PRECIPITATING FACTORS, CLINICAL PROFILE AND METABOLIC ABNORMALITIES OF DIABETIC KETOACIDOSIS IN CHILDREN WITH TYPE 1 DIABETES AND THEIR ROLE IN PREDICTING THE OUTCOME

Madhava Vijaya Kumar[1], Kalappurayil Manjusha[2]

[1]Associate Professor, Department of Paediatrics, Government Medical College, Kozhikode, Kerala.
[2]Junior Resident, Department of Paediatrics, Government Medical College, Kozhikode, Kerala.

ABSTRACT

BACKGROUND

The aim of the study is to study the clinical profile of diabetic ketoacidosis in children with type 1 diabetes to identify the precipitating factors, to assess the metabolic alterations due to this illness and to correlate these parameters with the outcome.

MATERIALS AND METHODS

This was a prospective observational study and 33 children admitted in PICU during the study period were recruited for the study.

RESULTS

24 children were newly-diagnosed cases and 9 children were already established cases of type 1 diabetes. Mean age group was 10.7 years. Major precipitating causes of DKA in established cases were intercurrent respiratory infections and omission of insulin. Nausea, vomiting, thirst and polyuria were the most common symptoms. Mean duration of symptoms before diagnosing DKA were 20 days in newly-diagnosed cases and 4 days in established cases. ¾ of children had dehydration at the time of admission. Severity was more in younger children. Commonest biochemical abnormality was hypokalaemia. Late diagnosis and delay in the initiation of treatment were the commonest predisposing factors for the development of cerebral oedema.

CONCLUSION

DKA is a life-threatening complication of type 1 diabetes and the red flag signs of bad outcome were young age, late diagnosis, late referral and late initiation of treatment. Hence, a high index of suspicion is necessary to diagnose DKA in first presentation of diabetes as well as in established cases.

KEYWORDS

Type 1 Diabetes, Diabetic Ketoacidosis (DKA), Cerebral Oedema, Insulin Therapy.

HOW TO CITE THIS ARTICLE: Kumar MV, Manjusha K. Precipitating factors, clinical profile and metabolic abnormalities of diabetic ketoacidosis in children with type 1 diabetes and their role in predicting the outcome. J. Evid. Based Med. Healthc. 2017; 4(8), 393-400. DOI: 10.18410/jebmh/2017/76

BACKGROUND

Childhood diabetes is a traumatising experience both for the affected children and their parents.[1] Type 1 diabetes constitute more than 90% diabetes in children and is characterised by frequent episodes of Diabetic Ketoacidosis (DKA).[2] About half of the cases present with ketoacidosis (DKA) as their first clinical manifestation. In already established cases, DKA occur when these children forget to take insulin injections or during febrile episodes like respiratory tract infection or diarrhoea.[3] DKA is the commonest cause of death in children with type 1 diabetes. Many of the affected cases come to the hospital at a later stage when the metabolic abnormalities have advanced to a stage where recovery is not possible.[4] Hence, prevention and recognition of early signs of DKA are of paramount importance in reducing the morbidity and mortality of this dreaded complication of diabetes.[5]

Financial or Other, Competing Interest: None.
Submission 12-12-2016, Peer Review 20-12-2016,
Acceptance 10-01-2017, Published 24-01-2017.
Corresponding Author:
Dr. Madhava Vijaya Kumar,
House Number 13/1831, Visakham,
Near Silver Hills Public School,
Paroppady, Marikunnu P. O,
Kozhikode-673012, Kerala.
E-mail: drmvijaycalicut@gmail.com
DOI: 10.18410/jebmh/2017/76

AIMS AND OBJECTIVES

1. To study the clinical profile of Diabetic Ketoacidosis (DKA) in children admitted in the Paediatric Intensive Care Unit (PICU) of Government Medical College, Kozhikode, Kerala.
2. To identify the precipitating factors.
3. To assess the biochemical alterations due to this complication.
4. To correlate these parameters with the outcome.

MATERIALS AND METHODS

This was a prospective observational study and 33 children admitted in PICU during the study period were recruited for the study.

Study Design
Prospective observational study.

Study Period
From June 2013 to June 2016 (three years).

Sample Size
33 children admitted in PICU during the study period were enrolled for the study after getting informed consent from the parents.

Methods of Data Collection
Data were collected by interviewing the parents by examining the children and going through the investigation records. These children were followed up during the hospital stay and during follow up visits in the endocrinology clinic.

