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**COURSE: BIOCHEMISTRY IV**

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**QUESTIONS**

1. DEFINE THE FOLLOWING TERMS

A. KETOGENESIS

B. KETONAEMIA

C. KETONURIA

D. KETOGENESIS

2. WHAT ARE THE CONSEQUENCES OF KETOSIS

3. WRITE CONCISELY 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

**B.** The term **ketonemia** indicates the level ketone bodies in blood, molecules produced when the source of energy are fats. Typically this parameter remains at low values. But if the energy supply is especially low in carbohydrates, particularly by too much alcohol intake or there is a presence of diabetes there can be increase in ketone levels which becomes dangerous to ones health.

**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.

**D.** **Ketogenesis** is the biochemical process through which organisms produce ketone bodies through breakdown of fatty acids and ketogenic amino acids. This process supplies energy under circumstances such as fasting or caloric restriction to certain organs, particularly the brain, heart and skeletal muscle.

**2.** **WHAT ARE THE CONSEQUENCES OF KETOSIS**

Like any significant change to your diet, when starting a ketogenic diet, it is normal to experience one or more side effects as the body adapts to a new way of eating.

When going on a ketogenic diet, the body has to switch its fuel source from the glucose in carbohydrate to using its own fat stores, and this can lead to experiencing some of the following side effects:

**Loss of salts**

**Keto-flu**

**Changes in bowel habits**

**Leg cramps**

**Bad breath**

**Loss of energy**

Usually these side effects are temporary and can usually be remedied.

**LOSS OF SALTS**

There are some changes with fluid balance that can typically occur within the first couple of weeks of a ketogenic diet. This happens as the body uses up its stored sugar (glycogen) which releases water into the blood that gets passed out of the body through urine. As fluid is passed out of the body, salts in the body can get depleted too. As a result, you may experience a loss of fluid and salts as you move into and maintain ketosis. Make sure you keep yourself hydrated through the day. Water is the best drink for hydration but tea and coffee are also fine as long as they’re not very milky.

Ensure you have enough salt as this can prevent side effects such as headaches and wooziness. You are free to add sea salt to your food and can take salts by drinking vegetable or bone broths and bouillons too. Potassium and magnesium are other important salts. As long as you are eating healthy, natural foods (such as nuts, meat, fish, dairy and a range of vegetables), you shouldn’t have a problem getting enough magnesium and potassium.

**KETO-FLU**

The first few weeks of transitioning to a ketogenic diet can be challenging for some people. Whereas others adapt to it more easily. Your body may be used to relying mainly on glucose for energy and so it will need to switch to using ketones for fuel. This adaptation process is known as keto-adaption.

Keto-adaption may result in some initial ‘brain fog’, but this will disappear once the body has fully adapted and some people feel sharper at this point. It is estimated that keto-adaption takes around four weeks on average but the side effects themselves often disappear sooner. During that time, and especially at the end of the first week, it is likely that you may feel some symptoms that are similar to the flu, such as:

Brain fog / slow thinking

Dizziness

Fatigue

Racing heart rate when lying down

Insomnia

Cravings

**CHANGES IN BOWEL HABITS**

Changing to a ketogenic diet may bring about changes in bowel habits such as constipation.

This is often the case with any major change in diet as the body’s own gut bacteria will need to adapt to handle different foods in different amounts. Bowel habits should usually improve within a couple of weeks. If they don’t, it could be that you’re not getting enough fibre.

Drink plenty of water and consider increasing your consumption of non-starchy, fibrous vegetable, legumes, nuts and seeds, as these are all good low-carbohydrate sources of fibre.

**LEG CRAMPS**

The development of muscle cramps is a possible side effect of a ketogenic diet. These cramps are typically benign in nature, but they can be bothersome. One of the causes of leg cramps on a ketogenic diet is a condition called hyponatremia, which occurs when the level of sodium (salt) in the blood is too low. This can be alleviated by the recommendation we gave above about keeping hydrated and having enough salt.

**BAD BREATH**

Bad breath, sometimes referred to as keto-breath, can sometimes occur as you enter the fat-burning state of ketosis. Ketones can be released in the breath, as well as in the urine and sweat. Acetone is a form of ketone that when released on the breath may lead to a metallic taste in the mouth or a less-than-pleasant smelling breath.

