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Diagnostic and Management Approach of Diabetic ketoacidosis in Emergency Department, Review Article

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ABSTRACT

Diabetes is one of the most common chronic diseases in the world, thus its complications have been studied and acknowledged as a critical aspect of modern medicine. When we talk about the most serious, acute, and life-threatening emergencies in these patients, hyperglycemic comas are the most common. This entity includes both diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) in diabetic patients. Generally, patients will show features of insulinopenia, severe hyperglycemia, ketoacidosis, and hyperosmolality. Our objective was to look into the literature concerning diabetic ketoacidosis and particularly the diagnosis process and management. PubMed database was used for articles selection, papers were obtained and reviewed. Nowadays, diabetes is one of the most chronic diseases and thus its complications are seen more in the clinical setting. Diabetic ketoacidosis is one of the most dangerous side effects which is seen in the emergency department. The main challenges of this condition are in the vague symptoms and in some patients, it may be the first presentation of diabetes. Fortunately, diagnosing DKA has been easier due to easier access to lab tests and the guidelines of diagnosis. Moreover, management of these cases has been the same with vigorous fluid, insulin, and electrolyte replacement therapy as the cornerstone.

Keywords: *Diabetic ketoacidosis, Management, Diagnosis, DKA*

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INTRODUCTION

Diabetes is one of the most common chronic diseases in the world, thus its complications have been studied and acknowledged as a critical aspect of modern medicine. When we talk about the most serious, acute, and life-threatening emergencies in these patients, hyperglycemic comas are the most common. This entity includes both diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) in diabetic patients. Nevertheless, they are usually studied in a different shed of light, they both share the cause, which is poorly controlled diabetes leading to a hyperglycemic emergency (Misra & Oliver, 2015). Generally, DKA and HHS can happen in both types of diabetes 1 and 2, but the frequency of age population affected defer. DKA is a preventable condition and usually occurs in young adults with type 1 diabetes (T1D) (Ahmed *et al*., 2019). Alarmingly, DKA has increased by up to 30% in the last decade and has been a higher cause of admission than HHS (Centers for Disease Control and Prevention, 2013). Generally, patients will show features of insulinopenia, severe hyperglycemia, ketoacidosis, and hyperosmolality. Under all these circumstances, modern medicine has been focusing on early diagnosis and management in order to avoid severe life-threatening complications (e.g. coma) (Alali *et al*., 2019). This has been very important to improve patient outcomes and reduce overall mortality (Kitabchi *et al*., 2009; Fayfman *et al*., 2017). Herein we will review diabetic ketoacidosis with a focus on diagnosis, and provide some insight into the recommendations related to the management of these cases.

MATERIALS AND METHODS

PubMed database was used for articles selection, and the following keys were used in the mesh ((Diabetic ketoacidosis) OR (DKA)) AND (management)) OR (Diagnosis)). In regards to

the inclusion criteria, the articles were selected based on the inclusion of one of the following topics; diabetic ketoacidosis, diagnosis, management, and treatment. Exclusion criteria were all other articles that did not have one of these topics as their primary endpoint.

Review

Diabetic ketoacidosis is usually encountered first in the emergency department, even though it is a preventable condition. However, it must be noted that a lot of inpatients can develop DKA and this has been noted more widely in a concerning way. Nevertheless, it has been reported that up to 140,000 admissions per year in the US are because of this complication. Even though it is a known condition it is sadly usually mismanaged on the ER department level, which leads to higher overall morbidity and length of stay. This can be attributed to the fact that this condition is the first presentation of diabetes in 20% of adults with diabetes mellitus. Fortunately, with the recent advances in diagnosis and overall management and care, mortality rates majorly decreased (reported as low as 1% in some studies) (Karges *et al*., 2015; Maahs *et al*., 2015).

DKA usually has an underlying precipitating factor or even more than once in the same patient. These factors do range from psychological factors to pathological and even pharmacological ones. Infection is considered to be the most common underlying factor for ketoacidosis in most studies. Other factors include neurovascular accidents, myocardial infarction, and pancreatitis. Moreover, consuming alcohol has been associated as well. Psychological factors such as depression and eating disorders have been noted to cause more effect on young adults and lead to a recurrence of DKA in these patients due to poor adherence to therapy or as a result of a typical antipsychotic intake. Other medications reported to alter the carbohydrate metabolism, leading to DKA include beta-blockers, thiazide diuretics, glucocorticoids, and some chemotherapy agents (Randall *et al*., 2011; Goguen & Gilbert, 2013). In addition, noticeably, SGLT2-inhibitors have been reported with an increase of an atypical "euglycemic" DKA, which leads to further complications of ascertaining the diagnosis and delaying the treatment. Potential mechanisms for this phenomenon are the higher glucagon levels in these patients, and/or lowering the daily insulin needs which result in less suppression of ketogenesis and lipolysis which results in a decreased excretion of ketones by urine (Peters *et al*., 2015).

