ANALYSIS

22(89), January - February, 2018

ISSN
2321–7359
EISSN
2321–7367

Medical Science

Clinical, demographic, and biochemical profile of pediatric diabetic ketoacidosis patients in King Khalid Civilian Hospital, Tabuk

Mohammad Zubair[1]☼, Nagwa Gad Mohamed[2], Marai Al Amri[3], Shamina Begum[1], Anwar Al-Balawy[4], Rana Sokair[4], Ibrahim Ajwa[4]

1.Department of Medical Microbiology,
Faculty of Medicine,
University of Tabuk, Tabuk,
Kingdom of Saudi Arabia

2.Department of Pediatrics,
Faculty of Medicine,
University of Tabuk, Tabuk,
Kingdom of Saudi Arabia

3.Department of Surgery,
Faculty of Medicine,
University of Tabuk, Tabuk,
Kingdom of Saudi Arabia

4.MBBS Students, 6th Year,
Faculty of Medicine,
University of Tabuk, Tabuk,
Kingdom of Saudi Arabia

☼**Corresponding author:**
Dr. Mohammad Zubair,
Email: mohammad_zubair@yahoo.co.in

Article History
Received: 05 October 2017
Accepted: 30 November 2017
Published: January-February 2018

ANALYSIS ARTICLE

Citation

Mohammad Zubair, Nagwa Gad Mohamed, Marai Al Amri, Shamina Begum, Anwar Al-Balawy, Rana Sokair, Ibrahim Ajwa. Clinical, demographic, and biochemical profile of pediatric diabetic ketoacidosis patients in King Khalid Civilian Hospital, Tabuk. *Medical Science*, 2018, 22(89), 70-77

ABSTRACT

Objective: The objective of this study was to assess pediatric patients presenting with DKA regarding aspects of demographics, presentation, findings, and management and probable risk factors associated with DKA in Tabuk, Kingdom of Saudi Arabia.

Methods: A retrospective descriptive study with review of medical records of patients admitted to King Khalid Civilian Hospital from 2013 to 2016. A total of 98 patients were included and divided into two groups with age matched (±3 years): Group "A=49: previously diagnosed T1DM, Group B=49: newly diagnosed T1DM. The following data were analyzed: age, sex, weight loss, basic signs & symptoms and severity on admission, blood gas, blood glucose, glycated hemoglobin, and risk factors. The insulin dosage, time of continuous insulin use, volume administered in the expansion phase and in the first 24 h, length of stay, and complications such as electrolyte disturbances, hypoglycemia and cerebral edema were compared between the two groups.

Results: Patients in group B were older at admission, with mean-age of 9.5 years, reported more nausea or vomiting, polydipsia, fatigue, and polyuria, and showed more weight loss ($p < 0.01$). This study also observed a higher blood glucose (mean) 438±86.2mg/dl and mean HbA1c of 10.3±2.3 and longer hospital stay of 32±3.4 days in group B.

Conclusions: Significant differences in severity between groups were observed. The study showed that newly diagnosed T1DM children were older at the time admission, high blood glucose level and had longer hospital stay.

Key words: Diabetic ketoacidosis, children, new vs old T1DM, Tabuk region

1. INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases in nearly all countries, and continues to increase in numbers and significance, as economic development and urbanization lead to changing lifestyles characterized by reduced physical activity, and increased obesity. Estimates of the current and future burden of diabetes are important in order to allocate community and health resources, to emphasize the role of lifestyle, and encourage measures to counteract trends for increasing prevalence[1].Saudi Arabia (raw diabetes prevalence of 17.6%) and Kuwait (14.3%). Due to their different population structures, these countries both have an age-adjusted comparative prevalence of 20.0%. The countries with the largest number of adults with diabetes are Egypt (7.8 [3.8-9.0] million), Pakistan (7.0 [5.1-10.0] million) and Iran (4.6 [3.6-6.3] million). A further 30.2 million people in the region, or 7.8% of the adult population, are estimated to have impaired glucose tolerance and are therefore at high risk of developing diabetes. It is estimated that the number of people with diabetes in the region will double to 72.1 million by 2040.

