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DIABETIC KETOACIDOSIS IN PAEDIATRICS

Running title: DKA in Pediatrics

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Abstract:
Diabetic ketoacidosis (DKA) is one of the most important emergencies in paediatric population. Children with diabetic ketoacidosis do not present clinically with the typical manifestations of polydipsia, polyurea, polyphagia, confusion, abdominal pain, vomiting, and dyspnoea adults. Therefore, a high index of suspicion should be there for appropriate timely diagnosis and management of this condition among paediatric age group. The most common risk factors for paediatric ketoacidosis are infection, incompliance with insulin regimen, and psychological stress. Though the most important laboratory tests for diagnosis of DKA in children are the blood glucose level and arterial blood gases, many other lab tests can help confirmation of the diagnosis, predicting the outcome, and monitoring of treatment. The mainstay treatment lines are insulin therapy and correction of hypovolemia. Electrolyte imbalance and cardiac monitoring are fundamental during the management plan, This article will discuss the epidemiology, aetiology, risk factors, pathophysiology, clinical presentation, diagnosis, and management of diabetic ketoacidosis in paediatric population.

Keywords: *Diabetic Ketoacidosis, DKA, paediatrics.*

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INTRODUCTION

Diabetic ketoacidosis (DKA) is one of the most important emergencies in paediatric population. It is a metabolic derangement characterized by a triad of hyperglycaemia, acidosis, and ketone body formation [1]. In general, diabetic ketoacidosis results from insulin deficiency (either relatively or absolutely) in patients with type 1 or type 2 diabetes [2]. In paediatrics, type 1 diabetes (or insulin dependent diabetes mellitus (IDDM)) is more prevalent, and more commonly associated with diabetic ketoacidosis [3]. DKA can be the presenting manifestation of IDDM in paediatric age group or can occur during the course of the disease.

This article will review and discuss the epidemiology, aetiology, risk factors, pathophysiology, clinical presentation, diagnosis, and management of diabetic ketoacidosis in paediatric population.

EPIDEMIOLOGY OF DKA AMONG PEDIATRIC POPULATION

The exact prevalence of diabetic ketoacidosis is not exactly known. However, it is estimated to occur in around 4 to 8 cases per 1000 patients with diabetes mellitus [4]. In children, around 25% of patients with insulin-dependent diabetes mellitus present with diabetic ketoacidosis [5]. Diabetic ketoacidosis was reported to be more prevalent among white children [6].

ETIOLOGY AND RISK FACTORS FOR DKA IN PEDIATRIC POPULATION

Diabetic ketoacidosis is caused by relative or absolute deficiency of insulin among patients with diabetes mellitus. It can be the presenting manifestation in up to one fourth of cases with type 1 diabetes mellitus or it can occur during the course of the disease due to certain risk factors that increase insulin demand [3]. The main risk factors of diabetic ketoacidosis are infection, poor compliance with insulin therapy regimen, inaccurate insulin doses or physical exercise, psychological stress, eating disorders, and substance use [7].

1. Infection

Infection remains the most common and the most important risk factor for development of ketoacidosis in paediatric age group[1]. Therefore, meticulous investigation for the presence of infection is fundamental in all cases of diabetic ketoacidosis in children. When infection is suspected, empirical antibiotics should stat immediately until the results of culture and sensitivity appear [7].

2. Poor compliance with insulin therapy regimens

Poor compliance with insulin therapy regimens is the second most common cause of development of diabetic ketoacidosis in paediatric ketoacidosis. Changes in either the frequency or the doses of insulin doses may lead to diabetic ketoacidosis[8]. Insufficient, missed, or less frequent doses if insulin will result in inability of the body tissues to utilize glucose and trigger the utilization of fat as a source of energy leading to ketosis and acidosis[9]. The most common causes of poor compliance with insulin therapy are frequent change in lifestyles, frequent travels, and poor family support.

3. Diet and exercise

Insulin therapy necessitates tight adjustment of daily life activities particularly diet and exercise. Children with type 1 diabetes mellitus must stick to a well-organized diet schedule in which insulin doses and meal time and size are accurately calculated. Insulin does should be followed with appropriately-sized meal to avoid hypoglycaemia [10]. Insulin underdosage, oversized meal, or inadequate physical activity in correlation with the insulin may result in hyperglycaemia, insensitivity to circulating glucose, and ketoacidosis as it will be detailed in the section of pathophysiology [11].

