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Question: 1.Define the following terms: A) Ketogenesis B) Ketonaemia C) Ketonuria

* 1. What are the consequences of ketosis.
	2. Write consisely on the management of ketoacidosis.

1.A)Ketogenesis is a catabolic pathway of metabolism. In this process, fatty acids and certain ketogenic amino acids are broken down to derive energy by alternative means. Ketone bodies are produced in the ketogenesis process.

Our body continuously produces ketone bodies in low amounts but in certain cases like starving, when carbohydrates are present in less amount in diet, ketogenesis is preferred to compensate for the energy requirements.

Ketone bodies accumulated in an excess amount may lead to a condition called ketoacidosis**,** which may be fatal.

 Ketone Bodies

Fatty acids undergo 𝛽-oxidation in the liver mitochondria to generate a high amount of energy and form three compounds, that are known as “ketone bodies”**.**These ketone bodies are water-soluble and do not require lipoproteins for transportation across the membrane. Ketone bodies are lipid molecules having a carbonyl group attached to two -R groups.

The three ketone bodies formed are:

* 1. Acetoacetate
	2. D-3-hydroxybutyrate
	3. Acetone

 Ketogenesis Pathway

Our body normally derives energy from stored carbohydrate by the process of glycogenolysis (glycogen to glucose) or from non-carbohydrate sources such as lactate by the process of gluconeogenesis**.**

Ketogenesis occurs continuously in a healthy individual, but under certain conditions, when there is increased concentration of fatty acid or carbohydrate reserves are decreased, ketogenesis happens at a higher rate:

* 1. Under low blood glucose level, e.g. during fasting or starvation
	2. On exhaustion of carbohydrate reserve, e.g. glycogen
	3. When there is insufficient insulin, e.g. Type-1 diabetes

All the main body parts such as the brain, skeletal muscles, heart, etc. can utilise the energy formed by ketogenesis.

Insufficient gluconeogenesis results in hypoglycemia and excessive production of ketone bodies resulting in a fatal condition called ketoacidosis**.**

 Ketogenesis Steps

The ketogenesis process occurs primarily in the mitochondria of liver cells. Below are the steps in the process of ketogenesis:

* 1. Transfer of fatty acids in mitochondria by carnitine palmitoyltransferase CPT-1
	2. 𝛽-oxidation of fatty acid to form acetyl CoA
	3. Acetoacetyl-CoA formation: 2 acetyl CoA form acetoacetyl CoA. The reaction is catalyzed by the enzyme thiolase
	4. 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthesis: the step is catalyzed by HMG-CoA synthase
	5. Acetoacetate formation: HMG-CoA is broken down to acetoacetate and acetyl-CoA by the action of HMG-CoA lyase

Acetoacetate thus produced forms other ketone bodies, acetone by decarboxylation and D-3-hydroxybutyrate by reduction.



Liver, which produces ketone bodies primarily in the mitochondria, cannot utilise it due to lack of an enzyme 𝛽-keto-acyl-CoA transferase.

Acetoacetate and D-3-hydroxybutyrate are used by the body to get energy. These ketone bodies are circulated out of the liver cell.

In the extrahepatic tissues, the following reactions occur:

* 1. D-3-hydroxybutyrate is converted back to acetoacetate by 𝛽-hydroxybutyrate dehydrogenase
	2. Acetoacetate is converted back to acetyl-CoA by 𝛽-keto-acyl-CoA transferase
	3. Acetyl-CoA enters the citric acid cycle (TCA or Kreb’s cycle) and produces 22 ATP molecules
	4. Acetone is excreted out

Ketogenesis process is regulated by Insulin. Hormones such as glucagon, thyroid hormones, catecholamines, cortisol increase ketogenesis rate by stimulating the breakdown of free fatty acids.

Significance of Ketogenesis

* 1. Ketogenesis is used to get energy by the brain, heart and skeletal muscles under fasting condition
	2. The ketogenic diet (low-carb, fat-rich diet) is used these days to lose weight. The idea is to utilise excess fat stored in the body to get energy but excess ketone bodies production can lead to various complications and ketoacidosis
	3. In ketoacidosis condition, the kidneys excrete extra ketone bodies with the water resulting in fluid loss
	4. Diabetic patients are greatly affected by ketoacidosis because insulin hormone is the main regulator of the process
	5. Symptoms of ketoacidosis include frequent urination, breath smelling like fruits or acetone, nausea, shortness of breath, fatigue, excessive thirst, etc.
	6. Level of ketone bodies present in the body can be tested by blood serum or urine sample analysis.