Inclusion Criteria
Children admitted as DKA during the study period were enrolled in the study. The following parameters were taken as the diagnostic criteria of DKA. Plasma sugar more than 200 mg/dL, acidosis with pH less than 7.3 and presence of ketone bodies in urine. Patients who were hesitant to give the consent were excluded from the study.

Exclusion Criteria
Patients admitted with type 1 diabetes who did not fulfil the criteria for DKA and patients who were hesitant to give the consent were excluded from the study.

Method of the Study
Details regarding the duration of diabetes, complications, insulin therapy, frequency of blood glucose testing (using glucometer), dietary habits and duration of symptoms were obtained. An attempt to detect the precipitating events were made in all children. Detailed physical examination including the vitals, anthropometry and examination of the systems were carried out. Essential laboratory parameters done before initiating the treatment included blood glucose, arterial blood gas, sodium, potassium, calcium, phosphorous, magnesium, complete blood counts, blood urea, serum creatinine and an electrocardiogram. Urine examination was done for routine analysis and for detecting ketone body. HbA1c was done in all children to look for long-term glycaemic status. Patients were followed up during the hospital stay by doing subsequent clinical assessments and by repeating the investigations. After discharge, these children were followed up in the endocrinology clinic.

Definitions
Criteria for the Diagnosis[1,2,3,4]

- Hyperglycaemia- Blood glucose levels more than 200 mg/dL (11.1 mmol/L).
- Metabolic acidosis- pH less than 7.3 and serum bicarbonate less than 15 mmol/L.
- Ketosis- Blood ketones more than 3 mmol/L or urine ketones more than 2+.

Features	Mild	Moderate	Severe
Dehydration (%)	<5	5-10%	>10
Blood glucose (mg/dL)	200-250	250-300	>300
pH	7.2-7.3	7.1-7.2	<7.1
Bicarbonate (mmol/L)	10-15	5-10	<5
Base excess (mmol/L)	-5 to-10	-10 to -15	<-15

Table 1. Classification of Disease Severity

Percentage of Dehydration	Clinical Features
5-10%	Dry mucous membrane, sunken eyes, absent tears, weak peripheral pulses, cool extremities, tachypnoea, abnormal skin turgor, prolonged capillary refill time (>2 seconds).
>10%	Weak or impalpable peripheral pulses, hypotension, oliguria

Table 2. Hydration Status

Serum sodium- Measured sodium levels are lower in the presence of hyperglycaemia and was corrected according to the formula below. Corrected sodium = measured sodium + ((glucose in mg/dL-100) x 1.6)/100.

Normal Serum Levels of Electrolytes	Reference Value
Sodium	134-143 mmol/L
Potassium	3.3-4.6 mmol/L
Phosphorous (inorganic)	3.7-5.6 mg/dL
Calcium (total)	8.8-10.8 mg/dL
Magnesium	1.5-2.3 mg/dL

Table 3. Reference Values

Statistical Analysis
Data were analysed using SPSS software package. The statistical significance of different variables was calculated using chi-square test. P value less than 0.05 was considered as statistically significant.

OBSERVATIONS
Among the study population, 11 children (33.3%) belonged to the age group 5-10 years. One child was younger than 5 years. 21 (63.6%) children were older than 10 years. Girls constituted 45% of all cases. Mean age was 10.7 years. 24 (73%) children were newly detected type 1 diabetes and their initial presentation was DKA. Six (18%) children were established cases of diabetes and already on insulin, but developed DKA following an episode of acute respiratory infection. Three children (9%) were defaulters who have temporarily discontinued few doses of insulin.

One newly-diagnosed adolescent girl was on thyroxine tablets for autoimmune thyroiditis during the past one year. No other children were on any long-term medications.

Precipitating Events	Frequency	Percentage (%)
Initial presentation	24	73
Intercurrent infections	6	18
Drug default	3	9

Table 4. Precipitating Events for Diabetic Ketoacidosis (DKA)

Nausea, vomiting, thirst and polyuria were the major symptoms at presentation. Abdominal pain and breathlessness were seen in some children. Six children were brought with altered sensorium mimicking encephalitis. One child was referred as a case of status epilepticus and altered sensorium.

