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Diabetic ketoacidosis: diagnosis and management

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Summary

The objective of this manuscript is to review the clinical manifestations, diagnosis and management of diabetic ketoacidosis, one of the most common acute complications of diabetes mellitus. We performed a medline search of the English-language literature using a combination of words (diabetic ketoacidosis, hyperglycemic crises) to identify original studies, consensus statements and reviews on diabetic ketoacidosis published in the past 15 years. Emphasis was placed on clinical manifestations of diabetic ketoacidosis, its diagnosis and treatment.Diabetic ketoacidosis (DKA) is an acute complication of diabetes mellitus that can be life-threatening if not treated properly. Once thought to occur only in patients with type 1 diabetes, diabetic ketoacidosis has also been observed in patients with type 2 diabetes under certain conditions. The basic underlying mechanism for diabetic ketoacidosis is insulin deficiency coupled with elevated levels of counter-regulatory hormones, such as glucagon, cortisol, catecholamines, and growth hormone. Diabetic ketoacidosis can be the initial presentation of diabetes mellitus or precipitated in known patients with diabetes mellitus by many factors, most commonly infection. The management of diabetic ketoacidosis involves careful clinical evaluation, correction of metabolic abnormalities, identification and treatment of precipitating and co-morbid conditions, appropriate long-term treatment of diabetes, and plans to prevent recurrence. Many cases of DKA can be prevented by better access to medical care, proper education, and effective communication with a health care provider during intercurrent illness. Provision of guidelines will also reduce mortality. Resources need to be redirected towards prevention by funding better access to care and educational programs.

Keywords: *Diabetes mellitus; ketoacidosis; insulin; fluid management*

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Résumé 2929

L'objectif de ce manuscrit est de revoir les manifestations cliniques, les diagnostiques et la gestion du diabète kétoacide, l une des complications aigues les plus commune du diabète mellitus. Nous avons exécuté une recherche médline sur la littérature de la langue anglaise utilisant une combinaison des mots (diabète kétoacide, crises hyperglycemique) pour identifier les études originales, les déclarations de consensus, et les revus sur le diabète kétoacide publiés au cours des 15 dernières années. L'accent était placé sur les manifestations cliniques du diabète kétoacide, son diagnostique et son traitement. Le diabète kétoacide (DKA) est une complication aigue du diabète mellitus qui peut être une menace a la vie si mal traité, une fois que la préoccupation n'est dirigée que sur les patients avec le diabète de type 1, le diabète kétoacide a aussi été observé chez les patients de type 2 sous certaines conditions. Le mécanisme de base associé pour le diabète kétoacide est l'insuffisance de l'insuline associé a l'élévation du niveau du régulateur des hormones tel que le glucagon, le cortisol, le catécholamine, et la croissance des hormones. Le diabète kétoacide peut être la phase initiale du diabète mellitus ou précipitée chez les patients connus avec le diabète mellitus par plusieurs facteurs, l'infection la plus commune. La gestion du diabète kétoacide nécessite une évaluation clinique soigneux,la correction des anormalités métaboliques des précipités et les conditions co-morbides,le traitement approprié à long terme du diabète, et les plans de prévention de la réapparition . Plusieurs cas de DKA peuvent être prévenu par un accès meilleurs aux soins médicaux. Une bonne éducation et une communication effective avec des soins de santé appliqués durant la maladie. Les dispositions et les soins vont aussi réduire la mortalité. Les ressources doivent être redirigées vers la prévention par les fonds pour un accès meilleur aux soins et aux programmes éducationnel.

Introduction

Diabetic ketoacidosis is a life threatening medical emergency requiring prompt medical attention. It carries with it high mortality if not properly managed. We reviewed existing literature with emphasis on the clinical manifestations, diagnosis and management of diabetic ketoacidosis, one of the most common acute complication of diabetes mellitus. We performed a

Medline search of the English-language literature using a combination of words (diabetic ketoacidosis, hyperglycemic crises) to identify original studies, consensus statements and reviews on diabetic ketoacidosis published in the past 15 years. Emphasis was placed on clinical manifestations of diabetic ketoacidosis, its diagnosis and treatment.

Definition

Diabetic Ketoacidosis (DKA) is a clinical state characterized by the biochemical triad of hyperglycemia (plasma glucose >250mg/dL), ketonaemia and acidaemia (pH<7.0) [1].