Clinical features

Patients with DKA are usually presented to the ER with a variety of clinical symptoms which usually confuses physicians. Nevertheless, the course of these symptoms is usually short and the classical hyperglycemia symptoms are reported upon further history taking, these include polydipsia, weight loss, and polyuria. The most common symptoms are gastrointestinal complaints, which are usually in a form of diffuse abdominal pain (around half the patients), nausea, and vomiting (in around two-thirds of patients). Other commonly reported symptoms to include, lethargy, stupor, and round quarter patients present with loss of consciousness. At the level of ER physical examination is very helpful. Many signs can be noticed, dehydration can be noted on different levels, with poor skin turgor, dry mucous membranes, hypotension, and/or tachycardia. Moreover, certain characteristics are seen with – classical- acetone (fruity) breath odor, and Kussmaul respiration (Fayfman *et al*., 2017; Evans, 2019).

Diagnosis

Globally, there are main differences between how physicians shall diagnose this disease, with the UK, and the USA having some major differences. The most striking one is while the UK criteria consider patients to have DKA or not, the American criteria have a severity criterion (mild, moderate, and severe). However, both share the main criteria of diagnosis and treatment. The main criteria for diagnosis of this disease are plasma glucose levels, ketones levels, and acidosis. Nevertheless, other criteria are implemented, such as anion gap, pH levels (usually arterial), hydroxybutyrate, and mental status (Kitabchi *et al*., 2009; Scott, 2015). In the UK, the diagnosis is made in the lights of physical finings with the following criteria; glucose concentration higher than 200 mg/dl (11 mmol/L), presence of ketones (either higher than 3 mmol/L or higher than +2 in urine ketone sticks), confirmation of acidosis (either by blood pH lower than 7.3 or by serum bicarbonate less than 15 mmol/L). Moreover, the usual pH levels measurement is done via veinous pH instead of arterial, this is attributed to recent studies determining that the difference between the both is very minor (Dhatariya *et al*., 2016; Fayfman *et al*., 2017). Moreover, testing of 3-beta-hydroxybutyrate is available at the bedside so the usage of urine ketones levels has dropped. People with DKA are usually dehydrated, and thus, urine output is low; it may be several hours before the urine is produced, further delaying the instigation of appropriate management. Any estimation of urine ketones collected in this way will be an average of the concentration within the urine held in the bladder since the last void. Finally, as the DKA resolves, β-hydroxybutyrate is converted to acetoacetate, which is then excreted into the urine, giving the (false) impression that the condition is taking longer to resolve than it is. For these reasons, urine ketone testing is not routinely recommended in the UK guideline. Even though it doesn't classify DKA based on severity, the lower glucose cut-off point insure that euglycemic DKA is more diagnosed than under the US guidelines. Not using anion gap for diagnosis in the UK is partly because chloride (required to count anion gap) is not routinely reported in the blood gas analysis, nor electrolyte concentrations. Moreover, usage of sodium chloride solution (0.9%) in treatment may cause hyperchloremic metabolic acidosis which may give the wrong impression of persistent ketones rather than the actual cause (Munro *et al*., 1973; Gokel *et al*., 2000; Herrington *et al*., 2012; Fayfman *et al*., 2017). In the US, however, the diagnosis is subdivided into grades; mild, moderate, and severe. Nevertheless, all criteria share glucose levels of higher than 250 mg/dL (or higher than 13.9 mmol/L), and the presence of positive ketone (either urine or serum). The decisive factor of the severity is by acidosis (pH, and serum bicarbonate) and anion gap. Mild DKA is defined by pH of 7.25 to 7.3, serum bicarbonate of 15 to 18, and an anion gap of more than 10. Moderate is when the arterial pH is between 7 and 7.24, serum bicarbonate of 10 to 14, and an anion gap of more than 12. Lastly, severe DKA is when pH is less than 7, bicarbonate levels of less than 10, and anion gap higher than 12 (Fayfman *et al*., 2017; Dhatariya & Vellanki, 2017). However, in both criteria, a prior history of diabetes regardless of glucose concentrations fulfills the criteria of glucose concentration. Earlier we

mentioned one of the reasons that the anion gap is not used in the UK, moreover, insulin administration may cause hyperchloremia which decreases the anion gap before increasing the bicarbonate. Thus, clinicians must be wary of the bicarbonate levels rather than only the anion gap (Munro *et al*., 1973; Herrington *et al*., 2012; Dhatariya & Vellanki, 2017).