Diabetic ketoacidosis (DKA) is one of the major complications in patients with type 1 diabetes mellitus (T1DM). DKA is one of the serious complications of diabetes in the pediatric population[2] and its prevalence increases by an annual rate of 3% worldwide[3]. Kuwait and Saudi Arabia also have some of the world's highest annual incidence rates of T1DM in children, with 37.1 and 31.4 new cases per 100,000 populations, respectively. Saudi Arabia has 16,100 children with T1DM, by far the highest number in the region, and over a quarter of the region's total of 60,700[4].DKA treatment has been widely studied and described in the literature; however,

there are few studies comparing the clinical characteristics and outcomes between patients admitted for DKA with previously diagnosed T1DM and those with no prior diagnosis of T1DM. The objective of this study was to assess pediatric patients presenting with DKA regarding aspects of demographics, presentation, findings, and management in Tabuk, Kingdom of Saudi Arabia (KSA).

2. METHODOLOGY

This was a retrospective hospital based study of 98 pediatric patients. Categorized into two groups, Group A: n=49, previously diagnosed T1DM children and Group B, n=49, newly diagnosed cased of T1DMadmitted in the King Khalid Civilian Hospital, Tabuk, Kingdom of Saudi Arabia during the period 1st of February 2013 to 1st of February 2016. All patients gave informed consent to take part in this research, and subject in groups A were matched for age (±3 years) in group B. Patients with inflammatory or infectious diseases, autoimmune and rheumatic diseases, cancer, haematological diseases, as well as those who were under treatment with anti-inflammatory drugs, were excluded. To be very sure, then verified the completeness of the charts. Exclusion criteria will include patients with incomplete documentation of DKA episode despite the system labeling them as DKA.

Briefly, detailed history and physical examination was carried out for every subject. Age, sex, anthropometric measurements (body mass index), glycemic control prior to-and during the hospital stay, compliance to treatment, precipitating factor to DKA, clinical presentation of the child with DKA as vomiting, abdominal pain, disturbed level of consciousness, and biochemical findings as blood glucose, ABGs, serum electrolytes were evaluated. Inclusion criteria will include patients admitted due to DKA, and were less than 15 years old. To be accurate in enrollment, we verify that admission criteria were consistent with DKA definition by the International Society for Pediatric and Adolescent Diabetes[5].

Statistical methodology

The results were analyzed using the Sigma Plot Version 11.1 program. The Shapiro–Wilk test was used to evaluate normality of variables. The differences between the groups were calculated with Student "t" or the nonparametric Mann–Whitney U tests. Results are expressed as mean (95% CI) for continuous variables and percentages for categorical data, with $p < 0.05$ considered significant. Risk for DKA was also estimated by odds ratios (OR) and risk ratio (RR) with 95% confidence intervals (CIs) that independently predict the DKA factor independent of other cofactors.

3. RESULTS

A total of 98 admissions were analyzed, corresponding to 49 newly diagnosed T1DM (group B), 69.3% were females. Baseline characteristic of Group A (previously diagnosed as T1DN) in comparison with group B are given in Table 1. In group A, 59.2% of subjects were male, while 30.6% of subjects in group B were male. It was observed that children in group B were older at the time of hospital admission and more frequently had polydipsia, polyuria, weight-loss, polyphagia, blurring of vision, experience of fatigue and high blood glucose levels.

When the groups were compared, no statistically significant difference were found with regard to insulin dose and time of continuous insulin use, intravenous volume administered in the expansion phase and in the first 24 h (Table 1).The prevalence of electrolyte disturbances was similar between the two groups; however, when analyzed separately, the mean pCO2 (mmHg) were 20.1±8.8 and 18.4±8.2 in group A and B respectively. Patients who did not know they were diabetics also had greater length of hospital stay (32±3.4 days) compared to group A (24±5.6 days). In the severity index scale of DKA, 55.0% of the subjects in group B had severe grade of DKA followed by 36.7% and 12.2% had moderate and mild status respectively. Whereas, in group A, majority (55.1) had moderate DKA followed by severe grade (28.5%) and mild (16.3%).