B) Ketonaemia: a term used to describe ketones in the bloodstream, is a physiological consequence of lipid metabolism. Ketogenesis is the normal pathway by which ketones are formed in the liver. Ketosis is the production of excessive ketones.

Ketones are a valuable energy source for tissues such as the brain and muscle. Also, they are involved in regulating the utilization of other energy sources.

C) **Ketonuria** is a medical condition in which ketone bodies are present in the 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. Production of ketone bodies is a normal response to a shortage of glucose, meant to provide an alternate source of fuel from fatty acids.

 Causes

* 1. Metabolic abnormalities such as [diabetes](https://en.m.wikipedia.org/wiki/Diabetes_mellitus), renal [glycosuria](https://en.m.wikipedia.org/wiki/Glycosuria), or [glycogen](https://en.m.wikipedia.org/wiki/Glycogen) storage disease.
	2. Dietary conditions such as [starvation](https://en.m.wikipedia.org/wiki/Starvation), fasting, [low-carbohydrate diets](https://en.m.wikipedia.org/wiki/Low-carbohydrate_diet), prolonged [vomiting](https://en.m.wikipedia.org/wiki/Vomiting), and [anorexia](https://en.m.wikipedia.org/wiki/Anorexia_%28symptom%29) including caused by [hyperemesis gravidarum](https://en.m.wikipedia.org/wiki/Hyperemesis_gravidarum).
	3. Conditions in which metabolism is increased, such as [hyperthyroidism](https://en.m.wikipedia.org/wiki/Hyperthyroidism), fever, pregnancy or [lactation](https://en.m.wikipedia.org/wiki/Lactation).

In non-diabetic persons, ketonuria may occur during acute illness or severe stress. In a diabetic patient, ketone bodies in the urine suggest that the patient is not adequately controlled and that adjustments of medication, diet, or both should be made promptly. In the non diabetic patient, ketonuria reflects a reduced carbohydrate metabolism and an increased fat metabolism.

2) **Ketosis** is a metabolic state characterized by elevated levels of ketone bodies in the blood or urine. Physiologic ketosis is a normal response to low glucose availability, such as low-carbohydrate diets or fasting, that provides an additional energy source for the brain in the form of ketones. In physiologic ketosis, ketones in the blood are elevated above baseline levels, but the body's acid-base homeostasis is maintained.

In ketosis, parts of the body and brain use ketones for fuel instead of carbs. It can take some time for your body to adapt to this.

 Consequences

* 1. 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

* 1. Bad breath: is another common side effect of ketosis, often described as fruity and slightly sweet.

It's caused by acetone, a ketone that is a byproduct of fat metabolism. Blood acetone levels are elevated in ketosis, and your body gets rid of some of it via your breath. Occasionally, sweat and urine can also start to smell like acetone. In ketosis, your breath, sweat and urine may smell like acetone. This ketone is produced by the liver from fat and increases on a ketogenic diet.

* 1. Muscle cramps: some people may experience leg cramps. Although 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. Glycogen, the storage form of glucose in muscles and liver, binds water. This gets flushed out when you reduce carb intake, and is one of the main reasons why people lose weight rapidly in the first week of a very low-carb diet.
	2. Elevated heart rate: some people also experience increased heart rate as a side effect of ketosis.This is called heart palpitations or a racing heart, and can happen during the first few weeks of a ketogenic diet.
	3. **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.
	4. **Kidney stones:** Although uncommon, some epileptic children have developed kidney stones on a ketogenic diet.
	5. **Raised cholesterol levels:** Some people get increased total and low-density lipoprotein (LDL) cholesterol.

3. Ketoacidosis, is an uncontrolled production of ketones that occurs in pathologic states and causes a metabolic acidosis, which is a medical emergency. Ketoacidosis is most commonly the result of complete insulin deficiency in type 1 diabetesor late-stage type 2 diabetes. Ketone levels can be measured in blood, urine or breath and are generally between 0.5 and 3.0mM in physiologic ketosis, while ketoacidosis may cause blood concentrations greater than 10 mM. Treatment usually involves:

* 1. **Fluid replacement.** You'll receive fluids — either by mouth or through a vein (intravenously) — until you're rehydrated. The fluids will replace those you've lost through excessive urination, as well as help dilute the excess sugar in your blood.

Initial correction of fluid loss is either by isotonic sodium chloride solution or by lactated Ringer solution. The recommended schedule for restoring fluids is as follows:

* 1. Administer 1-3 L during the first hour.
	2. Administer 1 L during the second hour.
	3. Administer 1 L during the following 2 hours
	4. Administer 1 L every 4 hours, depending on the degree of dehydration and central venous pressure readings

When the patient becomes euvolemic, the physician may switch to half the isotonic sodium chloride solution, particularly if hypernatremia exists. Isotonic saline should be administered at a rate appropriate to maintain adequate blood pressure and pulse, urinary output, and mental status.

