is converted to acetoacetate via the enzyme beta-hydroxybutyrate dehydrogenase, and acetoacetate is converted back to acetyl-CoA via the enzyme beta-ketoacyl-CoA transferase. Acetyl-CoA goes through the citric acid cycle, and after oxidative phosphorylation produces 22 ATP per molecule. Acetone does not convert back to acetyl-CoA, so it is either excreted through urine or exhaled.

*Regulation of Ketogenesis*

Ketogenesis can be upregulated by hormones such as glucagon, cortisol, thyroid hormones, and catecholamines by causing greater breakdown of free fatty acids, thus increasing the amount available to be used in the ketogenic pathway. However, insulin is the main hormonal regulator of this process.

Insulin regulates many key enzymes in the ketogenic pathway, and a state of low insulin triggers the process. A **low insulin** state leads to:

* Increased free fatty acids (FFAs)
* Due to decreased inhibition of hormone-sensitive lipase
* Increased uptake of FFAs into the mitochondria
* Due to decreased activation of acetyl-CoA carboxylase, decreasing malonyl CoA, which disinhibits Carnitine Palmitoyltransferase 1 (CPT1)
* Increased production of ketone bodies
* Due to increased HMG-CoA activity

Both acetoacetate and beta-hydroxybutyrate are [acidic](https://en.wikipedia.org/wiki/Acid), and, if levels of these ketone bodies are too high, the [pH](https://en.wikipedia.org/wiki/PH) of the blood drops, resulting in [ketoacidosis](https://en.wikipedia.org/wiki/Ketoacidosis). Ketoacidosis is known to occur in untreated [type I diabetes](https://en.wikipedia.org/wiki/Diabetes_mellitus_type_1) (see [diabetic ketoacidosis](https://en.wikipedia.org/wiki/Diabetic_ketoacidosis)) and in [alcoholics](https://en.wikipedia.org/wiki/Alcoholic) after prolonged binge-drinking without intake of sufficient carbohydrates (see [alcoholic ketoacidosis](https://en.wikipedia.org/wiki/Alcoholic_ketoacidosis))

Ketogenesis can be ineffective in people with beta oxidation defects

Individuals with diabetes mellitus can experience overproduction of ketone bodies due to a lack of insulin. Without insulin to help extract glucose from the blood, tissues the levels of malonyl-CoA are reduced, and it becomes easier for fatty acids to be transported into mitochondria, causing the accumulation of excess acetyl-CoA. The accumulation of acetyl-CoA in turn produces excess ketone bodies through ketogenesis. The result is a rate of ketone production higher than the rate of ketone disposal, and a decrease in blood pH.

There are some health benefits to ketone bodies and ketogenesis as well. It has been suggested that a low-carb, high fat [ketogenic diet](https://en.wikipedia.org/wiki/Ketogenic_diet" \o "Ketogenic diet) can be used to help treat epilepsy in children. Additionally, ketone bodies can be anti-inflammatory. Some kinds of cancer cells are unable to use ketone bodies, as they do not have the necessary enzymes to engage in ketolysis. It has been proposed that actively engaging in behaviors that promote ketogenesis could help manage the effects of some cancers.

b) Ketonaemia: ketonemia is due to increased production of ketone bodies by the liver rather than to a deficiency in their utilization by extrahepatic tissues. While acetoacetate and D(−)-3-hydroxybutyrate are readily oxidized by extrahepatic tissues, acetone is difficult to oxidize in vivo and to a large extent is volatilized in the lungs. In moderate ketonemia, the loss of ketone bodies via the urine is only a few percent of the total ketone body production and utilization. Since there are renal threshold-like effects (there is not a true threshold) that vary between species and individuals, measurement of the ketonemia, not the ketonuria, is the preferred method of assessing the severity of ketosis.

**c) Ketonuria** is a medical condition in which [ketone bodies](https://en.wikipedia.org/wiki/Ketone_bodies) are present in the [urine](https://en.wikipedia.org/wiki/Urine).

It is seen in conditions in which the body produces excess ketones as an indication that it is using an alternative source of energy. It is seen during starvation or more commonly in [type 1 diabetes mellitus](https://en.wikipedia.org/wiki/Diabetes_mellitus_type_1). Production of ketone bodies is a normal response to a shortage of [glucose](https://en.wikipedia.org/wiki/Glucose), meant to provide an alternate source of fuel from [fatty acids](https://en.wikipedia.org/wiki/Fatty_acids).

Pathophysiology

Ketones are metabolic end-products of [fatty acid metabolism](https://en.wikipedia.org/wiki/Fatty_acid_metabolism#Fatty_acid_catabolism). In healthy individuals, [ketones](https://en.wikipedia.org/wiki/Ketone_bodies) are formed in the [liver](https://en.wikipedia.org/wiki/Liver) and are completely metabolized so that only negligible amounts appear in the [urine](https://en.wikipedia.org/wiki/Urine). However, when [carbohydrates](https://en.wikipedia.org/wiki/Carbohydrates) are unavailable or unable to be used as an energy source, [fat](https://en.wikipedia.org/wiki/Fat) becomes the predominant body fuel instead of carbohydrates and excessive amounts of ketones are formed as a metabolic byproduct. Higher levels of ketones in the urine indicate that the body is using fat as the major source of energy.

