An Overview of Diabetic Ketoacidosis

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Abstract

Diabetic ketoacidosis (DKA) is an acute diabetic complication that is due to insulin deficiency with elevated blood levels of counter-regulatory hormones which inhibit the utilization of glucose and promote fatty acid oxidation with the production of ketone bodies and metabolic acidosis. The incidence of DKA decreases with increasing age hence younger children are mostly at risk. The condition is precipitated by several situations which include skipped insulin doses, newly diagnosed type 1 diabetes, infections, inter-current illness among others. Patients present with nausea, vomiting, polyuria, polydipsia and weight loss. The most consistent clinical finding is dehydration which is reflected by hypotension, renal hypo perfusion, electrolyte imbalance and altered sensorium. Symptoms associated with the precipitating factors could also be identified. The patient evaluation includes the serial measurement of blood glucose, electrolyte, ketones, blood gases and ph. These investigations are done in regular intervals as they determine treatment outcome. The patient monitoring is an inseparable component of the management process. Treatment of DKA basically revolves around fluid and insulin therapy and electrolyte replacement. The fluid therapy is instituted to correct the dehydration and electrolyte imbalance while the insulin reduces the blood glucose and also corrects the dehydration. Insulin is given initially as bolus then as a continuous infusion. Accurate treatment is required to prevent complications e.g. hypoglycemia, hypokalemia, shock, cerebral edema or mortality. While historical trends have affirmatively illustrated a decrease in mortality from DKA, contemporary data indicate that the mortality is still significant particularly in developing countries. Hence, more work is required to improve the situation.

Keywords: Diabetic Ketoacidosis; Insulin; T1DM

Introduction

DKA is the most important acute complication of diabetes mellitus. Although it most often affects patients with type I diabetes (T1DM), those with type II diabetes (T2DM) are not spared. It is a life-threatening emergency and inability to act promptly or accurately could result in avoidable mortality. DKA is a state of severe insulin deficiency which causes hyperglycemia and ketonemia with resultant metabolic acidosis. It is characterized biochemically as blood glucose levels of more than 250 mg/dl, serum pH of less than 7.3, serum ketones greater than 5 mEq/L and bicarbonate of less than 18 mEq/L. Patients with DKA cardinally present with dehydration requiring urgent and copious amount of fluids for rehydration. Also, the associated electrolyte imbalance necessitates a focused therapy involving regular monitoring of the parameters to avoid devastating complications. Considering the challenges of living with diabetes especially type I diabetes, patients should be meticulously educated about DKA to prevent its occurrence.

Epidemiology

The international diabetes federation estimated that 415 million adults were diabetic in 2015. Among children less than 15 years old the estimate for type 1 diabetes was 542,000 with a yearly incidence of 86,000 [1]. Northern European (Finland, Sweden and Norway) and Persian Gulf (Kuwait and Saudi Arabia) countries have a very high incidence of type I diabetes. The highest incidence is between the ages of 10 - 14 [1]. The incidence of DKA in Denmark is about 12.9 per 100,000 per year and higher in males than females. The mortality was 4% and higher in those above 70 years of age [2]. The observable trend is a higher incidence of DKA in developing countries which in most cases have a lower prevalence of T1DM [3]. These countries also account for a significantly higher mortality rates [4,5]. A possible explanation for this paradox might be the socioeconomic question. High income countries have better access to healthcare facilities and more often have adequate preventive and interventional measures which could reduce the incidence of serious emergencies like DKA. Healthcare workers in low income countries with low prevalence of T1DM or DM in children may be unfamiliar with the clinical situations of diabetes in children3 hence ignoring alarm signs with consequent delayed diagnosis or misdiagnosis.

Age: The prevalence of DKA varies inversely with increasing age. Although it can occur in any age it is more common in T1DM which is mostly diagnosed in children and adolescents. In the SEARCH for diabetes program the prevalence was highest (39%) in 0 - 4 age group and lowest in (23%) in 15 - 19 age group [6]. T2DM was more in 10 - 14 than 15 - 19 age group [6]. Figures from National Danish patient's registry has shown that 36% of patients were less than 30 years old, 27% were 30 - 50 years old, 23% were 51 - 70 old years and 14% above 71 years [2].

