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DIABETIC KETOACIDOSIS IN CHILDREN

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Abstract

The object of this review is to provide the definitions, frequency, risk factors, pathophysiology, diagnostic considerations, and management recommendations for diabetic ketoacidosis (DKA) in children and adolescents, and to convey current knowledge of the causes of permanent disability or mortality from complications of DKA or its management, particularly the most common complication, cerebral edema (CE). DKA frequency at the time of diagnosis of pediatric diabetes is 10%–70%, varying with the availability of healthcare and the incidence of type 1 diabetes (T1D) in the community. Recurrent DKA rates are also dependent on medical services and socioeconomic circumstances. Management should be in centers with experience and where vital signs, neurologic status, and biochemistry can be monitored with sufficient frequency to prevent complications or, in the case of CE, to intervene rapidly with mannitol or hypertonic saline infusion. Fluid infusion should precede insulin administration (0.1 U/kg/h) by 1–2 hours; an initial bolus of 10–20 mL/kg 0.9% saline is followed by 0.45% saline calculated to supply maintenance and replace 5%–10% dehydration. Potassium (K) must be replaced early and sufficiently. Bicarbonate administration is contraindicated. The prevention of DKA at onset of diabetes requires an informed community and high index of suspicion; prevention of recurrent DKA, which is almost always due to insulin omission, necessitates a committed team effort.

DEFINITION:

Diabetic ketoacidosis (DKA) is a serious condition which caused by dangerously high blood sugar levels. The child's blood sugar levels become high because the body does not have enough insulin. Insulin is a peptide hormone produced by beta cells of the pancreatic islets; it is considered to be the main anabolic hormone of the body as. It regulates the metabolism of carbohydrates, fats and protein by promoting the absorption of glucose from the blood into liver, fat and skeletal muscle cells. The lack of insulin forces the body to use fat instead of sugar for energy. As fats are broken down, they leave chemicals called ketones that build up in the blood. Ketones are dangerous at high levels. Diabetic ketoacidosis (DKA) is considered to be a is a potentially life-threatening complication of type 1 diabetes mellitus (T1DM) and occasionally, type 2 diabetes mellitus (T2DM) in children. Insulin stops the use of fat as an energy source by inhibiting the peptide hormone glucagon. Without insulin, glucagon levels rise resulting in the release of free fatty acids from adipose tissue, as well as amino acids from muscle cells.[15,16,17]

***PATHOPHYSIOLOGY*:**

The pathophysiological processes of DKA passed throw many steps:

1- Deficiency of insulin:
When serum insulin concentrations are inadequate due to an absolute deficiency (as in the setting of progressive pancreatic β-cell failure due to autoimmune destruction in undiagnosed T1DM) or relative deficiency (18)(stress, infection, inadequate insulin intake) in relation to elevated counterregulatory hormone levels (catecholamines, cortisol, glucagon, and growth hormone).