Ketone bodies that commonly appear in the urine when fats are burned for energy are [acetoacetate](https://en.wikipedia.org/wiki/Acetoacetate) and [beta-hydroxybutyric acid](https://en.wikipedia.org/wiki/Beta-hydroxybutyric_acid). Acetone is also produced and is expired by the lungs.[[1]](https://en.wikipedia.org/wiki/Ketonuria#cite_note-1) Normally, the urine should not contain a noticeable concentration of ketones to give a positive reading. As with tests for [glucose](https://en.wikipedia.org/wiki/Glucose), acetoacetate can be tested by a dipstick or by a lab. The results are reported as small, moderate, or large amounts of acetoacetate. A small amount of acetoacetate is a value under 20 mg/dl; a moderate amount is a value of 30–40 mg/dl, and a finding of 80 mg/dl or greater is reported as a large amount.

One 2010 study admits that though ketonuria's relation to general metabolic health is ill-understood, there is a positive relationship between the presence of ketonuria after fasting and positive metabolic health.

1. Same as number 1a

Consequences of Ketosis

* The Low-Carb/Keto Flu

In the beginning of ketosis, you may experience a range of negative symptoms. They are often referred to as "low-carb flu" or "keto flu" because they resemble symptoms of the flu. These may include:

* Headache.
* Fatigue.
* Brain fog.
* Increased hunger.
* Poor sleep.
* Nausea.
* Decreased physical performance

These issues may discourage people from continuing to follow a ketogenic diet, even before they start reaping all the benefits.

However, the "low-carb flu" is usually over within a few days.

* Bad Breath Is Also Common

One of the more common side effects of ketosis is bad breath, often described as fruity and slightly sweet. It's caused by acetone, a ketone that is a by-product of fat metabolism. Blood acetone levels are elevated in ketosis, and your body gets rid of some of it via your breath

* Leg Muscles May Cramp

In ketosis, some people may experience leg cramps. Although they're usually a minor problem, they're never pleasant and can be painful. Leg cramps in ketosis are usually connected to dehydration and loss of minerals. This is because ketosis causes a [reduction in water weight](https://www.healthline.com/nutrition/13-ways-to-lose-water-weight/). Glycogen, the storage form of glucose in muscles and liver, binds water. This gets flushed out when you [reduce carb intake](https://www.healthline.com/nutrition/15-ways-to-eat-less-carbs/), and is one of the main reasons why people [lose weight rapidly](https://www.healthline.com/nutrition/how-to-lose-weight-as-fast-as-possible/) in the first week of a very low-carb diet. That being said, there are many other potential causes of muscle cramps.

* Ketosis May Cause Digestive Problems

Dietary changes can sometimes lead to digestive issues, this is also true for ketogenic diets, and constipation is a common side effect in the beginning. This is most commonly due to not eating enough fibre and not drinking enough fluids. Some people may also get diarrhoea, but it's less common. If you made drastic changes to your diet in order to get into ketosis, it's more likely that you'll experience digestive symptoms. Nevertheless, digestive issues are usually over within a few weeks.

* Elevated Heart Rate

Some people also experience increased heart rate as a side effect of ketosis. This is also called heart palpitations or a racing heart, and can happen during the first few weeks of a ketogenic diet.

Other, less common side effects may include:

* **Ketoacidosis:** A few cases of ketoacidosis (a serious condition that occurs in uncontrolled diabetes) have been reported in breastfeeding women, likely triggered by a very low-carb diet. However, this is extremely rare
* **Kidney stones:** Although uncommon, some epileptic children have developed kidney stones on a ketogenic diet
* **Raised cholesterol levels:** Some people get increased total and low-density lipoprotein (LDL) [cholesterol levels](https://www.healthline.com/nutrition/low-carb-diets-and-cholesterol/)

3. The Management Of Ketoacidosis

You may have to go to the hospital. You'll probably get [insulin](https://www.webmd.com/diabetes/treat-your-diabetes-17/slideshow-blood-sugar-insulin) through an IV to bring your ketones down and fluids to get you hydrated and bring your blood chemistry back into balance. If you don't treat ketoacidosis, you could pass out, go into a [coma](https://www.webmd.com/brain/coma-types-causes-treatments-prognosis), and possibly die.

Your doctor may change your [insulin](https://www.webmd.com/diabetes/video/myths-and-facts-about-insulin) dose, or the kind you use, to prevent it from happening again. You should drink more water and sugar-free, non-[alcoholic](https://www.webmd.com/mental-health/addiction/understanding-alcohol-abuse-basics) beverages.

Good blood sugar control will help you avoid ketoacidosis.

* Take your medicines as directed.
* Follow your meal plan closely.
* Keep up with your [exercise program](https://www.webmd.com/fitness-exercise/default.htm).
* Test your blood sugar regularly.

Make sure your insulin hasn't expired. Don't use it if it has clumps. Insulin should either be clear or evenly cloudy with small flecks.

If you're on an [insulin pump](https://www.webmd.com/diabetes/insulin-pump), look closely for insulin leaks, and check your tube connections for air bubbles.

Talk to your doctor if your blood sugar levels are often out of your target range.