Newly diagnosed T1DM: The IDF Middle East and North Africa region has the highest rate of DKA globally among newly diagnosed diabetes (37.7 - 80%) [7]. A systematic review by Usher-smith., *et al.* (2012) reported that the United Arab Emirates (80%), Romania (67%), Taiwan (65%) and Saudi Arabia (59%) had the highest global rate while Sweden (14%), Canada (18.1%) and Finland (22%) had the lowest reported rates [3]. In the SEARCH for diabetes in the youth study the rate of DKA at diagnosis was determined at different periods. For T1DM, it was 30.2% in 2002 - 2003, 29.4% in 2004 - 2005 and 31.1% in 2008 - 2010 [6]. The authors concluded that the rate was stable for the period of study. They however noted a decline among T2DM patients with 11.7%, 6.3% and 5.7% at corresponding intervals respectively [6]. In contrast, a more recently published Colorado study which lasted from 1998 to 2012 produced conflicting results. It revealed an incidence of 29.9% in 1998, 35.0% in 2007 and 46.2% in 2012 [8]. Although, the publishers ascribed the rise in the incidence to the socioeconomic dynamics of the region where the research was conducted. Also, a Polish study of 650 T1DM patients followed over two years reported a DKA incidence of 5.2/100 per year with 58% of cases in newly diagnosed and 41.6% in established patients [9]. Epidemiological data are lacking in Africa but random studies have reported a frequency of 62.5% in Northwestern Nigeria [10], 35.8% from Ethiopia [5] and 69.8% from South Africa [11].

Inadequate compliance with insulin treatment: T1DM and some T2DM patients require daily insulin injections as the only effective therapy. Missing insulin doses could potentially tilt the delicate glycemic equilibrium towards DKA. The challenge of achieving this compliance among patients is well known. Children without optimal parental attention are vulnerable to missed doses. Patients from low social economic background could find insulin injections unaffordable due to financial impediments. Some studies have advanced this as the most common precipitant of DKA. A United States inner city minority group patients survey found that 68% of DKA cases resulted from non-compliance [12].

Infections: One of the most important consideration in established diabetic patients. Infections create a state of metabolic stress that promotes increased levels of counter-regulatory hormones which are involved in the pathophysiology of DKA. Mbuga., *et al.* (2005) identified infections in 23.4% of cases in a Kenya study [13]. Respiratory tract and urinary tract infections are the most common. Others are gastrointestinal tract infections and abscess.

Other causes: This includes myocardial infarction, surgery, trauma, pancreatitis, burns, pregnancy, emotional stress and idiopathic.

Drugs: Antipsychotics, cocaine, corticosteroids, glucagon, pentamidine, interferon, thiazide diuretics and SGLT-2 inhibitors.

Pathophysiology

The underlying hormonal alteration in DKA is characterized by a deficiency of insulin and excessive secretion of counter regulatory hormones e.g. cortisol, glucagon, growth hormone and catecholamines [14]. These counter regulatory hormones promote gluconeogenesis, glycogenolysis and inhibit glycolysis. Collectively, these alterations lead to hyperglycemia. They also promote lipolysis (at the expense of insulin induced lipogenesis) with elaboration of free fatty acids from the adipose tissue [14]. The insulin deficiency increases protein catabolism with ensuing increase in Body Urea Nitrogen (BUN) [16]. The consequences of hyperglycemia include hyperosmolality, renal glycosuria, osmotic diuresis, electrolyte imbalance and dehydration [16]. The hyperglycemia is worsened by concomitant insulin resistance [15], decreased renal function, increased serum free fatty acids and available amino acids for gluconeogenesis. The free fatty acids are oxidized in the liver to ketone bodies e.g. acetoacetate, beta-hydroxyl butyrate and acetone which leads to ketonemia [15]. When the production of ketone bodies exceeds the rate of removal by the buffer system ketonuria occurs. This process is associated with the generation of hydrogen ions and depletion of bicarbonate which leads to metabolic acidosis.

Electrolyte imbalance

Hypokalemia: The osmotic diuresis causes loss of potassium through the urine [17]. Acidosis promotes hydrogen ions movement into the cells and movement of potassium in the opposite direction causing intracellular potassium depletion. Potassium is also lost through the gastrointestinal tract [17] as well as through proteolysis. The administration of insulin further depletes the serum potassium by driving potassium into the cells [15-17]. Hypokalemia is associated with muscle weakness and cardiac arrhythmias [18,19] which may occur in DKA in the absence of adequate potassium replacement.

Hyponatremia: It is also caused by osmotic diuresis. The movement of water from the intracellular compartment in response to hyperglycemia causes dilutional hyponatremia [17]. The hyponatremia is largely responsible for the dehydration and hypotension observed in DKA [14].

Hypomagnesemia: Metabolic acidosis promotes magnesium loss [21]. Although hyperglycemia induced osmotic diuresis is the most important underlying mechanism [20]. Hypomagnesemia causes muscle weakness, tremors, seizures, tetany and cardiac arrhythmias. Hypokalemia and hypophosphatemia also enhance magnesium loss in DKA [17]. Insulin enhances movement of magnesium from intravascular compartment into the cells which could also account for hypomagnesemia.