Symptoms at Admission	Frequency	Percentage (%)
Nausea and vomiting	25	75.8
Thirst	25	75.8
Polyuria	22	66.6
Abdominal pain	12	36.4
breathlessness	9	27.3
Altered sensorium	6	18.2
Seizures	1	3.0

Table 5. DKA Symptomatology at Admission

Many cases were diagnosed (15) for the first time in children who were admitted for nonspecific complaints and diabetes was being picked up by blood glucose examination. 8 cases were suspected as having diabetes based on the symptomatology, worked up and referred after suspecting DKA. Hence, altogether, 73% of cases were newly diagnosed and had DKA at the onset. Remaining cases were already established cases and on insulin months or years before hospitalisation.

Mean duration of symptoms in newly-diagnosed cases was 20 days whereas it was 4 days in children with established diabetes. There was a statistical difference in the duration of symptomatology between the newly-diagnosed cases and already established diabetes with p value less than 0.05.

Presentation on Admission	Frequency	Percentage (%)
Nonspecific complains. Diagnosis picked up after hospitalisation	15	45.5
Newly diagnosed based on the symptoms and referred to the tertiary care unit	9	27.3
Already diagnosed and on insulin therapy	9	27.3

Table 6. Mode of Presentation of DKA

Younger the age group, more the chance of delay in diagnosis and management. Hence, chance of DKA at presentation is more in younger children. DKA in previously diagnosed children were also more in younger age groups.

Age Group	Total Number of Cases	Newly-Diagnosed Cases Presenting as DKA		DKA in Already Diagnosed Cases	
		Frequency	Percentage	Frequency	Percentage
<5 years	1	1	100	0	0
5-10 years	11	8	72.7	3	27.3
>10 years	21	15	45.5	6	55.5

Table 7. Age Group and Presentation of DKA

On examination, 22 children had features of dehydration and 1 had severe dehydration. Neurological status was evaluated by Glasgow Coma Scale. Seven children had GCS between 6 and 10. Four had GCS below 6. Tachypnoea was seen in 26 children (78.8%). Kussmaul respiration was noticed in one child. Abdominal guarding and tenderness were observed in 11 children. None had features of congestive cardiac failure.

Clinical Presentation	Severity	Frequency	Percentage (%)
Hydration status	No dehydration	10	30
	Dehydration	22	66.7
	Severe dehydration	1	3.3
Glasgow coma scale	<6	4	12.1
	6-10	7	21.2
	10-15	26	78.8
Respiratory rate	No tachypnoea	7	21.2
	Tachypnoea	26	78.8
Kussmaul respiration		1	3.3
Abdominal guarding or tenderness		11	33.3
Congestive heart failure		0	0

Table 8. Clinical Presentation of DKA

Many children had plasma glucose level above 300 mg/dL of which some had severe hyperglycaemia (above 400 mg/dL). Those who were diagnosed for the first time had severe hyperglycaemia (mean blood glucose 328 mg/dL) compared to those children who were already on insulin treatment (mean blood glucose 264 mg/dL). There was a statistically significant difference between the mean blood glucose value among the newly-diagnosed cases and already established cases, with a p-value less than 0.05.

Plasma Glucose Level at the Time of Hospitalisation	Frequency	Percentage (%)	Comments
>400 mg/dL	6	18.2	All cases were newly diagnosed
300-400 mg/dL	16	48.5	14 cases were newly diagnosed
200-300 mg/dL	11	33.3	3 cases were newly diagnosed

Table 9. Plasma Glucose Level at the Time of Hospitalisation

Among the biochemical parameters, 27 (81.2%) children had moderate acidosis (pH between 7.1-7.2) and one had severe acidosis (pH below 7.1). Bicarbonate values were below 10 mEq/L in 6 children (18.1%) and between 10-15 mEq/L in 27 children (81.2%). Altogether, 16% were having mild DKA and 81% were having moderate DKA.

24 children (72.7%) had normal serum sodium levels. Remaining children had hyponatraemia. Of the children with hyponatraemia, one boy was admitted with convulsions. High serum potassium levels (>4.5 mEq/L) were seen in 2 children between 3.3-4.5 mEq/L in 25 children and severe hypokalaemia with serum potassium level below 3.3 mEq/L in 6 children. Serum phosphorous levels were low (<3.7 mg/dL) in five patients. 2 children had serum calcium levels below 8.8 mg/dL. Serum magnesium values were less than 2 mg/dL in 27 patients, but none had a value below 1.5 mg/dL.

HbA1C levels were above 10.5% in 6 children. Between 8.6-10.5% in 21 children between 6.5-8.5% in 6 children. There was no statistically significant difference in $HbA1_C$ levels in both newly-diagnosed and already established cases.