Table 1 Baseline characteristics of study group patients

	Group A, n=49	**Group B, n=49**	
Characteristics	**Previous diagnosed T1DM**	**Newly diagnosed T1DM**	***P value***
Age at presentation	8.2±4.0	9.5±4.3	0.42
Sex			
Male	29(59.2)	15(30.6)	**0.04**
Female	20(40.8)	34(69.3)	
Location of Admission			

ER only	4(8.2)	12(24.4)	0.65
ICU	30(61.2)	9(18.3)	0.23
Diabetic Ward	15(30.6)	28(57.1)	**0.05**
Precipitation factors			
Unknown	37(75.5)	24(48.9)	0.4
Missed insulin dose	7(14.3)	19(38.7)	**0.04**
Fasting ramadan	1(2.0)	12(24.4)	**0.05**
Infection (sore throat)	1(2.0)	9(18.3)	0.45
UTI	2(4.1)	22(44.8)	**0.04**
Hospital Stay	24±5.6	32±3.4	**<0.05**
Sign & Symptoms			
Nausea & Vomiting	12(24.5)	27(55.1)	**0.001**
Abdominal Pain	15(30.6)	19(38.7)	0.78
Polydipsia	12(24.5)	26(53.0)	**0.05**
Polyphagia	9(18.3)	16(32.6)	0.06
Polyurea	13(26.5)	33(67.34)	**0.001**
Weight Loss	4(8.2)	21(42.8)	**0.001**
Fever	5(10.2)	8(16.32)	0.56
Drowsiness	4(8.2)	9(18.3)	0.21
Blurring of vision	8(16.3)	18(36.7)	0.34
Skin infection	21(42.8)	22(44.8)	0.11
Acidosis	6(10.2)	9(18.3)	0.17
Tachypnea	6(10.2)	13(26.5)	0.05
Acetone odour	4(8.2)	17(34.6)	0.04
Fatigue	2(4.1)	36(79.5)	0.04
Severity n(%)			
Mild	8(16.3)	6(12.2)	0.12
Moderate	27(55.10)	18(36.7)	**0.05**
Severe	14(28.5)	25(51.0)	**0.001**
IV Volume (IQR)			
Expansion, mL/kg	43.2±17.6	59.7±22.8	0.72
First 24h, mL/m^2	3698±1467	3779±1618	0.69
Gasometry at admission			
pH	7.11±0.14	7.01±0.9	**0.05**
Bicarbonates, mmol/mL	8.3±3.8	7.3±1.98	0.72
pCO_2 mmHg	20.1±8.8	18.4±8.2	0.69
Glycemia at admission mg/dL	403±89.0	438±86.2	**0.001**
HbA1c (%)	9.7±1.2	10.3±2.3	**0.04**
Serum osmolality , mOsm/L	322±15.8	304±11.7	**0.001**
Hypoglycemia	6(12.24)	15(30.6)	**0.05**
Insulin therapy			
Insulin Gumalog 6-8-6	28(57.1)	22(44.8)	0.08
Mixtured	2(4.1)	3(6.1)	
Lantous	2(4.1)	0(0)	
Regular	5(10.2)	1(2.0)	