This is usually temporary and will likely disappear after a few weeks without having to come out of ketosis by reintroducing carbs. If bad breath is a problem, minty sugar-free gum or breath freshener can help mask the smell. Another solution is to consider extra rigorous oral hygiene by brushing teeth and using mouthwash more frequently through the day.

**LACK OF ENERGY**

One of the biggest misconceptions about ketogenic diets is that a lack of glucose depletes the body of energy. Maintaining steady energy levels is actually more challenging on a standard diet as it varies according to fluctuations in blood sugar, which is dependent upon the insulin response to carbohydrate intake. Eating a lower amount of carbohydrates on a ketogenic diet does not prevents the roller-coaster of sugar levels.

Once in ketosis, the body can draw energy from its own fat stores and the liver is able to create as much glucose as the body needs -and not too much. As a result, by cutting out carbs, the body finds it easier to regulate sugar levels and energy.

Whilst you may notice a dip in energy initially during the adaptation phase, this should pass within a few weeks.

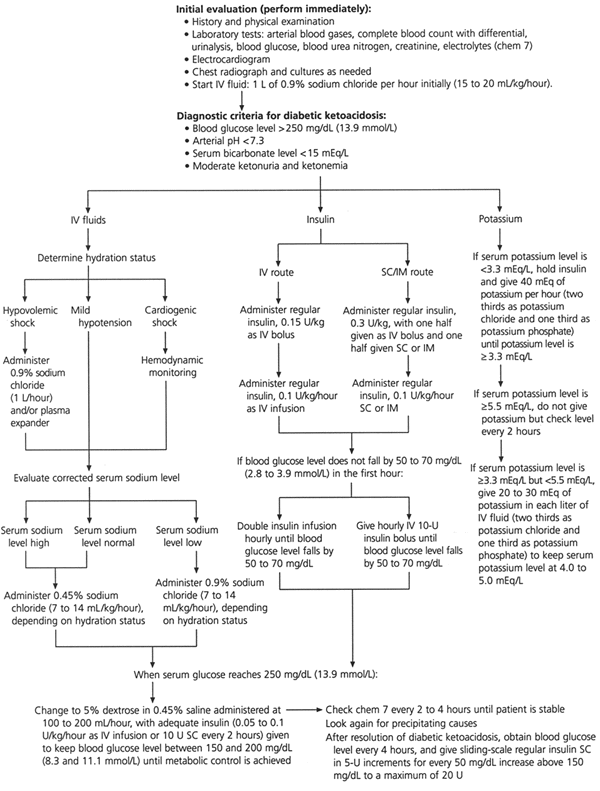
**3. WRITE CONCISELY ON THE MANAGEMENT OF KETOACIDOSIS**

Diabetic ketoacidosis is an emergency medical condition that can be life-threatening if not treated properly. The incidence of this condition may be increasing, and a 1 to 2 percent mortality rate has stubbornly persisted since the 1970s. Diabetic ketoacidosis occurs most often in patients with type 1 diabetes (formerly called insulin-dependent diabetes mellitus); however, its occurrence in patients with type 2 diabetes (formerly called non–insulin-dependent diabetes mellitus), particularly obese black patients, is not as rare as was once thought. The management of patients with diabetic ketoacidosis includes obtaining a thorough but rapid history and performing a physical examination in an attempt to identify possible precipitating factors. The major treatment of this condition is initial rehydration (using isotonic saline) with subsequent potassium replacement and low-dose insulin therapy. The use of bicarbonate is not recommended in most patients. Cerebral edema, one of the most dire complications of diabetic ketoacidosis, occurs more commonly in children and adolescents than in adults. Continuous follow-up of patients using treatment algorithms and flow sheets can help to minimize adverse outcomes. Preventive measures include patient education and instructions for the patient to contact the physician early during an illness.