Epidemiology

In the United States (US), DKA occurs at the annual rate of 5-8 episodes per 1000 patients with diabetes mellitus (DM) [2,3]. In epidemiological studies done 15 years ago in the US, it was estimated that hospitalizations for DKA during the past two decades are increasing [2,3]. The mortality rate of DKA prior to insulin treatment was 100%. With insulin treatment it is now about 2% in good centres [1,2,3]. This rises with age and the presence of concomitant infections. Episodes of DKA are more common in females than males [4]. In sub-Saharan African the mortality is very high both in treated patients with diabetes mellitus and those presenting to the hospital with diabetes mellitus for the first time [5]. In a retrospective study of 114 persons with diabetes mellitus by Ndububa and Erhabor over a six-year period, they reported a mortality of 21.9% [6]. Of these, 56% were newly diagnosed with diabetes mellitus while 44% had been on treatment for diabetes mellitus. DKA was reported to be the cause of death in eight (32%) of persons studied. DKA was reported to be the commonest cause of death in the study by Ndububa and Erhabor [6] and also the study by Akanji [7].

Precipitating factors

Infection is the most common precipitating factor in the development of DKA [1]. Others include cerebrovascular accident, alcohol abuse, pancreatitis, myocardial infarction, trauma (including surgery), and drugs. New onset type 1 diabetes or discontinuation of or inadequate dose of insulin in established type 1 diabetes commonly leads to the development of DKA. Drugs that affect carbohydrate metabolism, such as corticosteroids, thiazides, and sympathomimetic agents (e.g., dobutamine and terbutaline), may precipitate the development of DKA. Psychological problems, such as fear of weight gain, fear of hypoglycemia leads to omission of insulin in younger patients and may precipitate DKA. In a minority of patients (about 5%) no precipitating factor can be identified [8]. Psychosocial problems were reported as precipitants of DKA in the studies done in Ibadan and Ile-Ife [6,7].

Pathogenesis

The basic underlying mechanism for the development of DKA is a reduction in the net effective action of circulating insulin coupled with a concomitant elevation of counter regulatory hormones such as glucagons, catecholamines, cortisol, and growth hormone. In patients with DKA, the deficiency of insulin can be absolute or it can be insufficient relative to an excess of counter regulatory hormones (cortisol, glucagon, growth hormone, catecholamine) which rise in response to stress like infection, trauma etc.

Carbohydrate metabolism

Three processes that lead to the development of hyperglycemia when insulin is deficient are increased gluconeogenesis, accelerated glycogenolysis and impaired glucose utilization by the peripheral tissues [9,10]. Increased production of glucose by the liver and kidney represents the major pathogenic disturbance responsible for hyperglycaemia in these patients, and gluconeogenesis plays a greater metabolic role than glycogenolysis [11,12]. Glucose disposal in peripheral tissues is decreased as a result of both insulin deficiency and insulin resistance due to raised levels of counter regulatory hormones and free fatty acids (FFAs) [11,12].

Lipid and ketone metabolism

The increased production of ketones in DKA is the result of both insulin deficiency and increased concentration of catecolamines. These lead to activation of hormone sensitive lipase in adipose tissue [13-15]. The increased activity of tissue lipase causes breakdown of triglyceride into glycerol and free fatty acids FFAs [13-15]. The FFAs are oxidized to produce acetyl coA. Acetyl coA is converted in the liver to acetoacetate which is freely converted to β-hydroxybutyrate by redox reaction.

Water and electrolytes

Hyperglycemia leads to osmotic diuresis and electrolyte loss. The development of dehydration and sodium depletion in DKA is the result of increased urinary output and electrolyte losses [16]. Ketoanion excretion, which obligates urinary cation excretion as Na^+, K^+ and NH^+_4 salts, also contributes to a solute diuresis. Acidosis, lack of insulin and protein breakdown prevents K^+ uptake and increased serum

K^+ and its resultant loss in urine. Hyperventilation, fever and increased sweating also contribute to further fluid losses and the fluid deficit is about 6 litres or more at presentation [16-19].

Clinical features

DKA evolution in type 1 or type 2 diabetes tends to be rapid, over a period of less than 24 hours, with polyuria, polydipsia and weight loss. Nausea and vomiting are often seen in DKA and occasionally it could present with abdominal pain which could mimic acute abdomen [1]. Severe dehydration, weakness, clouding of sensorium, and finally coma can occur in DKA [16]. Physical findings may include loss of skin turgor, kussmaul's respiration, tachycardia, hypotension, alteration in mental status, shock, and ultimately coma. Though infection is a common precipitating factor for DKA, patients can have normal body temperature in the presence of infection. Patients with DKA may be hypothermic (a bad prognostic sign if present) because of peripheral vasodilatation. Focal neurological signs and seizures may be the dominant feature in some patients [16]. Upper gastrointestinal bleeding due to erosive oesophagitis occurred in 9% of patients hospitalized with DKA in one series [20] and correlated with blood glucose levels, admission to intensive care unit, duration of DM, and the presence of DM complications. Such signified a high non-bleeding-related mortality. Bleeding is generally self limiting, but blood transfusion may be required [20].