Table 2 Odds Ratio (OR) and Risk Ration (RR) analysis in predicting the DKA

Characteristics	OR(95% CI)	RR(95% CI)	p-value	Chi-sq	p-value
Age <7 years	3.69(1.45-9.49)	1.71(1.17-2.46)	0.004	8.219	0.004
Sex-Female	0.304(0.12-0.75)	0.54(0.32-0.86)	0.008	6.97	0.008
Location of Admission					
ER only	3.46(0.97-14.78)	1.66(0.98-2.18)	0.053	3.66	0.056
ICU	0.14(0.015-0.39)	0.34(0.17-0.61)	0.0002	17.64	<0.001
Diabetic Ward	3.02(1.21-7.59)	1.70(1.10-2.57)	0.014	5.97	0.014
Precipitation factors					
Unknown	0.31(0.12-0.79)	0.58(0.40-0.89)	0.011	6.25	0.012
Missed insulin dose	3.80(1.29-11.50)	1.75(1.13-2.37)	0.011	6.33	0.011
Fasting Ramadan	15.56(1.94-334.9)	2.72(1.33-2.34)	0.001	8.87	0.002
UTI	44.23(8.79-300.0)	16.0(4.0-63.13)	6.20	37.87	0.000
Sign & Symptoms					
Nausea & Vomiting	3.78(1.47-9.85)	2.25(1.26-4.17)	0.004	8.34	0.04
Abdominal Pain	1.43(0.57-3.60)	1.26(0.69-2.34)	0.52	0.40	0.52
Polydipsia	3.01(1.16-7.91)	1.94(1.09-3.62)	0.029	5.36	0.02
Polyphagia	2.15(0.77-6.12)	1.77(0.82-4.03)	0.163	1.93	0.164
Polyurea	5.71(2.20-15.11)	2.53(1.52-4.32)	0.003	14.79	0.0005
Weight Loss	8.43(2.38-32.67)	5.25(1.92-17.39)	0.001	13.75	0.0002
Fever	1.71(0.45-6.66)	1.60(0.50-5.39)	0.55	0.325	0.554
Drowsiness	2.53(0.64-10.70)	2.25(0.68-8.40)	0.23	1.41	0.233
Blurring of vision	2.97(1.04-8.65)	2.25(1.03-5.24)	0.038	4.23	0.03
Dizziness					
Acidosis	1.61(0.52-4.93)	1.5(0.57-3.89)	0.57	0.37	0.57
Tachypnea	2.58(0.89-7.49)	2.16(0.89-5.23)	0.12	2.35	0.12
Acetone odour	5.97(1.83-19.44)	4.25(1.54-11.72)	0.002	8.73	0.003
Fatigue	65.07(13.80-306.8)	18.0(4.58-70.6)	2.89	46.81	<0.0001
Severity of DKA n(%)					
Mild	0.71(0.22-2.33)	0.75(0.28-2.0)	0.77	0.08	0.77
Moderate	0.47(0.21-1.06)	0.66(0.42-1.04)	0.104	2.63	0.104
Severe	2.60(1.12-6.00)	1.78(1.06-3.00)	0.038	4.26	0.039
Glycemia>200 mg/dL	2.60(1.04-6.56)	1.78(1.02-3.19)	0.038	4.25	0.039
HbA1c >6.9 %	5.80(2.22-15.47)	2.17(1.42-3.26)	0.000	14.89	0.000
Insulin therapy					
Insulin Gumalog 6-8-6	0.67(0.27-1.35)	0.78(0.53-1.16)	0.31	1.02	0.312
Mixtured	1.53(0.24-9.60)	1.50(0.26-8.58)	-	-	-
Lantous	-	-	-	-	-
Regular	0.18(0.02-1.63)	0.2(0.02-1.65)	0.204	-	-

Univariate analysis

On Univariate analysis, the factors which showed a positive association in predicting the DKA were poor glycemic control (>200 mg/dl) [OR 2.60, RR 1.78], HbA1c (>6.9%) [OR 5.80, RR 2.17], weight loss [OR 8.43, RR 5.25], polydipsia [OR 3.01, RR 1.94], polyphagia [OR 2.15, RR 1.77], polyurea [OR 5.71, RR 2.53], acidosis [OR 1.61, RR 1.501], tachypnea [OR 2.58, RR 2.16], acetone odor [OR 5.97, RR 4.25], fatigueness [OR 65.07, RR 18.0] (Table 2).