If a patient is severely dehydrated and significant fluid resuscitation is needed, switching to a balanced electrolyte solution (eg, Normosol-R, in which some of the chloride in isotonic saline is replaced with acetate) may help to avoid the development of a hyperchloremic acidosis.

* 1. **Electrolyte replacement.** Electrolytes are minerals in your blood that carry an electric charge, such as sodium, potassium and chloride. The absence of insulin can lower the level of several electrolytes in your blood. You'll receive electrolytes through a vein to help keep your heart, muscles and nerve cells functioning normally.

Monitor serum potassium levels hourly, and the infusion must be stopped if the potassium level is greater than 5 mEq/L. The monitoring of serum potassium must continue even after potassium infusion is stopped in the case of (expected) recurrence of hypokalemia.

In severe hypokalemia, not starting insulin therapy is advisable unless potassium replacement is under way; this is to avert potentially serious cardiac dysrhythmia that may result from hypokalemia.

Potassium replacement should be started with initial fluid replacement if potassium levels are normal or low.

* 1. **Insulin therapy.** Insulin reverses the processes that cause diabetic ketoacidosis. In addition to fluids and electrolytes, you'll receive insulin therapy — usually through a vein. When your blood sugar level falls to about 200 mg/dL (11.1 mmol/L) and your blood is no longer acidic, you may be able to stop intravenous insulin therapy and resume your normal subcutaneous insulin therapy.
	2. Management of treatment- related complications:

**-** Cerebral edema: Can occur as a complication of management of ketoacidosis.The administration of fluids is slowed.

diagnostic criteria for cerebral edema that include abnormal response to pain, decorticate and decerebrate posturing, cranial nerve palsies, abnormal central nervous system respiratory patterns, fluctuating level of consciousness, sustained heart rate deceleration, incontinence, and more nonspecific criteria such as vomiting, headache, lethargy, and elevated diastolic blood pressure.

 Cerebral edema begins with mental status changes. Deterioration of the level of consciousness in spite of improved metabolic state usually indicates the occurrence of cerebral edema.It primarily affects children.

The ideal treatment of cerebral edema in DKA is not established, but intravenous mannitol and hypertonic saline(3%) are used—as in some other forms of cerebral edema, in an attempt to reduce the swelling. Cerebral edema that occurs at initiation of therapy tends to worsen during the course of treatment.

 It is the leading cause of DKA mortality in children.

* 1. Allowing blood glucose to drop to hypoglycemic levels is a common mistake that usually results in a rebound ketosis derived by counter-regulatory hormones. Rebound ketosis necessitates a longer duration of treatment. The other hazard is that rapid correction of hyperglycemia and hyperosmolarity may shift water rapidly to the hyperosmolar intracellular space and may induce cerebral edema.

* 1. Cardiac dysrhythmia: Cardiac dysrhythmia may occur secondary to severe hypokalemia and/or acidosis either initially or as a result of therapy in patients with DKA. Usually, correction of the cause is sufficient to treat cardiac dysrhythmia, but if it persists, consultation with a cardiologist is mandatory. Performing cardiac monitoring on patients with DKA during correction of electrolytes always is advisable.
	2. Myocardial injury: may occur in severe DKA, associated with minute elevations of myocardial biomarkers (troponin T and CK-MB) and initial ECG changes compatible with myocardial infarction (MI).
	3. Pulmonary edema: may occur for the same reasons as cerebral edema in patients with diabetic ketoacidosis. One has to be cautious of possible overcorrection of fluid loss, though it occurs only rarely.

Although initial aggressive fluid replacement is necessary in all patients, particular care must be taken in those with comorbidities such as renal failure or congestive heart failure. Diuretics and oxygen therapy often suffice for the management of pulmonary edema.

•Correction of Acid-Base Balance

Sodium bicarbonate only is infused if decompensated acidosis starts to threaten the patient's life, especially when associated with either sepsis or lactic acidosis. If sodium bicarbonate is indicated, 100-150 mL of 1.4% concentration is infused initially. This may be repeated every half hour if necessary. Rapid and early correction of acidosis with sodium bicarbonate may worsen hypokalemia and cause paradoxical cellular acidosis.

Bicarbonate typically is not replaced as acidosis will improve with the above treatments alone. Administration of bicarbonate has been correlated with cerebral edema in children.

•Treatment of Concurrent Infection

In the presence of infection, the administration of proper antibiotics is guided by the results of culture and sensitivity studies. Starting empiric antibiotics on suspicion of infection until culture results are available may be advisable.