Diabetic ketoacidosis is a triad of hyperglycemia, ketonemia and acidemia, each of which may be caused by other conditions. Although diabetic ketoacidosis most often occurs in patients with type 1 diabetes (formerly called insulin-dependent diabetes mellitus), more recent studies suggest that it can sometimes be the presenting condition in obese black patients with newly diagnosed type 2 diabetes (formerly called non–insulin-dependent diabetes mellitus).

Major components of the pathogenesis of diabetic ketoacidosis are reductions in effective concentrations of circulating insulin and concomitant elevations of counterregulatory hormones (catecholamines, glucagon, growth hormone and cortisol).6 These hormonal alterations bring about three major metabolic events: (1) hyperglycemia resulting from accelerated gluconeogenesis and decreased glucose utilization, (2) increased proteolysis and decreased protein synthesis and (3) increased lipolysis and ketone production.7

Hyperglycemia initially causes the movement of water out of cells, with subsequent intracellular dehydration, extra-cellular fluid expansion and hyponatremia. It also leads to a diuresis in which water losses exceed sodium chloride losses. Urinary losses then lead to progressive dehydration and volume depletion, which causes diminished urine flow and greater retention of glucose in plasma. The net result of all these alterations is hyperglycemia with metabolic acidosis and an increased plasma anion gap.

**Management of Diabetic Ketoacidosis** 

**TREATMENT**

DKA is a complex life threatening problem and the management should not be left to inexperienced staff. There should be early consultation between A&E staff and specialist diabetes teams. Patients with DKA need four things;

Fluid

Insulin

Potassium

Education

Early venous access is essential. In shocked patients large bore cannulas should be sited and standard measures instituted (oxygen, cardiac monitor, regular measurement of pulse and blood pressure). Avoid central lines unless essential for monitoring in severely ill patients. Adjuncts to resuscitation should include a nasogastric tube in patients who are not alert (gastroparesis occurs and aspiration of gastric contents is a complication of DKA). A urinary catheter is needed if patients are haemodynamically unstable and need accurate measurement of urine output.

**Hydration**

A regimen suitable for patients who are not shocked or oliguric (<30 ml/h) is 500 ml/h of 0.9% saline for four hours followed by 250 ml/h for the next four hours. This is associated with as rapid a correction of acidosis and hyperglycaemia as a regimen using twice these rates.7 Unnecessarily large volumes of intravenous fluids should be avoided because of the high case fatality rate of cerebral oedema. Physiological (0.9%) saline is the fluid usually used in the initial management of DKA though no formal comparisons with 0.45% saline or Ringer’s solution have been reported. Volume status can be assessed on the basis of clinical assessment (such as heart rate and BP), from urine output (a high urine output may indicate only osmotic diuresis but a low urine output should trigger a thorough assessment of renal function and the state of hydration), from urea measurements, and (sometimes) from invasive monitoring.

In patients with significant comorbidity (especially cardiac disease) invasive haemodynamic monitoring may help to guide the rate of fluid replacement. This has not been subjected to prospective evaluation and the potential complications of attempted central cannulation in volume depleted patients should be borne in mind. This is not a group of patients in which to “practise” central cannulation.

Once [glucose] has fallen to around 14 mM (a value based on tradition more than anything else) 5% dextrose (with appropriate potassium) is given rather than saline. Administering hypertonic dextrose (1 litre 10% dextrose + 40 units insulin at 250 ml/h) rather than isotonic dextrose (1 litre 5% dextrose + 10 units insulin at 250 ml/h) may accelerate the clearance of ketone bodies but also causes a rise in [glucose] without an additional improvement in blood pH or bicarbonate.8

**Insulin**

**Type of insulin**

A soluble insulin is normally used with the aim of permitting more rapid titration of circulating insulin levels (though there are no trial data comparing soluble against other types of insulin). If an intravenous bolus is followed by an intravenous infusion steady state insulin levels are reached very quickly. The half life of circulating insulin is five minutes; use of an intravenous infusion has the advantage over intermittent boluses of permitting a more rapid reduction in insulin level.