4. DISCUSSION

Reports of DKA at presentation of T1DM from the Arab countries are scarce and are based on small sized data sets[6]. In this study, our results were based on the data collection of 98 children from Tabuk, Kingdom of Saudi Arabia. The world-wide incidence of

T1DM ranges from 0.1 to 36.8 cases per 100,000 inhabitants per year and, despite the educational programs run by the different governments and the numerous medical studies conducted, the DKA mortality rate remained around 1-2% since 1970[7]. The present study included 98 admissions, of these, 50% had a previous diagnosis of T1DM. The mean age of admission was 8.2±4.0 years in group A and 9.5±4.3 years in group B, which demonstrates the importance of parental involvement in better treatment of their children and in educational status of parents regarding this disease. As for the symptoms at admission, the most frequent were nausea and vomiting. Patients who did not know they were diabetics more often had records in their medical files of the classic symptoms of T1DM, such as polydipsia, polyphagia, fatigue, acidosis, tachypnea, acetone odour, polyuria, and weight loss. These findings were not observed in otherstudies[8,9]. This may have occurred because the patients who were already using insulin had more acute clinical decompensation, due to the inappropriate use of medication or due to the more objective medical approach when a diagnosis ofT1DM had already been established. The 0.1 IU/kg/min was most commonly use dose of continuous insulin, the same were recommended in the last consensus on DKA treatment[8, 10-12]. In another study the 0.05 IU/kg/h dose were as effective as 0.1 IU/kg/h in the treatment of 93 DKA episodes (at least in the initial 6 h of treatment)[13]. Another study suggest that a treatment with lower dose of insulin is safe, promoting safe gradual reduction in serum osmolality and which in later state will reduce the risk of cerebral edema[14]. Another study from Campinas, state of Sao Paulo, Brazil, showed that the laboratory abnormalities was directly proportional to time of continuous insulin use and, thus, to DKA severity[7]. The time of continuous insulin use in the present study was slightly longer in patients who had no diagnosis of T1DM prior to the DKA episode, but there was no statistically significant difference. Another study comparing 117 hospitalized DKA children from Pakistan showed longer continuous time of insulin use in patients that had no diagnosis of T1DM at admission, whereas, categorized as more severe case[15].

When abnormalities as disturbances in electrolyte level were evaluated, the groups showed no difference. There were no difference between groups when hypokalemia was evaluated as a complication of treatment in DKA[15], while in another study, most of the children had DKA as the first manifestation of T1DM, during treatment, hypokalemia was detected in 41% of cases[16]. The children there was 3-6 mmol/kg of potassium were the total body deficit DKA[10] and potassium is lost as a result of vomiting, osmotic diuresis, hyperaldosteronism and many hindered mechanism furthermore by volume depletion, which also promotes urinary excretion of potassium. Later on insulin administration and acidosis correction causes potassium diverted to the intracellular environment which further deplete the level of serum, which may predispose to arrhythmias[10, 17].

Data from 24 centers in Europe, the EURODIAB study, the incidence of DKA shows large variations in children across Europe, and a frequency of 33% and 9% as mild and severe DKA was reported respectively[18]. In our study, the frequency of severe DKA (28.5% and 51% in group Aand B respectively) is significantly much higher than in Spain (17.8%)[19] or France (14.8%)[20], but was much higher than that reported from Denmark (1.7%)[21].

In the present study, the frequency of severity category of DKA was notably higher in both groups. The similar incidence of DKA (34% and 54% in children aged 0–14 and < 3 years respectively) were reported by US Pediatric Diabetes Consortium[22].Another study from Northern Finland, showed 39.1% of children aged <2 years during 1992-2001[23]. It was also observed that not only the incidence of ketoacidosis was high in children less than 2 years of age but also the proportion of children from this age group with severe ketoacidosis is high. As HbA1c represents the average blood glucose levels in the past three months, the shorter duration of symptoms in children less than 2 years compared to children of 2–14 years argues for lower HbA1c levels. Hypoglycemia as a complication of treatment occurred in 30.6% & 12.2% of hospitalizations of group B and group A respectively, which is slightly higher compared to other studies[16, 24]. When the two groups were compared, children in group B had more hypoglycemia, and variations in glucose input used in this service can probably explain this fact. Regarding length of hospital stay, group B had longer hospital stay compared with group A, and this finding is similar to the reports published from Pakistan[15]. This fact can be best explained as these patients (group B) often require more time for insulin dose adjustment and for the family to get used to the treatment whereas patients is group A were already adjusted with the insulin dose and its consequences. In case of severity of disease, large no of patients were in moderate in group A whereas in group B in severe category, these factors do not seem to have influenced the length of hospital stay.