Hypophosphatemia: It is associated with respiratory and skeletal muscle weakness as well as rhabdomyolysis. It is also noted to cause myocardial dysfunction and cardiac arrhythmias [21]. Central nervous system manifestations range from drowsiness to coma. Phosphate is a component of 2,3 DPG which is necessary for oxygen delivery to the tissues by shifting the dissociation curve to the right [21]. In DKA, phosphate is lost through osmotic diuresis. Insulin also increases transport of phosphate into the cells. Initially the phosphate levels maybe normal or high but drop when treatment is commenced [17].

Bicarbonate: The ketoacids that are produced from ketone bodies oxidation bind with bicarbonate buffer in an attempt to neutralize the acidosis. Progressive production of ketoacids decreases the serum bicarbonate and increases metabolic acidosis. The respiratory compensation is by increasing the depth and rate of respiration due to stimulation of peripheral chemoreceptors and brainstem respiratory centers in order to expel the accumulated carbon dioxide [14]. The renal hypoperfusion secondary to dehydration inhibits the ability of the kidneys to excrete ketones which worsens the acidosis.

Clinical Presentation

The common presenting symptoms are nausea and vomiting. These symptoms are present together in up to 70% of patients [22]. There is usually associated abdominal pain. Polyuria, polydipsia and weight loss are almost universally present as the earliest symptoms [23]. They can present with drowsiness, confusion or (rarely) coma. Kussmaul breathing [24] which is associated with increased respiratory rate, occurs due the stimulation of central and peripheral chemoreceptors that regulate respiration in an attempt to expel the accumulated carbon dioxide. The breath may have the typical fruity odour of acetone which is highly characteristic of DKA. Symptoms of underlying disease can be present e.g. fever, cough, dysuria, chest pain etc. Signs of dehydration e.g. dryness of the tongue and mucous membranes, hypotension, tachycardia, dry skin or increase turgor occur to varying degrees.

Clinical Presentation

	Mild	**Moderate**	**Severe**
Plasma glucose (mg/dl)	> 250 (13.9 mmol/L)	> 250 (13.9 mmol/L)	> 250 (13.9 mmol/L)
Arterial PH	7.25 - 7.30	7.00 - 7.24	< 7.00
Serum bicarbonate (mEq/L)	15 - 18	10 - 15	< 10
Anion gap	> 10	> 12	> 12
Mental status	Alert	Alert or drowsy	Stupor or coma

Table: *Classification of DKA.*

Investigations

Initial investigations: Blood glucose, electrolytes, serum bicarbonate and phosphate, arterial or venous blood gases, urinalysis for ketones, blood ketones, blood urea nitrogen and creatinine, complete blood count, osmolarity and anion gap calculation and electrocardiograph.

Investigations for underlying cause: HbA1c, blood and urine cultures, chest radiograph, liver function tests and cardiac enzymes.

Treatment

Fluid replacement; this is the most important initial treatment [25]. DKA causes extensive fluid deficit of about 6 - 9 litres in adults [16]. In children and adolescent, the deficit can be calculated using 100 mls/kg [25]. Adequate fluid therapy improves acidosis [26], renal blood flow [26], electrolytes distribution and blood glucose levels [27]. The fluid is replaced over 24 - 48 [25] hours with initially large volumes in a short period and later spreading out of the remaining over longer period. However, care must be taken to avoid over-hydration as it could potentially lead to complications. The best indicators of response are clinical parameters i.e. blood pressure, heart rate, capillary refill, skin and mucous membranes. The usual replacement fluid is normal saline or Ringers lactate. Several guidelines are available for fluid replacement. A volume of 15 - 20 ml/kg of normal saline or I litre can be given per hour in the initial phase and then gradually reduced to 4 - 14 ml/kg or 250 - 500 ml per hour as the patient's condition improves [28]. Another approach is to give 1 - 3 liters in the first hour, one litre in the second hour, 1 litre in the next two hours and 1L four hourly depending on the degree of dehydration. Once sodium concentration is corrected or higher than normal 0.45% normal saline infusion is started [28].