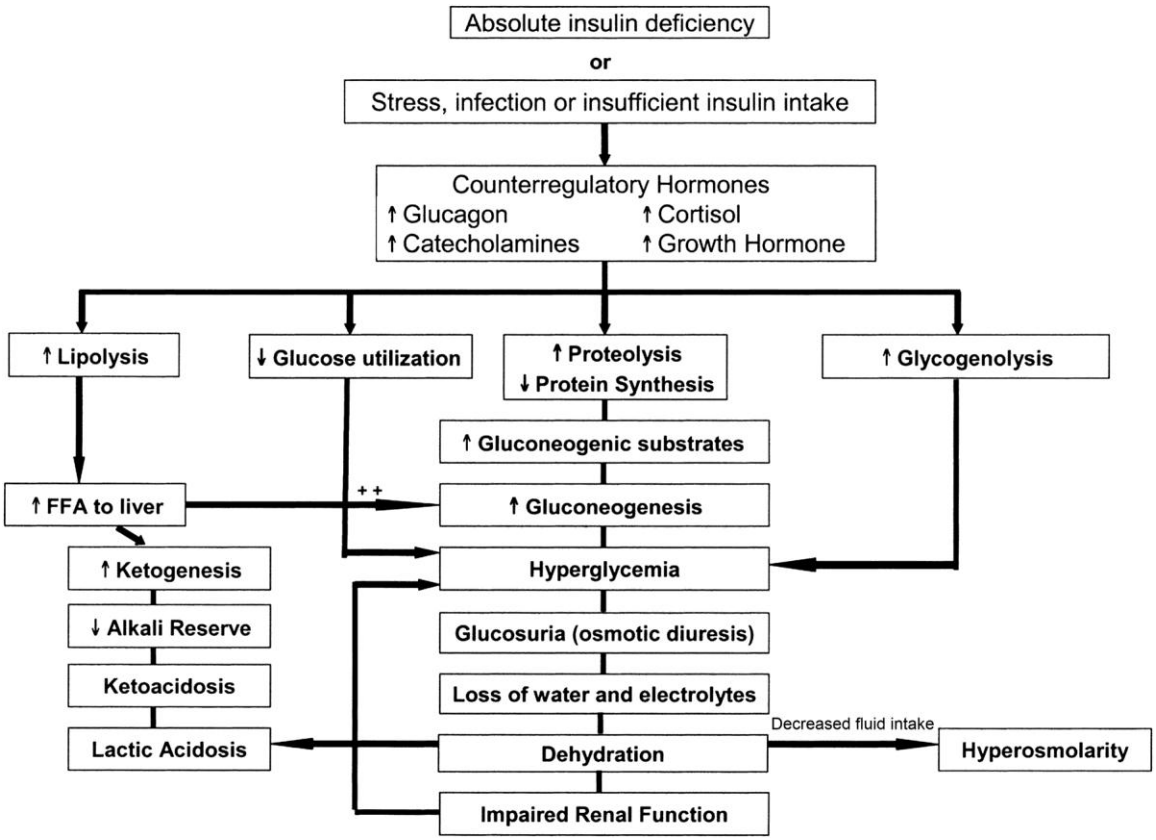
2- Increase the secretion of counter-regulatory hormones including glucagon, cortisol, growth hormone, and catecholamines.

3-Thus, inappropriate gluconeogenesis and liver glycogenolysis: This causes hyperglycemia, hyperosmolality, increased lipolysis, and ketogenesis. When the renal threshold for glucose is exceeded (~170–200 mg/dL [~9.4–11.1 mmol/L]), glucosuria and hyperketonemia cause osmotic diuresis, dehydration, and electrolyte wasting (including sodium, potassium, magnesium, calcium, and phosphate loss).

4-Accelerated catabolism from lipolysis of adipose tissue leads to increased free fatty acid circulation, which on hepatic oxidation produces the ketone bodies (acetoacetic acid and beta-hydroxybutyric acid) that cause the metabolic acidosis (19).

5-Potassium moves from the intracellular to the extracellular space in a switch with hydrogen ions that accumulate. Much of this extracellular potassium is then eliminated in urine, creating total body hypokalemia, this further stimulates stress hormone production, and if insulin, fluid, and electrolytes are not replaced, then worsening dehydration, metabolic and lactic acidosis, and even death can occur(22).

6-A vicious circle is usually set up as vomiting usually occurs compounding the stress and dehydration; the cycle can only be broken by providing insulin and fluids; otherwise, severe acidosis occurs and can be fatal.(29)



EPIDEMIOLOGY:

Diabetes is one of the most common chronic diseases in the world. at least 192,000 children in the United States had a diagnosis of diabetes, and the population incidence for DKA hospitalizations continues to increase, with 188,965 total admissions in 2014. Approximately 11% of these admissions for DKA were in children younger than 17 years. Despite an overall increase in hospital admissions, both hospital length of stay and mortality have decreased, with mortality decreasing to 0.33%.(4-9)There is wide geographic variation in the frequency of DKA at onset of type 1 diabetes; rates inversely correlate with the regional incidence of type 1 diabetes.DKA at diagnosis is more common in children aged under 5 years, and in children whose families do not have ready access to medical care for social or economic reasons.The risk of DKA in established type 1 diabetes is 1-10% per per year. The risk is increased in: 1) Children with poor metabolic control or previous episodes of DKA.2) peripubertal and adolescent girls.3) psychological considerations play a major role, including stress of chronic disease, rebellion against authority, fear of weight gain, and eating disorders, which have all been implicated as contributing factors4) Children with difficult or unstable family circumstances.5) Children who omit insulin dosage.6)(1,2) Children with limited access to medical services.7) acute gastroenteritis with persistent vomiting and inability to maintain hydration.8) Insulin

pump therapy (as only rapid- or short-acting insulin is used in pumps, interruption of insulin delivery for any reason rapidly leads to insulin deficiency).