Electrolyte Abnormalities	Frequency	Percentage
Hyponatraemia	9	27.3
Hyperkalaemia	2	6.1
Hypokalaemia	6	18.2
Hypophosphatemia	5	15.2
Hypocalcaemia	2	6.1

Table 10. Electrolyte Abnormalities at Presentation of DKA

Among the 9 established diabetic cases, one child was on insulin analogues and the rest were on plain insulin and NPH. Split mix regime was practiced in 4 children and basal bolus regime in 5 children. None of the children were on insulin pump.

Insulin Regime Used	Frequency	Percentage
Plain insulin + NPH - split mix	4	44.4
Plain insulin + NPH - basal bolus	4	44.4
Insulin analogues - basal bolus	1	11.1
Insulin pump	0	0

Table 11. Insulin Regime Used by Established Diabetic Children

Home monitoring using glucometer strips were practiced by all, but none was using at least 4 strips per day. One child was monitoring blood glucose thrice a day and 6 children were doing it twice a day. Financial constraints were the commonest reason for reduction in the home blood sugar monitoring testing.

Frequency of Home Monitoring Per Day	Frequency	Percentage
4 or more	0	0
3	1	11.1
2	6	66.7
1	2	22.2

Table 12. Home Monitoring of Blood Glucose. Number of Blood Sugar Monitoring Per Day (in Established Cases)

Children with clinical features of dehydration (70%) were given normal saline and others were given extra oral fluids. All children were put on intravenous insulin infusion. Children were transferred to intermediary care once general condition is stabilised and after initiating subcutaneous insulin therapy.

Most of the children had good improvement and mean duration of stay in PICU was 4.5 days in newly-diagnosed cases and 2.5 days in children with established diabetes. Mean duration of intravenous fluids was 42 hours in established diabetes and 52 hours in newly-diagnosed cases. Shift to subcutaneous insulin was earlier in established diabetes with mean duration of 36 hours compared to newly-diagnosed children in whom mean duration was 55 hours showing a statistical difference in these 2 groups with p values less than 0.05.

Total duration of hospital stay was also longer in new cases (mean duration-16 days) compared to established cases (mean duration 4 days). This was also statistically significant with p-value less than 0.05.

One child (3%) developed features of cerebral oedema and recovered after mannitol, oxygen and supportive care.

No mortality was observed in the study period.

Following risk factors were observed in the child who developed cerebral oedema.

- Presented with seizure.
- Newly diagnosed with late recognition of diabetes.
- Young age (<5 years).
- Low Glasgow coma scale (<6).

- Severe dehydration (>10%).
- Tachypnoea with Kussmaul respiration.
- High blood glucose level at the time of hospitalisation (>400 mg/dL).
- Severe acidosis (pH <7.1 and HCO3 <10 mEq/L).
- Hyponatraemia (serum sodium 128 mEq/L).
- Hypokalaemia (serum potassium 3.1 mEq/L).

DISCUSSION

Diabetic Ketoacidosis (DKA) is a life-threatening complication of childhood diabetes.[5,6] Quite often, DKA is the first clinical feature in a previously undiagnosed child.[7] Frequency of DKA at the onset range from 15-70% in Europe and north America.[8] Saira Waqar et al[9] noticed that 55.5% all cases of DKA were newly-diagnosed diabetes. Usher-Smith[(10)] reported 13-80% with highest rate in UAE (80%) and Romania (65%) and lowest rate in Hungary (23%) and Canada (18.6%). Lokulo-Sodipe[11] observed DKA as the presenting feature in 25% newly-diagnosed cases in UK. In the present study, 75.8% of the cases were newly diagnosed. All these observations clearly disclose that, in resource poor countries, there is an alarming delay in diagnosing childhood diabetes resulting in late diagnosis and in many cases children even die without being diagnosed as diabetes.[12]

Mean age of diagnosis in the present study was 10.7 years. Study by Azza Ali[13] showed that the mean age was 8.3 years and Lokulo-Sodipe et al[11] 10.3 years.

DKA at the diagnosis were common in younger children less than 5 years, often because the physicians were not thinking about this possibility in their differential diagnosis.[14] The present study also showed that younger the child, more the chance of DKA as the initial presentation. Lokulo-Sodipe[11] observed that DKA at diagnosis was more in children <2 years. In Canada and Europe, hospitalisation rates for DKA in children were 10 per 1,00,000 children over the past 20 years.[15]

Other autoimmune disorders like autoimmune thyroiditis, Addison disease or celiac disease have been reported to precipitate DKA in children who were not diagnosed as having diabetes previously as observed by Szypowska et al.[16] In the present study, one newly-diagnosed adolescent girl was on treatment for autoimmune thyroiditis.

