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MATRIC NO: 17/MHS01/073

LEVEL: 300 Level

COURSE TITLE: Medical Biochemistry IV

COURSE CODE: BCH 313

ASSIGNMENT TITLE: DIABETES, OBESITY AND CANCER.

DATE: 7th May, 2020.

 GROUP 2 CATEGORY (MBBS)

**QUESTION 1: Define the following terms**.

* KETOGENESIS:

 The **biochemical definition** of Ketogenesis is the biochemical process through which organisms produce ketone bodies through the breakdown of fatty acids and ketogenic amino acids. Ketogenesis is a metabolic pathway that produces ketone bodies which provide an alternative form of energy for the body. Ketogenesis is also said to be the production of ketone bodies (mainly by the *mitochondria* of liver cells).

 The synthesis of ketone bodies occur in response to an unavailability of blood glucose (such as during fasting), then the synthesis of these ketone bodies (acetoacetate, acetone and beta-hydroxybutyric acid) is initiated to make available energy that is stored as **fatty acids**. Ketogenesis occurs in places with low glucose levels in the blood after the exhaustion of other cellular carbohydrate stores such as *glycogen;* it can also take place when there is insufficient insulin (e.g. in Type 1 Diabetes Mellitus also called the **Juvenile onset diabetes** or **Insulin-dependent diabetes**). This ketogenic process usually provide the body with energy under different circumstances like fasting, caloric restriction to some certain organs particularly the brain, heart and skeletal muscle

* KETONAEMIA:

 Ketonaemia is defined as the metabolic state which is characterized or marked by an abnormal increase of ketone bodies in the circulating blood. It is said to be the presence of abnormally high concentration of ketone bodies in the blood.

* KETONURIA:

 Ketonuria is referred to a condition that occurs when the ketone levels in urine is unusually high. It is the excretion of abnormally large amount of ketone bodies in the urine and it is a characteristic of diabetes mellitus, starvation and other medical conditions. It can also be called **Ketoaciduria** or **Acetonuria**. Ketonuria is most common in individuals who have the diabetes particularly, the Type 1 diabetes mellitus. It can also occur to women who are pregnant or breastfeeding. Ketonuria (i.e. high ketone level in urine) can be caused by ketogenic diet, low insulin levels, starvation, pregnancy, taking/drinking excess alcohol, use of medications such as corticosteroids and diuretics etc.

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**QUESTION 2: What are the consequences of Ketosis**.

 Ketosis is a metabolic state characterized by raised or 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 source for the brain in the forms of ketones. The consequences of Ketosis are:

1. Bad breath:

This is one of the common side effects of ketosis. It is often described as fruity and slightly sweet. Bad breath is caused by *acetone* (a ketone which is a byproduct of fat metabolism produced by the liver). In ketosis, blood acetone levels are elevated or increased and the body may get rid of some of it via the breath. And also the sweat and urine can also smell like acetone.

1. Ketoacidosis:

Here, there is an uncontrolled production of ketones that occurs in pathologic state and causes metabolic acidosis which is a medical emergency. For people with diabetes, ketosis can trigger the dangerous condition called **Diabetic Ketoacidosis**. This occurs when the body stores up too many ketone which are acids produced as a by-product of burning fat; the blood becomes too acidic and can damage the liver, kidney and brain and if left untreated, it can be fatal..

1. 'Low-carb flu' or 'Keto-flu':

This is a set of symptoms that might/can occur in the initial stages of ketosis. These may include: Headache, fatigue, poor sleep, hunger, nausea, decreased physical performance etc. Some individuals do not continue the use of the ketogenic diet.

1. Leg muscles cramping:

 In ketosis, some people may experience leg cramps. They are usually connected by dehydration and loss of minerals. This is because ketosis causes a reduction in water weight. Loss of water and minerals increases the risks of leg cramps.

1. Digestive problems:

This is true for ketogenic diet and constipation is a common side effect of ketosis and diarrhea may occur in some people.