In our study, the factors which were significantly associated with the risk of DKA onset were age<7years, UTI, weight loss, polydipsia and polyuria and the most important were poor glycemic control. Similar results were also reported include younger age at onset of T1DM, ethnicity, and subscription to healthcare private insurance[6, 25-26]. Furthermore, low socioeconomic status and low parental education have been found associated with increased risk of DKA[26, 27]. T1DM is a major risk factor for diabetic ketoacidosis across the world and is prevalent in Kuwaiti children[28]. In our study, infection, particularly urinary tract infection (UTI), is known as the most common precipitating cause for DKA. UTI has been shown to be common in infants and children[29]. Pneumonia account for the majority of infections that act as risk factors for DKA. Up to 40% of clinical infections are caused by a pneumococcal strain that is resistant to at least one drug, and 15% are due to strains resistant to three or more drugs[30]. In some studies, the prevalence of

penicillin-resistant *S.pneumoniae* (PRSP) in the pediatric and elderly populations exceeds 60%; almost half of these strains are multidrug resistant[31, 32].

As this study was based on chart review, the data may have been lost, because clinical symptoms are frequently not recorded in the medical files. There was no statistically significant difference in the incidence of cerebral edema between the two groups, which was expected, since ketoacidosis severity at admission and the amount of administered volume were similar, and for the patient admitted in ICU, protocols for the treatment of DKA cases were not followed, which makes the management heterogeneous, possibly influencing the observed clinical outcomes.

It was also reported that the occurrence of DKA is substantially high worldwide, yet the opportunities to prevent DKA via awareness in public on the symptoms in order to diagnose the early stage and detection of metabolic deterioration before DKA develops[33]. This has been demonstrated in countries like Saudi Arabia as well. For example, a study from Saudi Arabia[34] indicated that the awareness campaigns reduce the DKA rate to 39% from 48% from 2010 to 2014 and 15.8% had severe DKA compared to 26.1% in 2005–2010 ($p < 0.01$). Studies in Parma Italy also have shown the similar results that it is possible to achieve a marked decrease in the frequency of DKA through educational campaigns that focused on one of the earliest symptom of diabetes namely, nocturnal enuresis in a dry child, and targeted schools and primary healthcarephysicians[35,36]. During the 8 years of public awareness regarding DKA, the cumulative frequency were dropped to 12.5% from 78% ina age group of 6–10 years old[35], which demonstrate a great success for the cause.

5. LIMITATIONS OF THE STUDY

First, we have not collected information on family income and parental education; secondly the study lacks information on duration of symptoms or degree of weight loss at presentation. A third limitation is that data was not recorded on the number of visits to the emergency room or primary health care centers before presentation to assess the causes of delay in diagnosis.

6. CONCLUSION

It was concluded that a significant differences were observed in severity between the group A and group B. Patients in group B were older at the time of admission, had greater length of hospital stay and had severe hyperglycemia. Further studies are needed to perform a better epidemiological assessment of these groups with larger sample size to minimize the statistical error.

CONFLICT OF INTEREST

No conflict of Interest between the authors regarding manuscript, financial and ethical issues.