CLINICAL MANIFESTATION:

Young children are more prone for hospital admission with manifestation of DKA as a complication of undiagnosed type1 diabetes than older children .DKA is the first presentation of diabetes in 30-40% of pediatric cases. The classic clinical signs of DKA include **polyuria**, **polydipsia**, **polyphagia**, and **weight loss**.(13-15) A good history and physical examination are necessary to prevent misdiagnosis in children who do not have classic presenting symptoms, and, even with classic signs, inexperienced providers may misdiagnose DKA. Clinical signs may progress rapidly and include **vomiting**, **abdominal pain**, **dehydration**, **weakness**, and **lethargy**. **Abdominal pain and ileus** can result from potassium depletion, acidosis, and poor splanchnic perfusion. Abdominal pain may be severe enough to **mimic an acute abdomen** in the initial phase of DKA. Dehydration causes tachycardia, delayed capillary refill time, poor skin turgor, and dry mucus membranes. Ketoacidosis stimulates both central and peripheral chemoreceptors that control respiration, resulting in **Kussmaul respiration** (rapid fast deep breathing) in an attempt to decrease Pco_2 and compensate for the metabolic acidosis. In addition, ketoacidosis may result in a **fruity odor to the breath**. Despite severe dehydration, children generally maintain their blood pressure, likely due to increased plasma catecholamines and increased release of antidiuretic hormone in relation to high serum osmolality. Eventually, when compensatory mechanisms are overwhelmed, children with severe DKA may present with hypotension, shock, and altered mental status. Also look for any evidence of **cerebral edema** (Warning signs and symptoms of developing brain injury include **headache, bradycardia, irritability, increased drowsiness**, **altered mental status, cranial nerve palsies, and new abnormal neurologic signs on examination, hypertension, unresponsiveness, and coma**.

***DIAGNOSTIC WORK-UP*:** Diagnosis of DKA should be done accurately due to a possibility of a confusing clinical picture such as dehydration, meningitis, acute abdomen, pneumonia, etc. Emergency assessment can be done by following the general guidelines of Pediatric Advanced Life Support. Immediate measures are a brief history and quick diagnosis, which is essential. Initial immediate assessment or investigation includes evaluation of the severity of dehydration, level of consciousness through Glasgow Coma Scale, body weight and height if the person is mobile. Baseline investigations involve the measurement of BG levels, beta-hydroxybutyric acid, serum electrolytes and renal functions. During physical examination, physician may look for signs of dehydration, acidosis, and electrolyte imbalance, including shock, hypotension, acidotic breathing, and central nervous system(24,25).

The biochemical criteria required for a diagnosis of DKA to be made are:

- Acidosis - indicated by blood pH of <7.3 or bicarbonate <18 mmol/L:
    - pH ≥7.1 indicates mild or moderate DKA.
    - pH <7.1 indicates severe DKA.
- Ketonaemia (indicated by blood beta-hydroxybutyrate above 3 mmol/L) or ketonuria (indicated by ++ or more on urine dipstick).

There is usually raised blood glucose >11 mmol/L. However, children and young people with normal blood sugar levels can develop DKA.

THERAPEUTIC OPTIONS:

The following is based on National Institute for Health and Care Excellence (NICE) and British Society for Paediatric Endocrinology and Diabetes (BSPED) DKA guidelines.

1-Always begin with resuscitation of the patient

Airway - check the airway is patent, attempt to open it if not. Seek urgent anesthetic review and discuss with pediatric critical care specialist if airway is not protected due to a reduced level of consciousness as intubation may be indicated. Consider need for nasogastric tube to decompress and empty the stomach and lower the risk of aspiration, particularly if there is reduced consciousness(10).

Breathing - consider need for oxygen -eg, if altered level of consciousness (if necessary 6-10L/min via Hudson mask)

Circulation - insert two intravenous (IV) cannula if possible, one for fluid and medications and one for blood sampling line. Attach cardiac monitor. Assess cardiovascular status and only give a fluid bolus (10 ml/kg 0.9% sodium chloride) if there is hypotensive shock. Discuss any further bolus and the use of inotropes with a paediatric critical care specialist.

Disability - assess conscious level early on. All patients should have GCS assessment or a modification of the verbal response score for younger children, and one-hourly neurological observations. If the patient is comatose

or semi-conscious, consider cerebral edema and institute treatment and arrange transfer to PICU/HDU (but do not delay therapy).