1. Kidney stones, etc.

**Note that**: the body may start experiencing headache, fatigue, dizziness, insomnia, difficulty in exercise tolerance, constipation and nausea especially in the first days and weeks of starting ketogenic diet (*ketogenic diet* is a low- carbohydrate, moderate protein diet that can lead to ketosis).

**QUESTION 3: Write concisely on the management of Ketoacidosis**.

 Ketoacidosis is a metabolic state of uncontrolled production of ketones that results in metabolic acidosis. Ketoacidosis is a specific pathological condition that results in changes in blood pH and requires medical attention. The MOST COMMON CAUSE of Ketoacidosis is- ***DIABETIC KETOACIDOSIS***; while other causes are *Alcoholic ketoacidosis and Starvation ketoacidosis, Toxins* etc.

 The main aim in the management and treatment of ketoacidosis is replacing the lost fluids and electrolytes while suppressing the high blood sugar and ketone production with insulin. The major treatment of this condition is initial rehydration (using isotonic saline) with subsequent potassium replacement and low-dose insulin therapy.

* MANAGEMENT AND TREATMENT DEPENDS ON ITS UNDERLYING CAUSE.

There are several causes of Ketoacidosis which are: Diabetes, Alcohol, Starvation, Toxins and medications

1. **Diabetic ketoketoacidosis:**

The most common cause of ketoacidosis is a deficiency of insulin in type 1 diabetes or late-stage type 2 diabetes. This is called **diabetic ketoacidosis** and is characterized by hyperglycemia, dehydration and metabolic acidosis. Other electrolyte disturbances such as hyperkalemia and hyponatremia may also be present. A lack of insulin in the bloodstream allows unregulated fatty acid release from adipose tissue which increases fatty acid oxidation to acetyl CoA, some of which is diverted to ketogenesis. This raises ketone levels significantly above what is seen in normal physiology

It is ***resolved*** with insulin infusion, intravenous fluids, electrolyte replacement and supportive care. Diabetic ketoacidosis occurs most often in patients with Type 1 diabetes or late-stage type 2. The management or treatment of DKA- Diabetics Ketoacidosis are done through:

* Fluid replacement:

 The amount of fluid replaced is dependent on the estimated degree of dehydration. **If dehydration is so severe** as to cause shock (severely decreased blood pressure with insufficient blood supply to the body's organs) or a depressed level of consciousness; there is need for the *recommendation of rapid infusion of saline (1 liter for adults, 10 ml/kg in repeated doses for children)* to restore circulating volume.

 **If the dehydration is moderate**, slower rehydration based on calculated water and sodium shortage may be possible and *saline is the recommended fluid again*. **If the dehydration is mild** and very mild ketoacidosis with no associated vomiting may be treated or administered with *oral rehydration and subcutaneous insulin may be recommended* rather than intravenous insulin under observation for signs of deterioration. Normal saline (0.9% saline) has generally been the fluid of choice.

* Insulin therapy:

 It has emphasized by modern management of diabetic ketoacidosis, the use of lower doses of insulin during insulin therapy. It is shown to be the most efficacious treatment in both children and adults with diabetic ketoacidosis. The current recommendation is to **give low dose (short-acting regular) insulin** after the diagnosis of diabetic ketoacidosis has been confirmed by laboratory tests and fluid replacement has been initiated.

 The standard low-dose insulin therapy consists of an initial intravenous bolus of *0.15 unit of regular insulin per kg* followed by the continuous intravenous infusion of regular insulin prepared in normal saline or hypotonic saline solution at a rate of *0.1 unit/kg/hour*.

NOTE THAT:

* In clinical situations in which continuous intravenous insulin cannot be administered, the recommended initial insulin dose is *0.3 unit/kg*, with one half of the dose given as an intravenous bolus and the remainder given subcutaneously or intramuscularly. Subsequently, the regular insulin should be given in a dosage of *0.1 unit/kg/hour* until the blood glucose is approximately **250mg/dL**.
* It is prudent to withhold insulin therapy until the serum potassium concentration has been determined. In rare patients who presents with hypokalemia (low potassium level), insulin therapy may worsen the condition and also may precipitate life-threatening cardiac arrhythmias.
* Electrolytes replacements:

Electrolytes such as potassium, bicarbonate, phosphate.