REFERENCE

1. Whiting DR, Guariguata L, Clara Weil, Jonathan Shaw. Global estimates of the prevalence of diabetes for 2011 and 2030. *Diab Res Clin Pract.,* 2011; 94: 311-321.
2. Rewers A, Chase HP, Mackenzie T, Walravens P, Roback M, Rewers M, et al. Predictors of acute complications in children with type 1 diabetes. *JAMA,* 2002; 287: 2511–2518.
3. Newhook LA, Curtis J, Hagerty D, Grant M, Paterson AD, Crummel C, et al. High incidence of childhood type 1 diabetes in the Avalon Peninsula, Newfoundland, Canada. *Diabetes Care,* 2004; 27: 885–888.
4. IDF Diabetes Atlas 2015 http://www.diabetesatlas.org/resources/2015-atlas.html#tab2.
5. Cengiz E, Connor CG, Ruedy KJ, Beck RW, Kollman C, Klingensmith GJ, et al. Pediatric diabetes consortium T1D New Onset (NeOn) study: clinical outcomes during the first year following diagnosis. *Pediatr Diabetes,* 2014;15:287-293.
6. Usher-Smith JA, Thompson M, Ercole A, Walter FM. Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: a systematic review. *Diabetologia,* 2012; 55: 2878–2894.
7. Castro L, Morcillo AM, Guerra-Júnior G. Diabetic ketoacidosis in children: treatment profile at a university hospital. *Rev Assoc Med Bras.,* 2008;54:548-553.
8. Wolfsdorf JI, Allgrove J, Craig ME, Edge J, Glaser N, Jain V, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Diabeticketoacidosis and hyperglycemic hyperosmolar state. *Pediatr Diabetes,* 2014; 15 Suppl 20:154-179.
9. Calagua-Quispe M, Falen-Boggio J, Villarreal UN, Del Águila-Villar C, Rojas-Gabulli MI. Clinical and biochemical characteristics of type 2 diabetes mellitus (DMt2) at InstitutoNacional de Salud del Niño. *An Fac Med.,* 2012;73:141-146.
10. 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: 1150-1159.