2-The next step in the management is correction of fluid loss

The essential principles of DKA treatment include careful replacement of fluid deficits, correction of dehydration, correction of acidosis and hyperglycemia with insulin administration, maintenance of glucose levels at the normal range, correction of electrolyte imbalance and treatment of any precipitating cause. Successful management of DKA requires constant clinical and biochemical monitoring and timely adjustment of insulin dose, fluid and electrolyte status. Antibiotics, oxygen, and cardiac monitoring can be used if required. **Fluid therapy** is initially used for the treatment of DKA, **followed by insulin therapy** if required. The main importance of fluid therapy is: Restoration of circulating volume, replacement of electrolytes, improvement of renal function and clearance of glucose and ketones from the blood(11,19,20).

Before starting fluid therapy, the physician should check if the child was treated earlier before the current admission. **During fluid therapy**, water and salt deficit are replaced using **0.9% normal saline and a 10-20 mL/kg normal bolus** may also be used for approximately 1-2 h. If the patient is in shock, several boluses may be given. Subsequent therapy is used for deficit replacement**. Normal saline or Ringer lactate is used over a period of 4-6 h**. Consequently, maintenance fluids are used. Usually, half normal saline (0.45%) with potassium chloride is given depending on the state of hydration and electrolyte levels. Fluid therapy is usually planned for a period of 48 h. However, a child may improve earlier than 48 h. Normal circulation is often achieved in 12 ± 6 h. In cases of mild DKA, no bolus is needed. The main principle of fluid therapy is to never infuse fluids more than 1.5-2 times the normal daily requirement. Moreover, constant monitoring and assessment of hydration is absolutely essential.

3- Replace insulin

Insulin therapy is essential to return the blood sugar level to normal limits, and to prevent further lipolysis and ketogenesis. Insulin should be given as an IV infusion at a dosage between **0.05 and 0.1 units/kg/hour**. Use pre-filled syringes containing 50 Units of soluble insulin in 50 ml 0.9% sodium chloride. An initial bolus is not recommended.it is worth mentioning that Continuous subcutaneous insulin pumps should be stopped while the IV infusion is given, but long-acting insulin treatment may be continued. **Subcutaneous insulin** may only be used along with oral fluids where the child or young person is alert, not nauseated or vomiting, and not clinically dehydrated.