Management

Treating DKA shall aim at saving the patient from any potential complications, especially life-threatening ones. Thus setting management goals is appropriate for these cases to help guide the overall treatment plan. Generally, these goals are oriented on the lab results are aim to reduce blood ketone concentration (by 0.5 mmol/L/hour), capillary blood glucose (by 3.0 mmol/L/hour). Moreover, clinicians shall aim to increase venous bicarbonate (by 3.0 mmol/L/hour) while maintaining potassium levels (between 4 and 5.5 mmol/L) (Joint British Diabetes Societies Inpatient Care Group The management of diabetic ketoacidosis in adults, 2013). The main treatment approach is by an appropriate fluid replacement and insulin administration. Insulin usually is given intravenously and at a formula of 0.1 units per kg per hour at a fixed rate. At the emergency level, estimation of the weight is acceptable and treatment must not be delayed. Fixed-rate intravenous insulin infusion (FRIII) is not used only for the reduction of glucose levels but it prevents further ketogenesis and corrects electrolyte imbalances. Fluids given are usually in the form of – intravenous- 10% dextrose, this will prevent going into hypoglycemia. Thus, allowing the FRIII continuation. Usually, dextrose is started when glucose is below 14.0 mmol/L. Moreover, 0.9% sodium chloride solution is given as well, to maintain and correct circulatory volume. As a result, physicians usually have to give these two solutions concurrently (Joint British Diabetes Societies Inpatient Care Group The management of diabetic ketoacidosis in adults, 2013; Evans *et al*., 2019). Clinicians shall focus on monitoring the biochemical measurements needed in these cases, including; ketones, glucose, serum potassium, and pH (venous or arterial). In patients which do not reach the aforementioned targets, clinicians shall increase the FRIII because it is vital to clear ketones and lower the glucose levels. However, physicians shall first check the patency, placement of the cannula, and the correct rate of infusion for fluids. Moreover, an overview of any secondary and concomitant cause shall be ruled out, additionally, insulin resistance possibility shall be considered. These may warrant a change in the rate of insulin and/or intravenous fluids (Hisa *et al*., 2012; Fayfman *et al*., 2017; Evans, 2019).

The patient is considered to have a resolved DKA is when the abnormal biochemical measurement of pH is above 7.3, bicarbonate is higher than 15 mmol/L, and blood ketone is less than 0.6 mmol/L. Specialist review of the cases shall be obtained, either to review their regular basal diabetic therapy or start a new one in new cases of T1DM. Usually, the patient's basal analog insulin is started in the hospital before discharge when intravenous treatment is discontinued to assure that no rebound hyperglycemia occurs. Generally, this is started once the DKA is resolved and oral intake is possible. And the subcutaneous insulin must be taken after a meal and for at least half an hour up to one hour before discontinuing the intravenous insulin. However in most cases, FRIII is still continued and if the basal insulin is stopped by any means, an alternative form of insulin is given (e.g. stat dose of insulatard - 1/2 the usual daily basal dose) (Umpierrez *et al*., 2004; National Institute for Health and Care Excellence, 2016).

Ironically, hypoglycemia is the most common side effect of treatment (reported in up to a quarter of cases). This is due to failure to monitor properly (every 1 to 2 hours), thus not reducing the insulin infusion rate and/or not using dextrose when glucose is less than 200 mg/dL. Notably, these patients do not report the characteristics features of hypoglycemia such as sweating, fatigue, nervousness, hunger, and tachycardia. The second most common complication of therapy is hypokalemia. This is due to increased cellular uptake in peripheral tissues due to the insulin effect. Thus, monitoring potassium and starting replacement therapy when it is less than 5.2 mEq/l is warranted. If the patient admitted has serum potassium levels equal to or less than 3.3 mEq/L insulin shall not be started and held with replacement therapy started immediately. In some cases, patients will show signs of altered mental status/ consciousness, and/or abnormal neurological signs hours post-treatment. These symptoms may be a sign of cerebral edema which is commonly seen in children and unfortunately, the morbidity can reach up to 40%. Thus, this shall be treated immediately with mannitol (0.5 to 1 g/kg IV over 20 min) and to be repeated if there is no response in half an hour, if still no response hypertonic saline -3%- may be used (5 to 10 mL/kg over 30 min). Moreover, and in all cases of high fluid therapy, rhabdomyolysis shall be watched for, this can be done by monitoring creatine kinase levels (every 2 to 3 hours) to early detect any changes and act accordingly (Abramson & Arky, 1966; Glaser *et al*., 2001; Umpierrez & Korytkowski, 2016; Fayfman *et al*., 2017; Evans, 2019).

CONCLUSION

Nowadays, diabetes is one of the most chronic diseases and thus its complications are seen more in the clinical setting. Diabetic ketoacidosis is one of the most dangerous side effects which is seen in the emergency department. The main challenges of this condition are in the vague symptoms in some patients, it may be the first presentation of diabetes. Fortunately, diagnosing DKA has been easier due to easier access to lab tests and the guidelines of diagnosis. Even though these can be different from one country to another (e.g. UK and the US) there are a lot of points where they do agree on. Moreover, management of these cases has been the same with vigorous fluid, insulin, and electrolyte replacement therapy as the cornerstone. Also, physicians shall keep in mind that they must track and question any possible causes or conditions underlying and/or precipitating DKA. Even though this disease has been through many breakthroughs and research, further research to help the guidelines be more universal, whether diverse severity of patients require different management, and if the outcomes defer as a result is paramount.

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