Severity of DKA is directly proportional to the delayed initiation of treatment.[17] This complication often exists in families who do not have ready access to medical care due to lack of facility or due to financial burden.[18] In the present study, one child had cerebral oedema and he was from a tribal colony in Wayanad. Alvi et al showed that Asian children had an eight fold increased chance of DKA compared to non-Asian children.[19]

Most of the studies showed a slight female preponderance.[19,20] The present study showed a marginal male preponderance. Lokulo-Sodipe observed a male preponderance (54%).[11]

The risk of DKA in established type 1 diabetes is 1-10% per patient per year according to recent studies.[21,22] This risk is more in children who omit insulin during illnesses like respiratory tract infections or gastroenteritis.[23] Adolescent girls and children with psychiatric disorders pose a greater risk.[24,25] In the present study, respiratory infection was the commonest precipitating cause of DKA in children with established diabetes (66.7%) followed by drug default (33.3%). Satti Abdurahiman et al[26] observed that infections were the commonest precipitating events (81%) followed by poor compliance and insulin omission (17.9%). Moussa et al[27] showed that 27 to 60% of children presented with DKA after omitting insulin. Mean reason for insulin omission was non-availability in a study by Saira Waqar Lone et al.[9] In Western countries, major cause of drug default was behavioural problems.[28]

Major clinical presentations in the present study were nausea, vomiting, thirst and polyuria. Abdominal pain, often presenting as acute abdomen was a less common problem (36.4%). Breathless and altered sensorium were the other presenting symptoms. This was in accordance with the study by Ganesh R et al, which showed that 80% of the children were presented with vomiting, polyuria and polydipsia.[29] Commonest presenting complaints were respiratory distress (87.1%) and nausea (77.7%) in a study by Saira Waqar Lone et al.[9]

Presenting Complaints	Present Study Number 33		Saira Waqar Lone[9] Number 117		Satti Abdurahiman[26] Number 80	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Tachypnoea	9	27.3	102	87.2	56	71.3
Vomiting	25	75.8	91	77.8	56	71.3
Polyuria	22	66.6	84	71.8	54	67.5
Polydipsia	25	75.8	69	58.9	54	67.5
Abdominal pain	12	36.4	79	67.5	49	61.3
Altered sensorium	6	18.2	59	50.4	2	2.5

Table 13. Presenting Complaints of DKA. Comparison of Various Studies

Mean duration of symptoms before diagnosis varied greatly in newly-diagnosed cases (20 days) from already established diabetes (4 days) in the present study. Most of the newly-diagnosed cases were being treated for abdominal pain or urinary tract infection before the final diagnosis. Wolfsdorf J et al[30] opined that DKA is often missed than found out if the child didn't have any features of diabetes before, especially if he is very young.

Dehydration is a prominent clinical sign in DKA. 5-10% dehydration was seen in 25-75% of cases in various studies. Severe dehydration was rare. Ildiko et al[5] reported that 18 out of 37 children in their study group (48.7%) had

moderate dehydration and one had severe dehydration. In the present study, 66.7% of cases had moderate dehydration and one had severe dehydration, but Satti Abdurahiman[26] reported a high incidence of dehydration with all children having dehydration (100%) and 33 (43.4%) having severe dehydration. Koves IH et al[12] observed that degree of dehydration is more in younger children.

Other major clinical features in the present study were altered sensorium, tachypnoea and abdominal tenderness. Satti Abdurahiman et al[26] observed that tachypnoea (60%), acidotic breathing (60%), drowsiness (25%) and hepatomegaly (15%) as other prominent clinical features. Mahoney CP[31] et al observed that altered sensorium is the most dangerous sign of DKA and blunting of consciousness with seizure is a sign of impending cerebral oedema. This observation was true in the present study also.