4. Psychological stresses and eating disorders

Insulin is directly correlated to psychological stress. Stressed patients often have a decompensated metabolism and excessive release of stress hormones. It is well-established that stress hormones are essential for the manifestation s of ketoacidosis to occur [12]. Eating disorders also increase the risk for ketoacidosis. Children with certain eating diorders consume large amounts of meals that require hypersecretion of insulin [13], and in cases of type 1 diabetes, the relative or absolute absence of insulin in these situations will fail to reduce the blood glucose levels following meals resulting in hyperglycaemia, acidosis, and ketone body formation.

5. Other risk factors:

Other less common risk factors for ketoacidosis include substance abuse and endocrinological changes during adolescence [7].

PATHOPHYSIOLOGY OF DKA IN PEDIATRIC POPULATION

Diabetic ketoacidosis results from a complex pathophysiological process of several elements including hyperglycaemia, glucosuria, dehydration, hypokalaemia, acidosis, and ketosis. The provoking and key element for triggering the body metabolism

towards ketoacidosis is insulin deficiency [14]. In state of severe insulin deficiency, body tissues can not utilize glucose in spite of hyperglycaemia. The limited tissue capacity to uptake glucose stimulates glucagon to increase the process of gluconeogenesis and glycogenolysis [15]. This will lead to further increase in blood glucose level, but the tissues are insensitive to it. Such hyperglycaemia will result in serum hyperosmolarity, glucosuria, osmotic diuresis, excessive free water loss, dehydration, and substantial prerenal shut down [16].

When body tissues fail to utilize glucose, fat will be the subsequent source of energy production for these tissues. The vast majority of body fats are stored in the adipose tissue in the form of triglycerides. In insulin deficiency states, excess glucagon secretion will stimulate lipolysis and the liver will breakdown triglycerides into fatty acids and glycerol. The glycerol will be converted to glucose adding more to the state of hyperglycaemia, whilst the fatty acids and ketone bodies will serve as the source of energy for different body tissues. Ketone bodies can be produced during the process of lipolysis and proteolysis [15].

The resultant dehydration, hypovolemia, and tissue hypoperfusion – along with ketone body production – lead to metabolic acidosis. This results in electrolyte disturbance particularly hypokalaemia and hyponatremia [14]. Despite excessive excretion of potassium in urine, apparent hyperkalaemia occurs in ketoacidosis due to the extracellular shift of potassium from the intracellular compartment in response to acidosis and low insulin levels. Serum magnesium and phosphate concentrations show similar reduction in their levels [17]. Dilutional hyponatremia occur due to extracellular fluid shift as a result of elevated serum osmolality [17].

In advanced states of diabetic ketoacidosis, the cerebral homeostasis becomes negatively affected. Unlike muscles and various body tissues, neurons cannot utilize ketones or any non-glucose molecules as a source of energy. Furthermore, hyperglycaemia and elevated serum osmolality result in a considerable increase in intracellular osmolality [18]. This should be taken into consideration during management to avoid rapid correct of serum osmolarity and hyperglycaemia not to result in cerebral oedema, tonsillar herniation through the foramen magnum, and subsequently death.

CLINICAL PRESENTATION OF DKA AMONG PEDIATRIC POPULATION

Diabetic ketoacidosis may be the presenting manifestation in about 25% of children with type 1 diabetes mellitus [3]. Children with diabetic ketoacidosis often report history of polyuria, polydipsia, fatigue, weight loss, and poor concentration. When diabetic ketoacidosis develops, they report symptoms closely similar to gastroenteritis such as nausea, vomiting, and abdominal pain. The metabolic acidosis stimulates the respiratory system to compensate for the acidosis with hyperventilation to wash out carbon dioxide[6]. Therefore, children present with dyspnoea and tachypnoea, and their examination reveals Kussmaul breathing pattern.

Unlike in adults, the classic symptoms of diabetic ketoacidosis are not typical in children and, therefore, require a high index of suspicion [19]. The onset of DKA in children is often insidious and they experience fatigue, malaise, thirst, hunger, and sometimes fever [3]. Physical examination always reveals weight loss, signs of dehydration (due to osmotic diuresis and volume depletion), and rapid deep breathing. Their breath might show a fruity odour caused by acetone elimination through the lungs and respiratory tract. Vital signs may show fever (particularly if there was an underlying infection predisposing to diabetic ketoacidosis, tachycardia, and hypotension due to volume depletion and free water loss [20].