Laboratory findings

The initial laboratory evaluation of patients with suspected DKA should include determination of plasma glucose, urea, creatinine, serum ketones, electrolytes (with calculated anion gap), osmolality, urinalysis, urine ketones by dipstick, full blood count and differential count and electrocardiogram. Screening for sepsis should be done if an infection is suspected. The screening includes bacterial culture of urine, blood and throat etc. Leucocytosis is common in majority of patients with hyperglycemic emergencies and it is proportional to blood ketone body concentration. Serum sodium concentration is usually decreased because of the osmotic influx of water from the intracellular to the extracellular space in the presence of hyperglycemia. Serum potassium concentration may be elevated because of an extracellular shift of potassium caused by insulin deficiency, hypertonicity and acidaemia. Potassium may be low-normal or low. Careful cardiac monitoring and more vigorous potassium replacement is required because treatment lowers potassium further and can provoke cardiac arrhythmia.

Three of the following components should be present to establish the diagnosis of DKA:

1. Elevated plasma glucose (>250mg/dL),
2. The presence of ketones (in serum or urine),
3. The presence of acidosis (serum bicarbonate <18 mmol/L and/or arterial pH <7.3) [1].

Effective osmolality should be calculated using the following formula: 2{Na^+ (mmol/L)} + glucose (mg/dl)/18. (Normal = 285±5mOsm/kg). Blood Urea Nitrogen is not included in the formula because it is freely permeable through the intracellular compartment [21]. The anion gap [Na^+ - (Cl^- + HCO_3^-)] is elevated. (Normal is 10±2mmol/L) [17]. Corrected serum sodium is calculated using Na^+ + {1.6 x [(glucose in mg/dL – 100)/100]} [17,18,19]. The extreme metabolic disturbance of DKA can lead to physical and laboratory findings that may be misleading. It is thus important to be aware of these pitfalls.

Differential diagnosis

Not all patients with ketoacidosis have DKA. Starvation ketosis and alcoholic ketoacidosis (AKA) are distinguished by clinical history and by plasma glucose concentration. The anion gap is elevated in AKA while it is normal in starvation ketosis. Other causes of high anion gap metabolic acidosis include lactic acidosis, ingestion of drugs such as salicylates, methanol, ethylene glycol, and paraldehyde and chronic renal failure (which is more typically hyperchloraemic acidosis rather than high-anion gap acidosis).

Treatment

Therapeutic goals

These consist of :-

1. Improving circulatory volume and tissue perfusion.
2. Decreasing serum glucose and plasma osmolality towards normal levels.
3. Clearing serum and urine of ketones at a steady rate.
4. Correcting electrolyte imbalances.
5. Identifying and treating precipitating events, and
6. Preventing the recurrence of DKA.

Monitoring

Serum glucose monitoring of values should be done every 1 – 2 hours initially, then 4 hourly. Serum

electrolytes, phosphates, and pH must be assessed every 2 – 6 hours depending on the clinical response of the patient. A flow chart for recording vital signs, volume and rate of fluid administration, insulin dosage and urine output should be instituted.