Insulin therapy: Insulin promotes glucose utilization by enhancing glycolysis, glycogen formation and inhibiting gluconeogenesis. The presence of adequate insulin and the utilization of glucose as fuel prevent beta oxidation of fatty acids which is responsible for the acidosis. Insulin is initially given as 0.1 unit/kg bolus and then as an infusion at a rate of 0.1 unit/kg per hour [25]. It is started about an hour after the commencement of fluid replacement. This gives time for correction of potassium as insulin drives potassium from the intravascular space into the cells. A blood glucose reduction rate of 50 - 70 mg/dl per hour is appropriate [15]. When the blood glucose has reduced to 250 mg/dL, the intravenous fluid is changed to dextrose containing fluids e.g. 5% dextrose with 0.45% normal saline [28].

Electrolyte replacement: The most important focus is potassium replacement. Apparently normal serum potassium levels may mask the intracellular potassium depletion in DKA. The deficit can be 3 - 5 mEq/L [27]. In a situation where serum potassium is less than 3.3 mEq/L insulin therapy should be delayed until potassium is corrected [28]. KCL is added to the intravenous fluid and titrated against the current potassium levels. The target range is 4 - 5 mmol/L. The Joint British Diabetes Societies Inpatient Care Group (JBDS IP) recommend that in the first 24 hours no potassium replacement is required if concentration is more than 5.5 mmol/L. At a value between 3.5 - 5.5 mmol/L, 40 mEq/L should be given and a higher dose may be required if less than 3.5 mmol/L after expert review [25]. Several recommendations by different organizations are also available and whichever is used depends on the experience of the local institution. Urine output should be monitored during replacement and serum levels should be checked hourly to determine when to discontinue.

Bicarbonate replacement is not routinely recommended during DKA treatment [29,30]. Fundamental measures like fluid and insulin therapy are usually enough to annul the acidosis. Multiple trials conducted to examine the potential benefit of bicarbonate administration in DKA have not revealed any significant benefit even if there is no controversy regarding the risk profile which includes cerebral oedema (mostly in children), worsening hypokalemia and intracellular acidosis [29,30]. However, it can be used in severe acidosis when the serum pH is less than 6.9 to prevent myocardial dysfunction [28].

Hypophosphatemia is associated with important clinical manifestations. Although there is no substantial evidence that routine phosphate replacement is beneficial but when serum phosphate is less than 1 mg/dL or when there is severe skeletal muscle weakness or respiratory muscle weakness then phosphate should be administered by adding potassium phosphate to intravenous fluids [16]. The approach to hypomagnesemia is the same. Replacement is considered only in very low serum levels or severely symptomatic patients [27,28].

Complications

These include cerebral oedema, hypoglycemia, hypokalemia, pulmonary oedema, acute renal failure, shock and vascular thrombosis. Most of these complications result from treatment. Hence, caution is required to avoid overzealous interventions. Cerebral oedema is the most feared complication and it occurs more in children. It is related to fluid and electrolyte therapy. It affects about 1% [31] of cases but the mortality could be as higher as a quarter of those affected [32].

Conclusion

Diabetic ketoacidosis continues to be an indispensible issue in the management of diabetes. Although the mortality has apparently reduced over time in developed countries, it still significantly accounts for mortality among diabetics in developing countries where healthcare resources are restricted. The role of health workers in ameliorating this situation cannot be overemphasized. Patients and caregivers should be adequately educated about the precipitating factors and how to prevent or manage such situations. Practical steps should be given on how to improve insulin compliance, manage situations of intercurrent illness and infections. DKA patients on admission should be closely monitored with both clinical and laboratory parameters as specified in the protocol. A single missed step may lead to serious complications. After discharge from the hospital, the patients should be followed up appropriately to avoid recurrence.

Bibliography

1. The International Diabetes Federation diabetes atlas, Seventh edition 2015. The International Diabetes Federation (2015).

2. Otto M Henriksen., *et al*. "Diabetic Ketoacidosis in Denmark Incidence and Mortality Estimated from Public Health Registries". *Diabetes Research and Clinical Practice* 76.1 (2007): 51-56.

3. Usher-Smith JA., *et al*. "Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: A systematic review". *Diabetologia* 55.11 (2012): 2878-2894.

4. Vardaman Poovazhagi. "Risk factors for mortality in children with diabetic ketoacidosis in developing countries". *World Journal of Diabetes* 5.6 (2015): 932-938.

5. Helen Siyoun Atkilt., *et al*. "Clinical characteristics of diabetic ketoacidosis in children with newly diagnosed type 1 diabetes in Addis Ababa Ethopia A cross sectional survey". *PloS One* 12.1 (2017): e0169666.

6. Dana Dabelea., *et al*. "Trends in the prevalence of diabetes ketoacidosis at diagnosis The SEARCH for Diabetes in the Youth Study". *Pediatrics* 133.4 (2014): e938-e945.