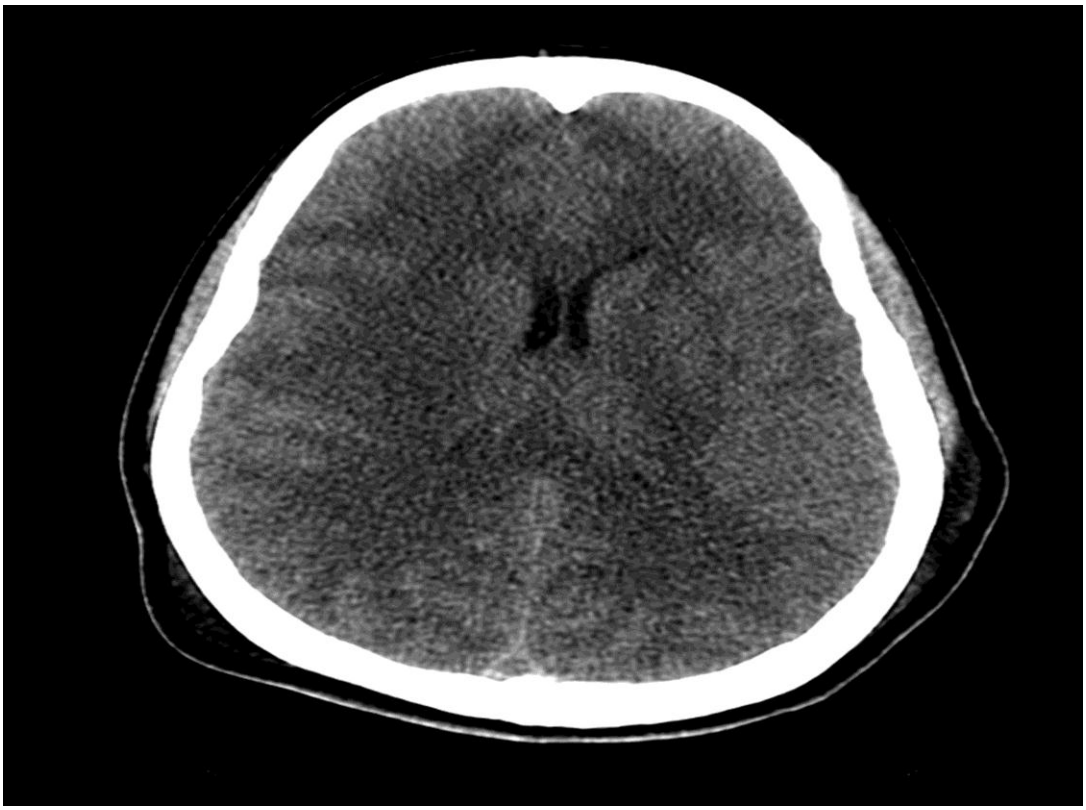
4- Potassium replacement

Potassium replacement therapy is used when the total body potassium deficit is nearly ~3-6 mmol/kg. If the patient is hypokalemic, start potassium replacement at the time of initial volume expansion and before starting insulin therapy. Otherwise, start replacing potassium after initial volume expansion and concurrent with starting insulin therapy. If the patient is hyperkalemic, defer potassium replacement therapy until urine output is documented. If children are hypokalemic on presentation, potassium should be replaced, and as long as the patient has adequate renal function, rehydration fluid should contain potassium. Depletion of intracellular phosphate is also seen in DKA due to losses from osmotic diuresis, and severe hypophosphatemia should be treated. Bicarbonate administration is not recommended because this has not shown benefit in the resolution of DKA, and bolus administration has been historically associated with worse outcomes. Administration of bicarbonate potentially may cause harm due to paradoxical central nervous system acidosis. Therefore, bicarbonate administration should be reserved for the treatment of severe hyperkalemia or severe acidosis (pH ≤6.9) causing impaired cardiac contractility.

Prognosis of DKA:

When DKA is recognized and treated immediately, the prognosis is excellent. However, when a patient has prolonged or multiple courses of DKA or if DKA is **complicated by cerebral edema** then the prognosis can be very poor .The mortality rate of children with DKA in the UK is approximately 0.31%, with the majority of these deaths occurring as a result of cerebral edema. Cerebral edema associated with DKA is more common in children than in adults. In the UK around 70-80% of diabetes-related deaths in children less than 12 years of age are caused as a result of cerebral edema. DKA at the time of diagnosis of type 1 diabetes may be associated with poor long-term metabolic regulation and residual beta cell function(28,27).

Cerebral edema:



Computed tomographic scan showing effacement of the cerebral sulci consistent with cerebral edema.

Cerebral edema occurs in 0.5-0.9% of all episodes of DKA. It is considered to be a major cause of death in childhood DKA. Risk factors include initial pH of <7.1, abnormal baseline mental status, newly diagnosed patients who are <5 years old, patients suffering from dehydration and severe acidosis with lower partial pressure of carbon-dioxide, rapid rehydration (>50 cc/kg in the first 4 h), insulin given before or within 1st h of fluid initiation, persistent hypernatremia and high blood urea at presentation.

Treatment:

- Exclude hypoglycaemia with RBS.
- If cerebral edema is suspected or any typical late features develop, treat immediately with the most readily available of mannitol (20%, 0.5-1 g/kg over 10-15 minutes) or hypertonic sodium chloride (2.7% or 3%, 2.5-5 ml/kg over 10-15 minutes).
- Mannitol may need to be repeated after two hours.
- Reduce rate of fluid administration - halve the maintenance dose and discuss with a senior clinician.

- Transfer to ICU may require - may need intubation and ventilation,.
- CT brain scan will help delineate the cause of alternative diagnoses (eg, thrombosis, haemorrhage, infection).

Risk factors include:

- Younger age.
- New-onset diabetes mellitus.
- Longer duration of symptoms of DKA

Other complications

- Hypoglycaemia.
- Hypokalaemia.
- Systemic infections.
- Aspiration pneumonia.
- pneumothorax, interstitial pulmonary oedema, hyperosmolar hyperglycaemic non-ketotic coma.

Prevention of recurrence:

The best way to prevent DKA is to help the child to control his or her diabetes. Ask the child's healthcare provider for more information on how to manage the child's diabetes.

- Therapy adherence.
- Early symptoms detection of DKA.
- Managing undercurrent illnesses (sick day rules).
- Sources of support and advice.