In advanced non-treated cases, cerebral oedema evolves manifesting as disturbed level of consciousness or altered mentation. Signs of cerebral oedema and increased intracranial tension include headache, papilledema, irritability, projectile vomiting, bradycardia, hypertension, and reduction in level of consciousness. If not urgently managed, tonsillar and medullary herniation through the foramen magnum may occur leading to cardiopulmonary failure and death [18].

DIAGNOSIS

Because the classical symptoms of diabetic ketoacidosis are absent in children, high index of clinical suspicion and urgent investigations are essential for diagnosis. DKA is diagnosed with laboratory testing. The presence of hyperglycaemia and acidosis are diagnostic of the condition, but other tests may be required. Elevated ketone bodies confirm the diagnosis, but they are not essential[21]. The following laboratory tests are used for diagnosis and management of diabetic ketoacidosis in paediatric age group.

1. Blood glucose level

Hyperglycaemia is a fundamental laboratory criterion

for diagnosis of diabetic ketoacidosis. Blood glucose level is always elevated above the accepted normal level of random blood glucose i.e. above 11 mmol/L (or 200 mg/dL) [22]. Children are different from adults in that, during diabetic ketoacidosis, they may have just slight elevation of blood glucose levels [19].

2. Arterial Blood Gases

Arterial blood gases are fundamental for diagnosis and management of diabetic ketoacidosis. The test often reveals metabolic acidosis with or without compensatory respiratory alkalosis. Low pH and low bicarbonate level are often encountered. However, a pH below 7.2 is very dangerous and need a prompt action [21].

3. Ketone bodies

The main ketone molecule produced in cases of diabetic ketoacidosis is beta-hydroxybutyrate. The other two less commonly produced ketones are acetone and acetoacetate[23,24]. Beta-hydroxybutyrate constitutes about three fourths of the produced ketones in cases of DKA and is the best predictor for severity of the condition. Ketones can be measured in blood and urine. Blood strips are used for evaluation and quantification of beta-hydroxybutyrate, whilst urine strips are available for acetone and acetoacetate [222].

Testing blood beta-hydroxybutyrate is preferred to urinary ketones testing because the beta-hydroxy butyrate has the advantage that it tests positive in blood 24 hours before the appearance of acetone and acetoacetate in urine [2]. Additionally, urinary ketones may persist in urine even after treatment of DKA in children. Furthermore, many conditions may result in false positive ketone bodies in urine such as the use of certain medications (e.g. valproate), delayed sample testing, and expired strips[25]. Normally, beta-hydroxybutyrate is below 0.6 mmol/L. In children with DKA, the level is always above 3 mmol/L. Urine ketones should be three plus (+++) to confirm diagnosis of DKA, but they are not used for monitoring or follow up [3,25].

4. Serum electrolytes level

Serum potassium, sodium, phosphorus, and magnesium levels are essential for diagnosis, monitoring, and management of diabetic ketoacidosis in children. Hyperkalaemia is often found in patients with DKA [7]. However, it is an apparent or pseudo-hyperkalaemia that resulted from the insulin- and acidosis-induced extracellular shift of potassium to the circulation. Patients with hypokalaemia have a poor prognosis. Those patients are at risk for hypokalaemia-induced cardiac dysrhythmia and they should be very closely monitored during management [16].

5. Other laboratory tests

Other laboratory tests are essential for assessing the risk factors for the development of diabetic ketoacidosis, potential complications, prognosis, and during monitoring treatment process. For instance, a complete blood picture showing leucocytosis would suggest infection a predisposing factor for DKA [22]. Additional sepsis workup such as urine or sputum cultures should be considered in these cases. Elevated serum blood urea nitrogen (BUN) and creatinine levels may indicate prerenal shut down and potential acute kidney injury [21]. Serum osmolarity, serum chloride, serum phosphate, serum calcium, serum magnesium, serum chloride levels are essential during monitoring process and they predict the response to treatment regimens. In classical situations, serum bicarbonate level is often below 18 mmol/L and the anion gap is increased, often above 15 mEq/L (normal anion gap is between 6-12 mEg/L). The reason for such an increase is that the anion gap is calculated by subtracting serum chloride and serum bicarbonate level from serum sodium and potassium levels, discarding the elevated ketoacids [26].