In the present study, 16% had mild, 81% of children had moderate and 3% had severe DKA. Studies in west including a Danish study by Fredheim[32] showed a marginal increase in mild DKA (46%) compared to moderate DKA (44%). Studies from middle east showed increased incidence of moderate DKA similar to the present study.[33,34,35,36]

Duration of stay in PICU was longer in newly-diagnosed cases (4.5 days) compared to established cases (2.5 days) in the present study. Total duration of hospital stay was also more in newly-diagnosed cases. Many studies confirmed this finding.[37,38] This is due to more time spent in educating the parents about the illness.[39]

In many resource poor setting, conventional plain insulin and NPH were in use. Insulin analogues were the treatment of choice in developed countries.[40] In many countries, insulin pumps were being used.[41] Conventional plain insulin and NPH were the mainstay (88.9%) in the present study. Many resource rich countries were doing daily 4-6 blood glucose measurements per day using glucometer.[42] Because of the exorbitant cost, most of the children in the present study were doing the test once or twice a day, which was the situation in many Indian studies.[43]

Reported mortality from DKA remains fairly constant as per the studies in developed countries and it varies from 0.15% in USA, 0.18% in Canada and 0.31% in UK.[44,45,46] In places with less developed medical facilities, the risk of death from DKA is greater.[47] It is a depressing fact that many children die before receiving any specific treatment.[48]

Cerebral oedema is the major cause of mortality causing 60-80% of all deaths due to DKA.[49] In the present study, there was no death. One child who developed cerebral oedema was referred late. A study by Gruber et al[50] revealed that children presenting late had more severe acid base abnormalities and more risk of mortality. Nicole Glaser et al[51] noticed that clinically apparent cerebral oedema occurred in 0.9% of hospitalisation for DKA.

SUMMARY AND CONCLUSION

Diabetic ketoacidosis is a life-threatening complication of childhood diabetes. This condition is often the first clinical presentation in a previously undiagnosed case. It can occur in already diagnosed cases also, usually following intercurrent infections or due to omission of insulin. Commonest symptomatology at presentation are nausea, vomiting, polyuria and polydipsia. Later the diagnosis of DKA, more will be the morbidity and mortality. Cerebral oedema is the commonest cause of mortality and poor prognostic factors are low Glasgow coma scale, seizures, severe dehydration, severe acidosis, very high blood glucose levels, severe hyponatraemia and hypokalaemia.

Limitation of This Study

Sample size was small. Since, this is a hospital-based study, it is not a true reflection on the incidence of DKA in the country. Serum ketone measurements were not done in this study due to lack of facility.

ACKNOWLEDGEMENT

The authors thank the children and their parents who gave their consent and wholeheartedly participated in the study.

Contribution

MV has contributed in researching and assimilating the required material. He was involved in writing the manuscript, citation search, literature review and bibliography. KM has helped in collecting the cases and noting down the relevant information. MV will act as a guarantor.

REFERENCES

[1] Dunger DB, Sperling MA, Acerini CL, et al. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. Arch Dis Child 2004;89(2):188-194.
[2] Wolfsdorf J, Craig ME, Daneman D, et al. Diabetic ketoacidosis, ISPAD Clinical Practice Consensus Guidelines 2006–2007. Pediatr Diabetes 2007;8:28-43.
[3] Irani A. Acute and chronic complications of diabetes in childhood. In: Desai MP, Menon PSN, Bhatia V, eds. Pediatric endocrine disorders. 3rd edn. Hyderabad: University Press 2014:344-354.
[4] Bajpai A. Diabetic ketoacidosis. In: Irani AJ, Menon PSN, Bhatia V, eds. Type 1 diabetes mellitus in children and adolescents in India. Clinical Practice Guidelines 2011. 1st edn. Lucknow: ISPAE 2011:68-82.
[5] Irani A. Principles and goals of management. In: Irani AJ, Menon PSN, Bhatia V, eds. Type 1 diabetes mellitus in children and adolescents in India. Clinical Practice Guidelines 2011. 1st edn. Lucknow: ISPAE 2011:12-17.
[6] Rosenbloom AL. Hyperglycemic crises and their complications in children. J Pediatr Endocrinol Metab 2007;20(1):5-18.
[7] Craig ME, Hattersley A, Donaghue K, et al. ISPAD Clinical Practice Consensus Guidelines 2006-2007. Definition, epidemiology and classification. Pediatr Diabetes 2006;7(6):343-351.
[8] Marcin JP, Glaser N, Barnett P, et al. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. J Pediatr 2002;141(6):793-797.
[9] Lone SW, Siddiqui EU, Muhammed F, et al. Frequency,