**Dose of insulin**

We usually give a bolus of six units then an infusion of 6 units/h when starting treatment of an adult with DKA (0.1 units/kg for patients who weigh less than 60 kg). Higher doses are associated with an increased risk of hypoglycaemia. A target reduction in [glucose] of 5 mM/h has been suggested though this has not been subjected to evaluation.9 Rather than using a “sliding scale”, we suggest that an infusion rate is started and then reviewed by a doctor every one to two hours (they should be reviewing the patient at least this frequently anyway). This is analagous to reviewing hypotensive or shocked patients frequently rather than prewriting their fluids for several hours.

Failure to achieve a reduction with this regimen for insulin should prompt a check of intravenous access, all connections, and the infusion device. If no mechanical cause is found a failure to respond may represent untreated infection or inadequate volume replacement. An additional bolus of insulin (equivalent to the previous hourly rate) should be given and the infusion rate doubled.

Conventional insulin infusion rates are often insufficient to achieve normoglycaemia in patients on an adrenaline (epinephrine) infusion because of the antagonistic effects of adrenaline; the insulin infusion rate should be increased until [glucose] falls at the desired rate. There is no unsafe upper limit provided frequent clinical and biochemical reassessment is carried out.

**Duration of insulin infusion**

Ketone bodies are cleared more slowly than glucose. The insulin infusion should be continued until ketosis and acidosis have cleared. Discontinuing insulin on the basis of (near) normal glucose levels can result in recurrence of ketoacidosis. If, however, the insulin infusion is continued after [glucose] normalises there is a danger of hypoglycaemia unless hypertonic dextrose in infused. The first subcutaneous injection must be given before the insulin infusion is stopped; otherwise insulin levels may fall too low and ketoacidosis recur. In most hospitals staffing is better in office hours than out of hours. It may therefore be preferable to change from intravenous to subcutaneous insulin in the morning rather than in the evening.

**Potassium**

Significant hypokalaemia is the most common life threatening electrolyte derangement that occurs during the treatment of DKA. Intravenous potassium replacement will be required after insulin is given as potassium will move into cells. Potassium replacement should not be started before insulin treatment; extracellular levels may otherwise rise dangerously high. Potassium replacement should be given as soon as insulin and fluid are started and the [K] level is known to be below the upper limit of the reference range. Regimens for potassium supplementation have not been formally evaluated. One suitable regimen for potassium replacement has been proposed10:

**Education**

Many cases of DKA occur after incorrect reduction or omission of insulin treatment. It is vital that patients who develop DKA receive, before discharge from hospital, education about how to manage their insulin in the event of intercurrent illness. This information should have been provided previously to all patients treated with insulin.

**Bicarbonate**

Severe acidosis has adverse effects on many organs, especially the brain and the heart. It may, therefore, seem appealing to give bicarbonate as treatment for the metabolic acidosis that occurs in DKA. There is no evidence to support this. Studies (not RCTs) have failed to find evidence of faster biochemical recovery with bicarbonate treatment even in severely patients.11–14 One prospective study found no metabolic benefits from bicarbonate administration and that bicarbonate (1 litre 150 mM sodium bicarbonate over one hour) delayed the fall in total ketone bodies and lactate levels.15

Sodium bicarbonate is both hypertonic and hyperosmolar. This can depress cardiac activity and lead to fluid shifts increasing the intravascular volume (which can provoke pulmonary oedema). The increase in pH shifts the Hb-O2 dissociation curve to the left, potentially decreasing tissue oxygenation and increasing lactate production. Bicarbonate infusions can cause a rise in PaCO2; rapid diffusion across cell membranes can actually worsen intracellular acidosis, especially in situations when the patient is unable to compensate by increasing carbon dioxide excretion. During the recovery phase of DKA any lactate produced during tissue hypoxia is metabolised to bicarbonate leading to rebound alkalosis.

**Phosphate**

Phosphate levels are affected in DKA in much the same way as potassium (that is, extracellular shift but depleted total body levels). A small study found that the addition of phosphate to standard treatment did not reduce the time taken to reach recovery indices of bicarbonate, pH, or glucose.16 Differences in magnesium and 2,3DPG levels and in P50 (the PaO2 at which haemoglobin is 50% saturated) were not statistically significant. In another study phosphate supplementation (15 or 45 mmol) did not affect the rate of correction of [glucose], [bicarbonate] or pH.17