* Potassium therapy:

 Although in diabetic ketoacidosis, typical potassium deficit is 500-700 mEq (500-700 mmol), but most patients are hyperkalemic at the time of diagnosis because of the effects of insulinopenia, hyperosmolality and acidemia. During rehydration and insulin therapies for diabetic ketoacidosis, the serum potassium concentration typically declines rapidly as potassium re-enters the intracellular compartment (i.e. Potassium levels can fluctuate severely during the diabetic ketoacidosis and this is because insulin decreases potassium levels in the blood by redistributing it into cells via Increased sodium-potassium pump activity).

 A procedure entails the *use of insulin and of intravenous fluids* until the serum potassium concentration is less than 5.5 mEq/L (5.5 mmol/L). At this time, potassium is added to the intravenous fliuds in the amount of 20-40 mEq/L. The exact amount of potassium administered *depends on the serum potassium concentration*. When the serum potassium level is less than 3.3 mEq/L (3.3 mmol/L), the administration of 40 mEq per L of potassium is appropriate. If the serum potassium is greater than 3.3 mEq/L but less than 5.5 mEq/L, 20 to 30 mEq/L of potassium can be administered. The goal is to maintain the serum potassium concentration in the range of 4 to 5 mEq/L (4 to 5 mmol/L).

* Bicarbonate therapy:

 In general, supplemental bicarbonate therapy is no longer recommended for patients with diabetics ketoacidosis because the plasma bicarbonate concentration increases with the insulin therapy. Insulin administration inhibits ongoing lipolysis and ketogenesis and also promotes the bicarbonate regeneration.

 The use of bicarbonate in a patient with a pH greater than 7.0 is not recommended. Furthermore, bicarbonate therapy carries some risks, including hypokalemia with overly rapid administration, paradoxic cerebrospinal fluid acidosis and hypoxia. The recommended bicarbonate administration when the pH is less than 7.0 *is for the purpose of treating the possible adverse hemodynamic effects of profound acidemia*. If bicarbonate is used, it should be given as a nearly isotonic solution, which can be approximated by the addition of one of sodium bicarbonate in 300 mL of sterile water. The bicarbonate solution is administered over a one-hour period.

* Phosphate therapy:

 Osmotic diuresis leads to increased urinary phosphate losses. During insulin therapy, phosphate reenters the intracellular compartment, leading to mild to moderate reductions in the serum phosphate concentration. Phosphate therapy is to administer two thirds of the potassium as potassium chloride and one third as potassium phosphate. The use of phosphate for this purpose reduces the chloride load that might contribute to hyperchloremic acidosis and decreases the likelihood that the patient will develop severe hypophosphatemia during insulin therapy.

 Although studies have indicated **no clinical benefit for phosphate replacement in the treatment of diabetic ketoacidosis**and excessive phosphate replacement may contribute to hypocalcemia and soft tissue metastatic calcification.

1. **Alcoholic ketoacidosis:**

Alcoholic Ketoacidosis is caused by complex physiology that is usually the result of prolonged and heavy alcohol intake in the setting of poor nutrition. Chronic alcohol use can cause depleted hepatic glycogen stores and ethanol metabolism further impairs gluconeogenesis. This can reduce glucose availability and lead to hypoglycemia and increased reliance on fatty acid and ketone metabolism. An additional stressor such as vomiting or dehydration can cause an increase in counterregulatory hormones such as glucagon, cortisol and growth hormone which may further increase free fatty acid release and ketone production. Ethanol metabolism can also increase blood lactic acid levels which may also contribute to a metabolic acidosis.

It is ***treated*** with intravenous dextrose and supportive care and usually does not require insulin.

1. **Starvation ketoacidosis:**

Starvation is a rare cause of ketoacidosis, usually instead causing physiologic ketosis without ketoacidosis. Ketoacidosis from starvation, most commonly occurs in the setting of an additional metabolic stressor such as pregnancy, lactation, or acute illness.

It can be ***resolved*** with intravenous dextrose with attention to electrolyte changes that can occur with re-feeding syndrome.