clinical characteristics and outcome of diabetic ketoacidosis in children with type 1 diabetes at a tertiary care hospital. J Pak Med Assoc 2010;60(9):725-729.
[10] Usher-Smith JA, Thompson M, Ercole A, et al. Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: a systematic review. Diabetologia 2012;55(11):2878-2894.
[11] Lokulo-Sodipe K, Moon RJ, Edge JA, et al. Identifying targets to reduce the incidence of diabetic ketoacidosis at diagnosis of type 1 diabetes in the UK. Arch Dis Child 2014;99(5):438-442.
[12] Koves IH, Neutze J, Donath S, et al. The accuracy of clinical assessment of dehydration during diabetic ketoacidosis in childhood. Diabetes Care 2004;27(10):2485-2485-7.
[13] Shaltout AA, Channanath AM, Thanaraj TA, et al. Ketoacidosis at first presentation of type 1 diabetes mellitus among children: a study from Kuwait. Sci Rep 2016;6:27519.
[14] Lévy-Marchal C, Patterson CC, Green A, et al. Geographical variation of presentation at diagnosis of type I diabetes in children: the EURODIAB study. European and Dibetes. Diabetologia 2001;44(Suppl 3):B75-80.
[15] Lewis KR, Clark C, Velarde MC. Socioeconomic factors associated with pediatric diabetic ketoacidosis admissions in southern west Virginia. Clin Endocrinol 2014;81(2):218-221.
[16] Szypowska A, Skórka A. The risk factors of ketoacidosis in children with newly diagnosed type 1 diabetes mellitus. Pediatr Diabetes 2011;12(4 Pt 1):302-306.
[17] Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. Diabetes Care 1990;13(1):22-33.
[18] Ahmed AM, Al-Maghamsi M, Al-Harbi AM, et al. Reduced frequency and severity of ketoacidosis at diagnosis of childhood type 1 diabetes in northwest Saudi Arabia. J Pediatr Endocrinol Metab 2016;29(3):259-64.
[19] DIAMOND Project Group. Incidence and trends of childhood type 1 diabetes worldwide 1990-1999. Diabet Med J Br Diabet Assoc 2006;23(8):857-866.
[20] Shaltout AA, Qabazard MA, Abdella NA, et al. High incidence of childhood-onset IDDM in Kuwait. Kuwait Study Group of Diabetes in Childhood. Diabetes Care 1995;18(7):923-927.
[21] Jefferies C, Cutfield SW, Derraik JG, et al. 15-year incidence of diabetic ketoacidosis at onset of type 1 diabetes in children from a regional setting (Auckland, New Zealand). Sci Rep 2015;5:10358.
[22] Shaltout AA, Moussa MA, Qabazard M, et al. Further evidence for the rising incidence of childhood type 1 diabetes in Kuwait. Diabet Med 2002;19(6):522-525.
[23] Gabir MM, Hanson RL, Dabelea D, et al. The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. Diabetes Care 2000;23(8):1108-1112.
[24] al Khawari M, Shaltout A, Qabazard M, et al. Incidence and severity of ketoacidosis in childhood-onset diabetes in Kuwait. Kuwait Diabetes Study Group. Diabetes Res Clin Pract 1997;35(3-2):123-128.
[25] Abdul-Rasoul M, Al-Mahdi M, Al-Qattan H, et al. Ketoacidosis at presentation of type 1 diabetes in children in Kuwait: frequency and clinical characteristics. Pediatr Diabetes 2010;11(5):351-356.
[26] Satti SA, Saadeldin IY, Dammas AS, et al. Diabetic ketoacidosis in children admitted to pediatric intensive care unit of King Fahad hospital, Al-Baha, Saudi Arabia: precipitating factors, epidemiological parameters and clinical presentation. Sudan J Paediatr 2013;13(2):24-30.
[27] Moussa MA, Alsaeid M, Abdella N, et al. Prevalence of type 1 diabetes among 6- to 18-year-old Kuwaiti children. Med Princ Pract 2005;14(2):87-91.
[28] Vijayakumar M. Psychological aspects. In: Irani A, Menon PSN, Bhatia V, eds. Type 1 diabetes mellitus in children and adolescents in India. Clinical Practice Guidelines 2011. 1st edn. Lucknow: ISPAE 2011:88-95.
[29] Ganesh R, Arvindkumar R, Vasanthi T. Clinical profile and outcome of diabetic ketoacidosis in children. Natl Med J India 2009;22(1):18-19.
[30] Wolfsdorf J, Glaser N, Sperling MA. Diabetic ketoacidosis in infants, children and adolescents: a consensus statement from the American Diabetes Association. Diabetes Care 2006;29(5):1150-1159.
[31] Mahoney CP, Vlcek BW, DelAguila M. Risk factors for developing brain herniation during diabetic ketoacidosis. Pediatr Neurol 1999;21(4):721-727.
[32] Fredheim S, Johannesen J, Johansen A, et al. Diabetic ketoacidosis at the onset of type 1 diabetes is associated with future HbA1c levels. Diabetologia 2013;56(5):995-1003.
[33] Onyiriuka AN, Ifebi E. Ketoacidosis at diagnosis of type 1 diabetes in children and adolescents: frequency and clinical characteristics. J Diab Metabol Disorder 2013;12(1):47.
[34] Habib HS. Frequency and clinical characteristics of ketoacidosis at onset of childhood type 1 diabetes mellitus in northwest Saudi Arabia. Saudi Med J 2005;26(12):1936-1939.
[35] Abduljabbar MA, Aljubeh JM, Amalraj A, et al. Incidence trends of childhood type 1 diabetes in eastern Saudi Arabia. Saudi Med J 2010;31(4):413-418.
[36] Soliman AT, al Salmi I, Asfour M. Mode of presentation and progress of childhood diabetes mellitus in the Sultanate of Oman. J Trop Pediatr 1997;43(3):128-132.
[37] Schober E, Rami-Merhar B, Waldhör T, et al. Diabetic ketoacidosis at diagnosis in Austrian children in 1989-2008: a population-based analysis. Diabetologia 2010;53(6):1057-1061.