References:

1) 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

2) Dunger DB, Sperling MA, Acerini CL, et al; ESPE; LWPES. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. Arch Dis Child. 2004;89(2):188–194
3) Osaki A, Okada S, Saito T, et al. Renal threshold for glucose reabsorption predicts diabetes improvement by sodium-glucose cotransporter 2 inhibitor therapy. J Diabetes Investig. 2016;7(5):751–754
4) Nallasamy K, Jayashree M, Singhi S, Bansal A. Low-dose vs standard-dose insulin in pediatric diabetic ketoacidosis: a randomized clinical trial. JAMA Pediatr. 2014;168(11):999–1005
5) Association of Children's Diabetes Physicians, BSPED, Children and Young People's National Diabetes Network
6) British Society for Paediatric Endocrinology and Diabetes (BSPED)
7) NICE Guidelines
8) International Diabetes Federation and International Society for Pediatric and Adolescent Diabetes
9) de Vries L, Oren L, Lazar L, et al; Factors associated with diabetic ketoacidosis at onset of Type 1 diabetes in children and adolescents
10) Olivieri L, Chasm R; Diabetic ketoacidosis in the pediatric emergency department. Emerg Med Clin North Am
11) From https://www.drugs.com/
12) From https://www.ncbi.nlm.nih.gov/
13) From https://pubmed.ncbi.nlm.nih.gov/
14) From https://www.wikipedia.org/
15) From american academy of pediatrics
16) Golden M.P., Herrold A.J., Orr D.P. An approach to prevention of recurrent diabetic ketoacidosis in the pediatric population. *J Pediatr.* 1985;107:195–200. doi: 10.1016/S0022-3476(85)80124-
17) Rosenbloom A.L. Hyperglycemic hyperosmolar state: an emerging pediatric problem. *J Pediatr.* 2010;156:180–184. doi: 10.1016/j.jpeds.2009.11.057.

18) McDonnell C.M., Pedreira C.C., Vadamalayan B., Cameron F.J., Werther G.A. Diabetic ketoacidosis, hyperosmolarity and hypernatremia: are high-carbohydrate drinks worsening initial presentation? *Pediatr Diabetes.* 2005;6:90–94. doi: 10.1111/j.1399-543X.2005.00107.x.

19) Morales A., Rosenbloom A.L. Death caused by hyperglycemic hyperosmolar state at the onset of type 2 diabetes. *J Pediatr.* 2002;144:270–273.

20) Canarie M.F., Bogue C.W., Banasiak K.J., Weinzimer S.A., Tamborlane W.V. Decompensated hyperglycemic hyperosmolarity without significant ketoacidosis in the adolescent and young adult population. *J Pediatr Endocrinol Metab.* 2007;20:1115–1124. doi: 10.1515/JPEM.2007.20.10.1115.

21) Koves I.H., Neutze J., Donath S., et al. The accuracy of clinical assessment of dehydration during diabetic ketoacidosis in childhood. *Diabetes Care.* 2004;27:2485–2487. doi: 10.2337/diacare.27.10.2485.

22) Fagan M.J., Avner J., Khine H. Initial fluid resuscitation for patients with diabetic ketoacidosis: how dry are they? *Clin Pediatr.* 2008;47:851–855. doi: 10.1177/0009922808319960.

23) Teasdale G., Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet.* 1974;2:81–84. doi: 10.1016/S0140-6736(74)91639-0. 24. Malone J.I., Brodsky S.J. The value of electrocardiogram monitoring in diabetic ketoacidosis. *Diabetes Care.* 1980;3:543–547. doi: 10.2337/diacare.3.4.543.

24) Soler N.G., Bennett M.A., Fitzgerald M.G., Malins J.M. Electrocardiogram as a guide to potassium replacement in diabetic ketoacidosis. *Diabetes.* 1974;23:610–615.

25) Schatz D.A., Rosenbloom A.L. Diabetic ketoacidosis: management tactics in young patients. *J Crit Illness.* 1988;3:29–41.

26) Malone J.I., Root A.W. Plasma free insulin concentrations: keystone to effective management of diabetes mellitus in children. *J Pediatr.* 1981;99:862–867. doi: 10.1016/S0022-3476(81)80007-8.

27) Rosenbloom A.L., Hanas R. Diabetic ketoacidosis (DKA): treatment guidelines. *Clin Pediatr.* 1996;35:261–266. doi: 10.1177/000992289603500506.

28) Bonadio W.A., Gutzeit M.F., Losek J.D., Smith D.S. Outpatient management of diabetic ketoacidosis. *Am J Dis Child.* 1988;142:448–450.

29) Linares M.Y., Schunk J.E., Lindsay R. Laboratory presentation in diabetic ketoacidosis and duration of therapy. *Pediatr Emerg Care.* 1996;12:147–151. doi: 10.1097/00006565-199610000-00006