MANAGEMENT

Diabetic ketoacidosis in children represents a paediatric emergency that necessitates a prompt management. Management of DKA in children in multidisciplinary and requires early identification and admission at a paediatric intensive care unit. The mainstay treatments of paediatric DKA are insulin therapy and fluid resuscitation [20]. On hospital admission, the child airway and breathing should be secured. Most children experience Kussmaul breathing and they may require an oxygen mask with 100% oxygen breathing. Obtaining a wide-pored intravenous access is a critical and essential early step. Insulin therapy should be calculated meticulously according to body weight, and intravenous fluid administration should start simultaneously [21,22]. Because of the potential prerenal shut down, fluid balance must be strictly monitored. Insulin is administered as a continuous intravenous infusion of short-acting or regular insulin to manage the hyperglycaemia. Unlike in adults, there is no role for an insulin bolus dose at the start of infusion in children with DKA [11].

Whilst potassium depletion is common in DKA, apparent hyperkalaemia is often encountered. If potassium level fell dropped below 4 mEq/L,

potassium replacement should be replaced[1]. Cardiac rhythm monitoring is essential all through the management process and particularly if hypokalaemia occurred. In patients with hypokalaemia-induced cardiac dysrhythmia, insulin therapy should not be started before potassium replacement. Otherwise, insulin will enhance the intracellular potassium shift from the blood leading to exacerbation of the hypokalaemia and the dysrhythmia. Potassium levels should be tested regularly and replaced when required [27].

In paediatric DKA, bicarbonate has no role for treatment of metabolic acidosis. Acidosis is corrected with the hydration measures and the insulin therapy [28]. Several literature studies showed that the use of bicarbonate in cases of DKA in paediatric age group may worsen the acidosis and exacerbate cerebral oedema [29].

Investigating and treatment of the predisposing factor such as the infection is an essential step for successful management of DKA in children [22]. After stabilization of the child condition and resolution of the ketoacidosis, insulin infusion can be changed to the subcutaneous form and the diet can be gradually introduced.

CONCLUSION:

DKA is a paediatric emergency. It needs high suspicion of diagnosis because it presents with atypical manifestations unlike the adults. The most common risk factors for paediatric ketoacidosis are infection, incompliance with insulin regimen, and psychological stress. The most important laboratory tests for diagnosis of DKA in children are the blood glucose level and arterial blood gases. The mainstay treatment lines are insulin therapy and correction of hypovolemia. Electrolyte imbalance and cardiac monitoring are fundamental during the management plan,

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REFERENCES:

1. Gabriel E, Soni S. Diabetic ketoacidosis. *Hosp Med Clin*. 2014;3(4):556-566. doi:10.1016/j.ehmc.2014.06.007
2. Kitabchi AE, Nematollahi LR. Diabetic ketoacidosis. BMJ Best Practice.
3. EL-Mohandes N, Huecker MR. *Diabetic Ketoacidosis, Pediatric.*; 2018.
4. Bui H, To T, Stein R, Fung K, Daneman D. Is Diabetic Ketoacidosis at Disease Onset a Result of Missed Diagnosis? *J Pediatr*. 2010;156(3):472-477. doi:10.1016/j.jpeds.2009.10.001
5. Gosmanov A, Gosmanova E, Dillard-Cannon E. Management of adult diabetic ketoacidosis. *Diabetes, Metab Syndr Obes Targets Ther*. 2014;7:255-264. doi:10.2147/DMSO.S50516
6. Rewers A, Klingensmith G, Davis C, et al. Presence of Diabetic Ketoacidosis at Diagnosis of Diabetes Mellitus in Youth: The Search for Diabetes in Youth Study. *Pediatrics*. 2008;121(5):e1258-e1266. doi:10.1542/peds.2007-1105
7. Umpierrez GE, Kitabchi AE. Diabetic ketoacidosis: Risk factors and management strategies. *Treat Endocrinol*. 2003;2(2):95-108. doi:10.2165/00024677-200302020-00003
8. Syed M, Khawaja FB, Saleem T, Khalid U, Rashid A, Humayun KN. Clinical profile and outcomes of paediatric patients with diabetic ketoacidosis at a tertiary care hospital in Pakistan. *J Pak Med Assoc*. 2011;61(11):1082-1087.
9. Gavidia Quezada R, Edriss H. Diabetic ketoacidosis: Should current management include subcutaneous insulin injections? *Southwest Respir Crit Care Chronicles*. 2017;5(19):6. doi:10.12746/swrccc.v5i19.389
10. Deshmukh CD, Jain A. Diabetes Mellitus: A Review. *Int J Pure Appl Biosci*. 2015;3(3):224-230.
11. Cardella F. Insulin therapy during diabetic ketoacidosis in children. *Acta Biomed*. 2005;76 Suppl 3:49-54.
12. Schade DS, Eaton RP. Pathogenesis of diabetic ketoacidosis: A reappraisal. *Diabetes Care*. 1979;2(3):296-306. doi:10.2337/diacare.2.3.296
13. Macdonald P, Kan C, Stadler M, et al. Eating disorders in people with Type 1 diabetes: experiential perspectives of both clients and healthcare professionals. *Diabet Med*. 2018;35(2):223-231. doi:10.1111/dme.13555
14. Rosival V. Pathophysiology of diabetic ketoacidosis. *Diabet Med*. 2015;32(11):1527-1527. doi:10.1111/dme.12760
15. Hopely L, Schalkwyk J van. Diabetic ketoacidosis: pathophysiology. *AnaethetistCom*. 2002:1.
16. Nelson RW. Chapter 8 - Diabetic Ketoacidosis. *Canine Feline Endocrinol*. 2015:315-347. doi:10.1016/B978-1-4557-4456-5.00008-0
17. Nattrass M. Diabetic ketoacidosis. *Medicine (Baltimore)*. 2010;38(12):667-670. doi:http://dx.doi.org/10.1016/j.mpmed.2010.08.016
18. Levin DL. Cerebral edema in diabetic

ketoacidosis. *Pediatr Crit Care Med*. 2008;9(3):320-329. doi:10.1097/PCC.0b013e31816c7082
19. Department for Health and Ageing Government of South Australia. Diabetic Ketoacidosis (DKA) in Children. *South Aust Paediatr Clin Guidel*. 2012:1-15.
20. Ganesh R, Suresh N, Ramesh J. Diabetic ketoacidosis in children. *Natl Med J India*. 2006;19(3):155-158. doi:10.1016/j.pcl.2005.03.006
21. Fasanmade OA, Odeniyi IA, Ogbera AO, Ogbera A. Diabetic ketoacidosis: diagnosis and management. *Afr J Med Med Sci*. 2008;37(2):99-105.
22. Tenoutasse S, Mouraux T, Dorchy H. [Diabetic ketoacidosis: diagnosis, management, prevention]. *Rev Med Brux*. 2010;31(2 Suppl):S71-6.
23. Wisse B, Zieve D. Diabetic ketoacidosis. Medline Plus.
24. Savage MW. Management of diabetic ketoacidosis. In: *Clinical Medicine, Journal of the Royal College of Physicians of London*. Vol 11. ; 2011:154-156. doi:10.7861/clinmedicine.11-2-154
25. Diagnosis P. Ketones , Blood and Urine. In: *Davis's Comprehensive Handbook of Laboratory & Diagnostic Tests with Nursing Implications*. ; 2015:1004-1007.
26. G. L, M. Y, S. K. Anion gap versus ketones in diabetic ketoacidosis. *Pediatr Crit Care Med*. 2011;12(3 SUPPL. 1):A110-A111.
27. Popkiewicz F. Clinical management of diabetic ketoacidosis. *Endocr Rev*. 2015;36.
28. Wolfsdorf J, Glaser N, Sperling MA, American Diabetes Association. Diabetic ketoacidosis in infants, children, and adolescents: A consensus statement from the American Diabetes Association. *Diabetes Care*. 2006;29(5):1150-1159. doi:10.2337/diacare.2951150
29. Tiwari LK, Muralindharan J, Singhi S, Jayashree M, Muralindharan J, Singhi S. Risk factors for cerebral edema in diabetic ketoacidosis in a developing country. *Pediatr Crit Care Med*. 2012;13(2):e91-6. doi:10.1097/PCC.0b013e3182196c6d