11. Olivieri L, Chasm R. Diabetic ketoacidosis in the pediatric emergency department. *Emerg Med Clin North Am.,* 2013; 31: 755-773.
12. Steel ST, Shane M. Paediatric diabetic ketoacidosis. *BJA Educ.,* 2009; 9: 194-199.
13. Puttha R, Cooke D, Subbarayan A, Odeca E, Ariyawansa I, Bone M, et al. Low dose (0.05 units/kg/h) is comparable with standard dose (0.1 units/kg/h) intravenous insulin infusion for the initial treatment of diabetic ketoacidosis in children with type 1 diabetes--an observational study. *Pediatr Diabetes,* 2016; 11: 12-17.
14. Al Hanshi S, Shann F. Insulin infused at 0.05 versus 0.1units/kg/hr in children admitted to intensive care with diabetic ketoacidosis. *Pediatr Crit Care Med.,* 2011; 12:137-140.
15. Lone SW, Siddiqui EU, Muhammed F, Atta I, Ibrahim MN, Raza J. 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: 725-729.
16. Jayashree M, Singhi S. Diabetic ketoacidosis: predictors of out-come in a pediatric intensive care unit of a developing country. *PediatrCrit Care Med.,* 2004; 5: 427-433.
17. Piva JP, Garcia PC. Medicinaintensivaempediatria. 2nd ed. Riode Janeiro: Revinter; 2014.
18. Lévy-Marchal C, Patterson CC, Green A, EURODIAB ACE Study Group. Europe and Diabetes. Geographical variation of presentation at diagnosis of type I diabetes in children: the EURODIAB study. *Diabetologia,* 2001; 44: Suppl 3, B75–B80.
19. OyarzaballIrigoyen M, GarcíaCuartero B, Barrio Castellanos R, Torres Lacruz M, Gómez Gila AL, González Casado I, *et al.* Ketoacidosis at onset of type 1 diabetes mellitus in pediatric age in Spain and review of the literature. *Pediatr Endocrinol Rev Mar* 2012; 9: 669-761.
20. Choleau C, Maitre J, Pierucci FA, Elie C, Barat P, Bertrand AM,*et al.* Ketoacidosis at diagnosis of type 1 diabetes in French children and adolescents. *Diabetes Metab.,* 2014; 40, 137-142.
21. Fredheim S, Johannesen J, Johansen A, Lyngsøe L, Rida H, Andersen ML, *et al.* Diabetic ketoacidosis at the onset of type 1 diabetes is associated with future HbA1c levels. *Diabetologia,* 2013; 56:995-1003.
22. Pediatric Diabetes Consortium. The pediatric diabetes consortium: improving care of children with type 1 diabetes through collaborative research. *Diabetes TechnolTher.,* 2010; 12: 685-688.
23. 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; 30:861-866.
24. Tiwari LK, Jayashree M, Singhi S. Risk factors for cerebral edemain diabetic ketoacidosis in a developing country: role of fluidrefractory shock. *Pediatr Crit Care Med.,* 2012; 13: e91-e6.
25. Lansdown AJ, Barton J, Warner J, Williams D, Gregory JW, Harvey JN, *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 J Br DiabetAssoc.,* 2012; 29: 1506–1509.
26. Gruber N, Reichman B, Lerner-Geva L, Pinhas-Hamiel O. Increased risk of severe diabetic ketoacidosis among Jewish ultraorthodox children. *Acta Diabetol., 2015*; 52: 365–371.
27. Lewis KR, Clark C, Velarde MC. Socioeconomic factors associated with pediatric diabetic ketoacidosis admissions in Southern West Virginia. *Clin Endocrinol.,* 2014; 81: 218–221.
28. Moussa MA, Alsaeid M, Abdella N, Refai TM, Al-Sheikh N, Gomez JE. Prevalence of type 1 diabetes among 6- to 18-year-old Kuwaiti children. *Med Princ Pract.,* 2005; 14:87–91.
29. Saleh SI, Tuhmaz MM, Sarkhouh MY, El-Gawabi MA. Urinary tract infection in infants and children in Al-Jahra Area, Kuwait: An overview. *J Kuwait Med Assoc,* 2003; 35: 31–35.
30. Eng JV, Marcus R, Hadler JL, Imhoff B, Vugia DJ, Cieslak PR, *et al.* Consumer attitudes and use of antibiotics. *Emerg Infect Dis.,* 2003; 9:1128-1113.
31. Mokaddas EM, Rotimi VO., Albert MJ. Implications of streptococcus pneumoniae penicillin resistance and serotype distribution in Kuwait for disease treatment and prevention. *Clin Vaccine Immunol.,* 2008; 15:203–207.
32. Mokaddas EM, Wilson S, Sanyal SC. Prevalence of penicillin-resistant Streptococcus pneumoniae in Kuwait. *J Chemother.,* 2001; 13: 154–160.
33. Karges B, Kapellen T, Neu A, Hofer SE, Rohrer T, Rosenbauer J, Wolf J, *et al.* Long-acting insulin analogs and the risk of diabetic ketoacidosis in children and adolescents wuith type 1 diabetes: a prospective study of 10,682 patients from 271 institutions. *Diabetes Care.,* 2010; 33: 1031-1033.
34. Ahmed AM, Al-Maghamsi M, Al-Harbi AM, Eid IM, Baghdadi HH, Habeb AM. 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.
35. Vanelli M, Chiari G, Lacava S, Lovane B. Campaign for diabetic ketoacidosis prevention still effective 8 years later. *Diabetes Care,* 2007; 30: e12.
36. Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacalone T, Chiarelli F. Effectiveness of a prevention program for diabetic ketoacidosis in children. An 8-year study in schools and private practices. *Diabetes Care,* 1999; 22: 7–9.
37. Shaltout AA, Channanath AM, Thanaraj TA, Omar D, Abdulrasoul M, Zanaty N. Ketoacidosis at first presentation of type 1 diabetes mellitus among children: a study from Kuwait. *Scientific Reports,* 2016; 6: 27519.