Fluid replacement

A deficit of 5-7mmol of sodium, 200-350mmol of potassium, 350-500mmol of phosphate and 200-350mmol of chloride is present in an average adult with DKA at presentation [17,18]. The initial fluid therapy is directed towards expansion of the intravascular and extravascular volume and restoration of renal perfusion. Assessment of severity of fluid loss is thus very important. An orthostatic increase in pulse rate without change in blood pressure suggests a 10% decrease in extracellular fluid (ECF) volume (i.e. approximately 2L). An orthostatic drop in blood pressure (>15/10mmHg) indicates a 15 – 20% decrease in ECF volume (i.e. approximately 3 – 4 L). Supine hypotension indicates a decrease of >20% in ECF volume (i.e. >4 L). The goals of the fluid therapy is to replete the extracellular fluid volume by administration of intravenous isotonic saline. Fluid therapy also reduces counter regulatory hormones, lowers blood glucose and improves insulin sensitivity. Plasma sodium >140mmol/L and osmolality >340mOsm/kg are associated with large volume deficit, and plasma osmolality can be correlated with mental status. Stupor and coma are unusual with a plasma osmolality of <340mOsm/kg [17] hence another cause for altered conscious level should be sought if osmolality is below this level. The initial fluid of choice is isotonic saline (0.9% NaCl). This is infused at a rate of 10-20ml/kg/hr in the first hour in DKA. This is followed by either 0.45% or 0.9% NaCl depending on the corrected serum sodium and the haemodynamic status of the patient. If the corrected sodium concentration is high (155mmol/L) after the initial 1-2L of 0.9% NaCl, then 0.45% saline should be considered with close monitoring of electrolytes [17, 22-24]. European guidelines [23] recommend that, if used at all, no more than 1L of 0.45% saline should be given over 8 hours. This is more circumspect than the American Diabetic Association position statement and technical review [1,25]. Fluid replacement should correct estimated deficit within 24-48 hours. Suggested fluid replacement in DKA in practical terms is as shown below. When blood glucose is <250mg/dl, intravenous 0.9% NaCl should be changed to 5% dextrose/saline at a rate of 150-250mL/hr. This maintains plasma glucose levels and clears ketonaemia [25]. It also allows continued administration of insulin until ketogenesis is controlled and patient is tolerating orally. Too rapid correction of hyperglycemia may cause cerebral oedema [26]. The type of fluid and rate of administration may need to be adjusted in patients with congestive cardiac failure, renal failure; elderly and children. Osmotic diuresis reduces once glucose levels and ketone start dropping. This will lead to reduced urinary volume which will eventually lead to reduction in rate of fluid administration.

Table 1: Suggested IV 0.9% saline replacement in DKA.

Time	Volume
1st half hour/ 1hour	1L
2nd hour	1L
3rd hour	500ml - 1L
4th hour	500ml - 1L
5th hour	500ml - 1L
Total 1st 5 hours	3.5 – 5L
6th – 12 hours	200 – 500ml/hr.

Insulin therapy

Prospective randomized studies using low dose intravenous/subcutaneous insulin, or low doses of intramuscular insulin after aggressive rehydration showed similar outcomes [27,28] Furthermore, significant reduction in hypokalemia and no hypoglycemia was demonstrated in the low dose insulin group [1,17,27]. Comparative studies on the route of delivery with low dose insulin group showed similar outcomes [27]. The group receiving intravenous insulin showed a greater decline in plasma glucose and ketone bodies in the first two hours. Intravenous insulin has a half life of 4-5 minutes, intramuscular insulin has a half life of 2 hours and subcutaneous insulin has a half life of 4 hours [27]. Intravenous insulin given intermittently every hour leads to a much higher peak insulin levels that wanes within 30 minutes, thus continuous infusion of low dose insulin has become the standard of treatment [25]. Insulin therapy in adult starts by administering an intravenous bolus of regular insulin 10 units intravenously (IV) stat or 0.15 unit/kg body weight stat for an average 70kg man. Insulin therapy can also be initiated with 20 units of regular insulin or 0.3 unit/kg body weight; half of which is given IV bolus and the remaining half is given intramuscularly (IM) bolus. This is followed by infusion of regular insulin at 0.1unit/kg body weight/hour IV. Plasma glucose should be monitored hourly (use of a portable glucose meter may be required). If plasma glucose level does not fall by 50-75mg/dL per hour from the initial value

in the first hour, hydration status must be evaluated. If hydration is satisfactory then the insulin infusion rate can be doubled every hour until glucose falls at steady rate of 50-75mg/dL per hour [1]. Insulin administration is reduced to an insulin infusion rate of 3-6 unit per hour (0.05-0.1unit/kg/hr) when blood glucose is <250mg/dL and/or progressive improvement in clinical status with fall in blood glucose >75mg/dL per hour. The intravenous fluid is changed to 5% dextrose/saline infusion when plasma glucose is < 250mg/dL. If the patient is still in coma, or unable to tolerate meals, insulin should be added to the 5% dextrose/saline infusion (usually 5-8 units/500mls) to run at the rate of 150-250mL/hr. Blood glucose should be maintained between 140-180mg/dl and insulin infusion should be maintained at a rate of 0.05-0.1 unit/kg/hour. Once the patient is able to eat, route of insulin administration should be subcutaneously (SC). However an overlap of 1-2 hours is desirable with IV soluble insulin infusion. Stopping the IV infusion for >30-60 minutes without the rapid acting insulin should be avoided because of the short half life of IV insulin which may predispose to re-development of ketoacidosis. Intermittent low dose IM insulin can also be given every hour also as an acceptable treatment for DKA, especially in centres where IV treatment is difficult [25]. A study comparing IM and IV insulin administration in Lagos University Teaching Hospital (LUTH) showed that the mean rate of fall of plasma glucose was higher and the time required to lower it to 250mg/dL was shorter with IV route [28]. The use of Lispro and Aspart (rapid acting insulin analogues) subcutaneously in a small number of patients with uncomplicated DKA was found to be safe and effective [29,30].