7. The International Diabetes Federation Diabetes Atlas sixth edition 2013. International Diabetes Federation (2013).

8. Arlerta Rewers., *et al*. "Incidence of Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes in Colorado Youth, 1998-2012". *Journal of American Medical Association* 313.15 (2015): 1570-1572.

9. Pietrzak I., *et al*. "Epidemiology and Clinical Course of Diabetic ketoacidosis in Children and Adolescent with Type 1 Diabetes". *Journal of Pediatric Endocrinology and Diabetes* 19.4 (2013): 137-142.

10. Omoshalewa Ugege., *et al*. "Childhood Diabetes in Sokoto, Northwestern Nigeria: A ten-year review". *Sahel Medical Journal* 16.3 (2013): 97-101.

11. Y Reddy., *et al*. "Characteristics of Children Presenting with Newly Diagnosed Type 1 Diabetes". *South African Journal of Child Health* 7.2 (2013).

12. Lori Randall., *et al*. "Recurrent Diabetic Ketoacidosis in Inner City Minority patients Behavioral, socioeconomic and psychosocial factors". *Diabetes Care* 34.9 (2011): 1891-1896.

13. Mbugua PK., *et al*. "Diabetic ketoacidosis: clinical presentation and precipitating factors at Kenyatta National Hospital, Nairobi". *East African medical Journal* 82.12 (2005): S191-S196.

14. Jean-Louis Chiasson., *et al*. "Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state". *Canadian Medical Association Journal* 168.7 (2003): 859-866.

15. Abbas E Kitabchi., *et al*. "Hyperglycemic Crises in Adult Patients with Diabetes". *Diabetes Care* 32.7 (2009): 1335-1343.

16. Aidar R Gosmanov., *et al*. "Management of adult diabetic ketoacidosis". *Diabetes Metabolic Syndrome and Obesity: Target and Therapy* 7 (2014): 255-264.

17. George Liamis., *et al*. "Diabetes mellitus and electrolyte disorders". *World Journal of Clinical Cases* 2.10 (2014): 488-496.

18. Podrid PJ. "Potassium and ventricular arrhythmias". *American Journal of Cardiology* 665.10 (1990): 33E-52E.

19. Helfant RH. "Hypokalemia and arrhythmias". *American Journal of Medicine* 80.4A (1986): 13-22.

20. Liamis G., *et al*. "Hypomagnesemia in a department of internal medicine". *Magnesium Research* 25.4 (2012): 149-158.

21. Nikifor K Konstantinov., *et al*. "Respiratory failure in diabetic ketoacidosis". *World Journal of Diabetes* 6.8 (2015): 1009-1023.

22. Mussa H Almalki., *et al*. "Clinical and Biochemical Characteristics of Diabetes Ketoacidosis in a Tertiary Hospital in Riyadh". *Clinical Medicine Insights Endocrinology and Diabetes* 9 (2016): 7-11.

23. Al-Magamsi MS and Habib HS. "Clinical presentation of childhood type 1 diabetes mellitus in the Al-Madina region of Saudi Arabia". *Pediatric Diabetes* 5.2 (2004): 95-98.

24. Pankaj Seth., *et al.* "Clinical Profile of Diabetic Ketoacidosis: A Prospective Study in a Tertiary Care Hospital". *Journal of Clinical and Diagnostic Research* 9.6 (2015): OC01-OC04.

25. Joint British Diabetes Societies Inpatient Care Group. The Management of Diabetic Ketoacidosis in Adults (2010).

26. Arlan L Rosenbloom. "The management of diabetic ketoacidosis in children". *Diabetes Therapy* 1.2 (2010): 103-120.

27. David E Trachtenbarg. "Diabetic ketoacidosis". *American Family Physician* 71.9 (2005): 1705-1714.

28. Dyanne P Westerberg. "Diabetic Ketoacidosis evaluation and treatment". *American Family Physician* 87.5 (2013): 337-346.

29. Viallon A., *et al.* "Does bicarbonate therapy improve the management of severe diabetic ketoacidosis?" *Critical Care Medicine* 27.12 (1999): 2690-2693.

30. Horng Ruey Chua., *et al.* "Bicarbonate in diabetic ketoacidosis - a systematic review". *Annals of Intensive Care* 1.1 (2011): 23.

31. Desmond Bohn and Denis Daneman. "Diabetic ketoacidosis and cerebral edema". *Current Opinion in Pediatrics* 14.3 (2002): 287-291.

32. J Edge., *et al.* "The risk and outcome of cerebral oedema developing during diabetic ketoacidosis". *Archive of Diseases in Childhood* 85.1 (2001): 16-22.