[38] Neu A, Hofer SE, Karges B, et al. Ketoacidosis at diabetes onset is still frequent in children and adolescents: a multicenter analysis of 14,644 patients from 106 nations. Diabetes Care 2009;32(9):1647-1648.
[39] Dabelea D, Rewers A, Stafford JM, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for Diabetes in Youth Study. Pediatrics 2014;133(4):e938-e945.
[40] Karges B, Kapellen T, Neu A, et al. Long-acting insulin analogs and the risk of diabetic ketoacidosis in children and adolescents with type 1 diabetes: a prospective study of 10,682 patients from 271 institutions. Diabetes Care 2010;33(5):1031-1033.
[41] Irigoyen OM, Cuartero GB, Castellanos BR, et al. Ketoacidosis at onset of type 1 diabetes mellitus in pediatric age in Spain and review of the literature. Pediatr Endocrinol Rev 2012;9(3):669-671.
[42] Choleau C, Maitre J, Filipovic Pierucci A, et al. Ketoacidosis at diagnosis of type 1 diabetes in French children and adolescents. Diabetes Metab 2014;40(2):137-142.
[43] Vijayakumar M. Home monitoring. In: Irani A, Menon PSN, Bhatia V, eds. Type 1 diabetes mellitus in children and adolescents in India. Clinical Practice Guidelines 2011. 1st edn. Lucknow: ISPAE 2011:39-48.
[44] Pediatric Diabetes Consortium. The pediatric diabetes consortium: improving care of children with type 1 diabetes through collaborative research. Diabetes Technol Ther 2010;12(9):685-688.
[45] Hekkala A, Knip M, Veijola R. Ketoacidosis at diagnosis of type 1 diabetes in children in northern Finland: temporal changes over 20 years. Diab Care 2007;30(4):861-866.
[46] Edge JA, Hawkins MM, Winter DL, et al. The risk and outcome of cerebral edema developing during diabetic ketoacidosis. Arch Dis Child 2001;85(1):16-22.
[47] Vanelli M, Chiari G, Ghizzoni L, et al. Effectiveness of a prevention program for diabetic ketoacidosis in children. An 8-year study in schools and private practices. Diabetes Care 1999;22(1):7-9.
[48] Vanelli M, Chiari G, Lacava S, et al. Campaign for diabetic ketoacidosis prevention still effective 8 years later. Diabetes Care 2007;30(4):e12.
[49] Lansdown AJ, Barton J, Warner J, et al. Prevalence of ketoacidosis at diagnosis of childhood onset Type 1 diabetes in Wales from 1991 to 2009 and effect of a publicity campaign. Diabet Med 2012;29(12):1506-1509.
[50] Gruber N, Reichman B, Lerner-Geva L, et al. Increased risk of severe diabetic ketoacidosis among Jewish ultra-orthodox children. Acta Diabetol 2015;52(2):365-371.
[51] Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. N Engl J Med 2001;344(4):264-269.