Post hyperglycemic care

Known persons with DM can be given insulin at the dose they were using before the onset of DKA. Newly diagnosed patients should have insulin at 0.6 unit/kg body weight/day divided into at least 3 doses of short acting insulin, subsequently converting them to biphasic insulin or oral agents.

Lack of blood glucose response to insulin therapy

Inadequate hydration has been shown to delay blood glucose response to insulin therapy. Others include renal impairment, error in insulin infusion mixture and inadequate insulin dose.

Potassium therapy

Correction of fluid deficit, acidosis and insulin therapy shifts potassium back into the cells and causes a decrease in serum concentration. Potassium supplementation is started if the initial potassium is <5.5 mmol/L and urine output is adequate [17,28]. When potassium is <2.5 mmol/L, the patient is at risk of cardiac arrhythmias and respiratory muscle weakness, insulin should thus be withheld [17]. Potassium chloride is preferred for replacement but phosphate can be used if there is phosphate depletion. It is given in saline or dextrose infusion slowly. Below is the guideline for potassium replacement;

Table 2: Guideline for potassium replacement

Serum potassium (mmol/L)	Additional potassium (mmol/L) [17,23]
<3.5	40
3.5-4.5	20
4.5-5.5	10
>5.5	Stop K^+

Bicarbonate therapy

Replacement of bicarbonate is not routinely recommended. This is because insulin treatment often reverses the acid base imbalance [25]. Studies of bicarbonate therapy in individuals with pH >6.9 showed no therapeutic advantage [31,32]. Bicarbonate therapy still generates a lot of arguments against its use [33,34]. Hypokalaemia, hypocalcaemia, paradoxical cerebrospinal fluid acidosis [35,36], worsening intracellular acidosis [4,37,38] and hypoxia [35] are some of the disadvantages of bicarbonate therapy. However if PH is <7.0, 100mmol of sodium bicarbonate should be given with 20mmol potassium chloride over 30 minutes [17,23]. pH is checked 30 minutes later. A repeat dose of sodium bicarbonate should be given if there is no improvement.

Phosphate therapy

Despite whole body phosphate deficit in DKA, serum phosphate is often normal or increased at presentation. Prospective randomized studies have failed to show any beneficial effect of phosphate replacement on clinical outcome in DKA [26]. Replacement should be given only in severe hypophosphataemia (1.5mg/dL). Oral replacement is preferred to intravenous route [25].

Complications of treatment

The most common complications of DKA include hypoglycaemia due to overzealous treatment with insulin, hypokalaemia due to insulin administration and treatment of acidosis with bicarbonate, and

hyperglycaemia secondary to interruption/ discontinuation of intravenous insulin therapy after recovery without subsequent coverage with subcutaneous insulin. Other complications include hyperchloraemia, pulmonary oedema, cerebral oedema and deep venous thrombosis (DVT) [1,25].

Cerebral oedema is a rare complication in adult [1]. It is seen in 0.7-1.0% of children with DKA. Characteristic feature includes deterioration in the level of consciousness, lethargy, decrease in arousal and headache. Rapid neurological deterioration may occur with seizures, papillary changes, bradycardia and respiratory arrest. Mechanism of development of cerebral oedema is not known [1]. It has however been postulated that rapid movement of water into the central nervous system when plasma osmolality decline too rapidly may be responsible [1]. There is lack of information on the morbidity associated with cerebral oedema in adult. Gradual replacement of sodium and water deficit is advised [1].

Prognosis

Outcome is good as long as therapeutic guidelines are followed. Mortality rate of <5% in DKA is reported in the US [25]. Mortality increases with age and concomitant illnesses. The study done at Ilesa, southwest Nigeria, reported a mortality of 32% in persons with diabetes mellitus with DKA as the course of death in them [6]

Prevention

Many cases of DKA can be prevented by better access to medical care, proper education, and effective communication with a health care provider during intercurrent illness. Social support should also be available to reduce insulin cost. Provision of guidelines will also reduce mortality.

Conclusion

Management of DKA can be very challenging in a resource poor country like Nigeria and other parts of sub-Saharan Africa. Repeated admission for DKA drains the patient financially. Resources need to be redirected towards prevention by funding better access to care and educational programs. The use of standardized written guidelines for therapy will go a long way in reducing mortality.

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